

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

THE UNITED STATES OF AMERICA,

Plaintiff & Counterclaim-Defendant,

v.

GILEAD SCIENCES, INC. and
GILEAD SCIENCES IRELAND UC,

Defendants & Counterclaim-Plaintiff.

C.A. No. 19-02103-MN

**DEFENDANTS' FIRST AMENDED ANSWER AND AFFIRMATIVE DEFENSES
AND DEFENDANT GILEAD SCIENCES, INC.'S
FIRST AMENDED COUNTERCLAIMS**

Pursuant to Federal Rules of Civil Procedure 13 and 15(a), Defendant Gilead Sciences, Inc. (“GSI”) and Gilead Sciences Ireland UC (“GSIUC”) (collectively, “Defendants”) hereby file Defendants’ First Amended Answer and Affirmative Defenses and Defendant GSI’s First Amended Counterclaims in response to the Complaint of the United States of America (the “Government” or “Plaintiff”). This filing supersedes Defendants’ Answer and Affirmative Defenses and GSI’s Counterclaims, filed on January 23, 2020 (D.I. 7).

ANSWER

Defendants Gilead Sciences, Inc. (“GSI”) and Gilead Sciences Ireland UC (“GSIUC”) (collectively, “Defendants”) hereby respond to the Complaint of the United States of America (the “Government” or “Plaintiff”) as follows. Defendants deny each and every allegation contained in the Government’s Complaint that is not expressly admitted below. To the extent any factual allegation below is admitted, it is admitted only as to the specific admitted facts, not as to any purported conclusions, characterizations, implications, or speculations that arguably may follow from the admitted facts. No admission below should be construed as an admission or concession regarding the relevance of any allegation to any cause of action identified in the Complaint. No admission below should be construed as an admission concerning the accuracy, authenticity, admissibility, or relevance of any documents cited or referenced in the Complaint. No admission below with respect to GSI should be construed as an admission with respect to GSIUC, nor should any admission below with respect to GSIUC be construed as an admission with respect to GSI. Defendants deny that the Government is entitled to the relief requested in the Complaint or to any other relief.

1. Defendants admit that HIV is the cause of AIDS. Defendants admit that researchers, including Defendants’ researchers, have made and continue to make extensive efforts to develop treatments to prevent the spread and effects of HIV and AIDS. Defendants admit that millions of people are living with HIV and that millions have died due to AIDS. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 1 of the Complaint and therefore deny those allegations.

2. Defendants deny that CDC researchers “succeeded where others had not” and “conceived of and developed” the use of emtricitabine and “tenofovir or a tenofovir prodrug” as

pre-exposure prophylaxis, or PrEP. Defendants deny that CDC researchers used “new” and “precise” animal modeling methods. Defendants deny that the two-drug regimens described in Paragraph 2 were “innovative” as of the mid-2000s. Defendants admit that Truvada[®] (tenofovir disoproxil fumarate and emtricitabine) is indicated in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 2 of the Complaint and therefore deny those allegations.

3. Defendants admit that, as of 2006, at least some scientists and community advocates expressed concerns that PrEP could promote unsafe sexual practices and consequently increase the number of sexually transmitted diseases and questioned whether some patients would adhere to the PrEP regimen. Defendants deny the remaining allegations in Paragraph 3 of the Complaint.

4. Defendants deny that the CDC’s efforts constituted a “breakthrough” or that the CDC developed “new PrEP regimens.” Defendants admit that, following the CDC macaque research, researchers changed the methodology of at least one human PrEP trial. Defendants deny that the human PrEP trials used or demonstrated the efficacy of “CDC’s new PrEP regimens.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 4 of the Complaint and therefore deny those allegations.

5. Defendants deny that the four patents asserted in this case reflect any “innovative regimens” developed by the CDC. Defendants deny that the CDC is entitled to a “reasonable royalty.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 5 of the Complaint and therefore deny those allegations.

6. Defendants admit that one or both of GSI and GSIUC manufactures, markets, and sells Truvada[®] and Descovy[®], either in the United States or elsewhere in the world. Defendants admit that these products include a combination of (i) FTC and (ii) a tenofovir prodrug. Defendants admit that, when used as directed as part of a PrEP regimen and safe sex practices, these products are effective at reducing the risk of sexually transmitted HIV infection. Defendants admit that GSI received FDA approval for use of these products in treating HIV infections in combination with other medications. Defendants admit that GSI subsequently received FDA approval for the use of Truvada[®] and Descovy[®] as part of PrEP regimens. Defendants deny that the use of Truvada[®] and Descovy[®] as part of PrEP regimens is claimed and protected by CDC's patents. Defendants deny that the CDC's PrEP research was "groundbreaking." Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants deny that GSIUC has FDA approval to sell Truvada[®] or Descovy[®], including for use as PrEP regimens. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 6 of the Complaint and therefore deny those allegations.

7. Defendants admit that GSI markets and sells Truvada[®] and Descovy[®] in the United States for all of their indications, including their PrEP indications. Defendants deny that the PrEP regimens for which Truvada[®] and Descovy[®] are indicated are "protected by CDC's patents." Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to

form a belief as to the remaining allegations in Paragraph 7 of the Complaint and therefore deny those allegations.

8. Defendants deny the allegations in Paragraph 8 of the Complaint.

9. Defendants admit that they have not obtained a license from the CDC for any of the four patents asserted in the Complaint, which Defendants contend are invalid. Defendants admit that they have earned revenues from the sale of Truvada[®] and Descovy[®], either in the United States or elsewhere, and that Defendants have not paid and have no obligation to pay royalties to the CDC based on those sales revenues. Defendants lack sufficient knowledge or information to form a belief as to the vague allegation concerning “research funded by hundreds of millions of taxpayer dollars” and therefore deny that allegation. Defendants deny the remaining allegations in Paragraph 9 of the Complaint.

I. Nature of the Action¹

10. Paragraph 10 contains conclusions of law to which no response is required. To the extent a response is required, Defendants admit that Plaintiff has alleged that Defendants have infringed U.S. Patent Nos. 9,044,509 (the “’509 Patent”), 9,579,333 (the “’333 Patent”), 9,937,191 (the “’191 Patent”), and 10,335,423 (the “’423 Patent”) (collectively, the “Patents-in-Suit”) under 35 U.S.C. § 271 *et seq.* Defendants deny that they have infringed any valid and enforceable claim of the Patents-in-Suit.

II. Parties

11. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 11 of the Complaint and therefore deny those allegations.

¹ Defendants’ inclusion of the headings from the Government’s Complaint is for purposes of convenience only and should not be construed as an admission or concession regarding the accuracy, implications, or relevance of those headings.

12. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 12 of the Complaint and therefore deny those allegations.

13. Defendants admit the allegations in Paragraph 13 of the Complaint.

14. Defendants admit that Defendant GSIUC (formerly known as Gilead Sciences Limited) is an unlimited liability company formed under the laws of Ireland, with a principal place of business at IDA Business & Technology Park, Carrigtohill, County Cork, Ireland. Defendants admit that GSIUC is a wholly owned, indirect subsidiary of GSI. Defendants deny that GSIUC markets or sells Truvada[®] and Descovy[®] for PrEP in the United States or for the U.S. market. Defendants' investigation is ongoing, and based on the information currently known to Defendants, Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 14 and therefore deny those allegations.

15. Paragraph 15 of the Complaint contains conclusions of law to which no response is required.

III. Jurisdiction and Venue

16. Paragraph 16 of the Complaint contains conclusions of law to which no response is required.

17. Paragraph 17 of the Complaint contains conclusions of law to which no response is required. To the extent a response is required, Defendants admit that GSI is a Delaware corporation. Defendants admit that GSI and Emory University filed a complaint against Aurobindo Pharma Ltd. and Aurobindo Pharma USA, Inc. in Case No. 1:18-cv-00765 in the District of Delaware on May 18, 2018. Defendants admit that GSI and Emory University filed a complaint against Amneal Pharmaceuticals LLC in Case No. 1:17-cv-00943 in the District of Delaware on July 13, 2017.

18. Paragraph 18 of the Complaint contains conclusions of law to which no response is required. To the extent a response is required, Defendants admit that GSIUC has manufactured Truvada[®] and Descovy[®] products, at least for non-U.S. markets, and that Truvada[®] and Descovy[®] products have been labeled, marketed, distributed, and sold to residents of Delaware. Defendants admit that Janssen Pharmaceutica, N.V., Janssen Sciences Ireland UC, GSI, and GSIUC filed a complaint against Mylan Pharmaceuticals, Inc. and Mylan Inc. in Case No. 1:15-cv-00760 in the District of Delaware on August 31, 2015. Defendants admit that GSI and GSIUC filed a complaint against AbbVie, Inc. in Case No. 1:15-cv-00399 in the District of Delaware on May 19, 2015. Defendants' investigation is ongoing, and based on the information currently known to Defendants, Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 18 and therefore deny those allegations.

19. Paragraph 19 of the Complaint contains conclusions of law to which no response is required.

20. Defendants admit that GSI has earned revenues from the sale of Truvada[®] for PrEP and Descovy[®] for PrEP in the United States. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants deny the remaining allegations in Paragraph 20 of the Complaint.

21. Paragraph 21 of the Complaint contains conclusions of law to which no response is required.

IV. Technical and Historical Background

A. The Human Immunodeficiency Virus

22. Defendants admit the allegations in Paragraph 22 of the Complaint.

23. Defendants admit the allegations in Paragraph 23 of the Complaint.

24. Defendants admit that HIV infects human CD4⁺ cells (among others), uses those cells to replicate the virus, and kills CD4⁺ cells. HIV infection of CD4⁺ cells and HIV replication are complicated and involve numerous chemical and biological reactions. Defendants admit the basic steps outlined in Paragraph 24 of the Complaint, except to the extent that the description is overly simplistic and omits critical details in the infection and replication process.

25. Defendants admit that, over time, an HIV infection can lead to acquired immune deficiency syndrome (“AIDS”). Defendants likewise admit that AIDS is diagnosed when a person’s CD4⁺ T cell count falls below 200 cells/mm³ or the person has an AIDS-defining illness. Defendants further admit that a person diagnosed with AIDS often has opportunistic illnesses due to a weakened immune system. To the extent there are other allegations in Paragraph 25 of the Complaint, Defendants deny the allegations as being overly simplistic and omitting critical details.

26. Defendants admit the basic principles outlined in Paragraph 26, except to the extent that the description is overly simplistic and omits critical details in the infection process.

27. Defendants admit that HIV-1 and HIV-2 are the major types of HIV; that HIV-1 and HIV-2 can both lead to a weakening of an infected person’s immune system; that HIV-1 and HIV-2 are genetically distinct; that the recommended antiretroviral treatments may be different for patients infected with HIV-1 versus HIV-2; and that HIV-1 is the more predominant type of HIV found in human infections worldwide. To the extent there are other allegations in this paragraph, Defendants deny the allegations as being overly simplistic and omitting critical details.

28. Defendants admit the allegations in Paragraph 28 of the Complaint.

29. Defendants admit the allegations in Paragraph 29 of the Complaint.

B. The HIV/AIDS Epidemic

30. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 30 of the Complaint and therefore deny those allegations.

31. Defendants admit the allegations in Paragraph 31 of the Complaint, except to the extent that the efficacy of ART regimens can vary based on the type of therapy, patient compliance, and other factors.

32. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 32 of the Complaint and therefore deny those allegations.

33. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 33 of the Complaint and therefore deny those allegations.

34. Defendants admit the allegations in Paragraph 34 of the Complaint.

C. Treatment of HIV Infections

35. Defendants admit that current FDA-approved treatments for HIV are highly effective but not curative, and that these treatments can help people with HIV live longer, healthier lives but do not eliminate the virus from the human body or prevent reemergence of the virus when treatment is discontinued. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 35 of the Complaint and therefore deny those allegations.

36. Defendants admit the basic statements in Paragraph 36, except to the extent that the description is overly simplistic and omits critical details in the drug-resistance process.

37. Defendants admit that the current standard of care for HIV infection is the administration of three or more antiretroviral drugs from at least two different drug classes. Defendants further admit that the goal of this treatment strategy is to keep a patient's viral load (a measure of the amount of virus in the bloodstream) below detectable levels. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 37 of the Complaint and therefore deny those allegations.

38. Defendants admit that (i) nucleoside reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs), (ii) nonnucleoside reverse transcriptase inhibitors (NNRTIs), (iii) protease inhibitors (PIs), (iv) integrase inhibitors, and (v) entry or fusion inhibitors are different classes of antiretroviral drugs that can be used to treat HIV infections.

39. Defendants admit the basic statements in Paragraph 39 of the Complaint, except to the extent that the description is overly simplistic and omits critical details about the functioning of NRTIs and NtRTIs.

40. Defendants lack sufficient knowledge or information to form a belief as to the vague and overbroad allegations in Paragraph 40 of the Complaint and therefore deny those allegations.

41. Defendants lack sufficient knowledge or information to form a belief as to the vague and overbroad allegations in Paragraph 41 of the Complaint and therefore deny those allegations.

42. Defendants admit that, under the current standard of care for HIV infection, a standard ART regimen may include two NRTI/NtRTIs and one integrase inhibitor, NNRTI, or PI; however, the current standard of care also allows for treatment with other drug combinations. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 42 of the Complaint and therefore deny those allegations.

43. The document cited in Paragraph 43 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 43 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 43 of the Complaint and therefore deny those allegations.

44. The document cited in Paragraph 44 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 44 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 44 of the Complaint and therefore deny those allegations.

45. Defendants admit the allegations in Paragraph 45 of the Complaint.

46. Defendants admit that, using antiretroviral drugs currently approved by the FDA, a patient infected with HIV must use ART therapy for the remainder of the patient's life; otherwise, the patient's viral load of HIV may rise and the patient may transmit HIV to others. Defendants deny that a patient must adhere to one single ART treatment regimen continuously for the remainder of the patient's life. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 46 of the Complaint and therefore deny those allegations.

D. Truvada®

47. Defendants admit Truvada® is a registered trademark and is the proprietary name for a fixed-dose combination therapy that was invented and developed by GSI researchers for the treatment of HIV and later for the prevention of HIV infection, and that Truvada® consists of emtricitabine and tenofovir disoproxil fumarate.

48. Defendants admit that the Truvada® drug product, which was invented by GSI researchers, is a fixed-dose, two-drug combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) that is available in four strengths: (i) 200 mg FTC with 300 mg TDF, (ii) 167 mg FTC with 250 mg TDF, (iii) 133 mg FTC with 200 mg TDF, and (iv) 100 mg FTC with 150 mg TDF. Defendants further admit that the current package insert for Truvada® instructs the administration of only the strength containing 200 mg FTC with 300 mg TDF for adult use.

Defendants further admit that Truvada[®] was approved for sale by the FDA in 2004 for the treatment of HIV-1 infection in adults when used in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors). To the extent Paragraph 48 of the Complaint contains any additional allegations, Defendants deny them.

49. Defendants admit that TDF is a tenofovir prodrug; that TDF is enzymatically and/or chemically converted by metabolic processes in the body into tenofovir; and that tenofovir—which cannot be administered orally—is an NtRTI that was first discovered in the 1980s. To the extent Paragraph 49 of the Complaint contains any additional allegations, Defendants deny them.

50. Defendants admit that they developed tenofovir disoproxil fumarate, which is specifically designed to require initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Defendants further admit that tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase. To the extent that Paragraph 50 of the Complaint contains any additional allegations, Defendants deny them.

51. The document cited in Paragraph 51 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 51 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that FTC was discovered in the mid-1990s and is an NRTI that has been used in ART regimens at least since FDA's approval of Emtriva[®] in 2003. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 51 of the Complaint and therefore deny those allegations.

52. Defendants admit that Truvada[®], which was invented by GSI researchers, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg. Defendants further admit that, under current

guidelines, Truvada[®] may be used in an ART regimen in combination with an integrase inhibitor (for example, DTG or RAL); however, other combinations including Truvada[®] are also consistent with current treatment guidelines. Defendants further admit that Atripla[®], Complera[®], and Stribild[®] are the proprietary names for Defendants' products that contain FTC and TDF, among other components, and that these products may be administered as once-daily ART regimens. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 52 of the Complaint and therefore deny those allegations.

53. Defendants admit that GSI received FDA approval in 2012 to sell Truvada[®], which was invented by GSI researchers, as a tablet consisting of 200 mg FTC and 300 mg TDF for pre-exposure prophylaxis (PrEP), in combination with safer sex practices, to reduce the risk of sexually acquired HIV-1 in adults at high risk. Defendants deny that GSIUC has FDA approval to sell Truvada[®]. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC.

E. Descovy[®]

54. Defendants admit that Defendants manufacture, distribute, and sell the Descovy[®] drug product, either in the United States or elsewhere in the world. Defendants further admit that Descovy[®] is the proprietary name of a fixed-dose antiretroviral drug combination that includes FTC and tenofovir alafenamide, which is a phosphoramidate prodrug of tenofovir invented by GSI researchers.

55. Defendants admit that the Descovy[®] drug product does not contain TDF but does contain TAF. TAF is used to refer to tenofovir alafenamide, the free base. The form of tenofovir in the Descovy[®] drug product is tenofovir alafenamide (TAF) hemi-fumarate. Defendants deny that TAF is an ester of tenofovir. Defendants admit that the introduction of TAF in blood plasma

allows for permeation into cells. TAF is designed to intracellularly convert to tenofovir primarily through hydrolysis by cathepsin A followed by additional hydrolysis steps. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate.

56. Defendants admit that the FDA approved the Descovy[®] drug product, which was invented by GSI researchers, in April 2016 for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older in combination with other antiretroviral agents. Defendants further admit that Descovy[®] tablets approved by the FDA are available in one strength, a combination that includes 200 mg of FTC and 25 mg of TAF.

57. The document cited in Paragraph 57 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 57 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that, on October 3, 2019, GSI received FDA approval to sell Descovy[®] as a tablet consisting of 200 mg of FTC and 25 mg of TAF for the following indication: “DESCOVY is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating DESCOVY for HIV-1 PrEP.” Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. To the extent Paragraph 57 of the Complaint contains other allegations, they are denied.

F. Efforts to Develop Regimens to Prevent HIV Transmission

58. Defendants admit that patients whose HIV is fully suppressed by ART receive a clinical benefit and that poor adherence to the ART regimen reduces that benefit. Defendants further admit that persons living with HIV not receiving ART or who are unaware of their HIV-

positive status can spread HIV. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 58 of the Complaint and therefore deny those allegations.

59. Defendants admit that vaccines, post-exposure prophylaxis, and pre-exposure prophylaxis are being pursued as separate and distinct strategies in an effort to protect HIV-negative persons from infection, among other potential strategies for preventing transmission to HIV-negative persons, such as treatment of people living with HIV through ART. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 59 of the Complaint and therefore deny those allegations.

G. Decades of Unsuccessful Attempts to Create an HIV Vaccine

60. Defendants admit the allegations in Paragraph 60 of the Complaint.

61. The document cited in Paragraph 61 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 61 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 61 of the Complaint and therefore deny those allegations.

62. The document cited in Paragraph 62 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 62 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 62 of the Complaint and therefore deny those allegations.

63. Defendants admit that there has been extensive research into an effective HIV vaccine. Defendants further admit that they are unaware of the existence of any effective HIV vaccine, although promising vaccines are currently being studied, including through collaborations

with Defendants. To the extent that Paragraph 63 contains any additional allegations, Defendants lack sufficient knowledge or information to form a belief as to those allegations and therefore deny them.

H. Post-Exposure Prophylaxis (PEP) Regimens Based on Empirical Data

64. Defendants admit that post-exposure prophylaxis, or PEP, is a known type of HIV-prevention regimen. Defendants admit that PEP involves taking antiretroviral medication shortly after a potential exposure that presents a risk for HIV infection. The document cited in Paragraph 64 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 64 purporting to summarize that document to the extent they are inconsistent with that document.

65. The document cited in Paragraph 65 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 65 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 65 of the Complaint and therefore deny those allegations.

66. The document cited in Paragraph 66 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 66 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 66 of the Complaint and therefore deny those allegations.

67. The document cited in Paragraph 67 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 67 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 67 of the Complaint and therefore deny those allegations.

1. *Early Data Regarding Tenofovir Alone for PEP*

68. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 68 of the Complaint and therefore deny those allegations.

69. The document cited in Paragraph 69 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 69 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 69 of the Complaint and therefore deny those allegations.

2. *PEP Guidelines*

70. Defendants admit the allegations in Paragraph 70 of the Complaint.

71. The document discussed in Paragraph 71 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 71 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that the use of the Truvada[®] drug product for PEP, as described in the document discussed in Paragraph 71, anticipates claims 12 and 14-18 of the '509 Patent and claims 12 and 14-17 of the '333 Patent, all of which were disclaimed by the Government after the filing of this lawsuit. Defendants admit that neither the CDC nor HHS invented the use of Truvada[®] for PEP or PrEP. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 71 of the Complaint and therefore deny those allegations.

72. The document cited in Paragraph 72 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 72 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 72 of the Complaint and therefore deny those allegations.

73. The document cited in Paragraph 73 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 73 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 73 of the Complaint and therefore deny those allegations.

74. The document discussed in Paragraph 74 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 74 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 74 of the Complaint and therefore deny those allegations.

75. The document cited in Paragraph 75 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 75 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 75 of the Complaint and therefore deny those allegations.

76. The document cited in Paragraph 76 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 76 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 76 of the Complaint and therefore deny those allegations.

I. Pre-Exposure Prophylaxis (PrEP)

77. Defendants admit that pre-exposure prophylaxis (PrEP) refers to a regimen including oral medications that, when taken on a regular basis prior to exposure, prevent the spread of HIV. Defendants admit that PrEP research has been undertaken by multiple research groups,

including Defendants. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 77 of the Complaint and therefore deny those allegations.

78. The document cited in Paragraph 78 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 78 purporting to summarize that document to the extent they are inconsistent with that document. For example, Defendants deny that the cited source identifies PEP as a “28-course of antiretroviral therapy.”

79. Defendants admit that the applications for PrEP regimens for Truvada[®] and Descovy[®] that the FDA and foreign regulatory authorities have approved included animal data and data from randomized human clinical trials. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 79 of the Complaint and therefore deny those allegations.

80. The documents cited in Paragraph 80 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 80 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants admit that FTC/TDF and FTC/TAF, when taken in adherence to a prescribed PrEP regimen, have been estimated to reduce the risk of contracting HIV from sex with an effectiveness of about 99 percent. However, due to the vagueness of these allegations, including those concerning “effectiveness” and “evidence from several large clinical trials and observational studies of at-risk populations,” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 80 of the Complaint and therefore deny those allegations.

1. *Early PrEP Efforts*

81. Defendants deny that the CDC established “effective daily PrEP regimens in the mid-2000s.” Defendants admit that prior to the mid-2000s, concerns existed regarding, among other things, the sociological considerations surrounding PrEP’s overall efficacy, “risk compensation,” a person’s ability to adhere to a daily PrEP regimen, the safety and burden of a daily PrEP regimen for otherwise healthy people, and the potential for developing resistant HIV strains if PrEP fails. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 81 of the Complaint and therefore deny those allegations.

82. The document cited in Paragraph 82 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 82 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 82 of the Complaint and therefore deny those allegations.

83. The documents cited in Paragraph 83 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 83 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 83 of the Complaint and therefore deny those allegations.

84. The document cited in Paragraph 84 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 84 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that TDF received FDA approval in 2001 and that TAF was also known as GS-7340. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 84 of the Complaint and therefore deny those allegations.

85. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 85 of the Complaint and therefore deny those allegations.

86. The document cited in Paragraph 86 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 86 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 86 of the Complaint and therefore deny those allegations.

87. The document cited in Paragraph 87 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 87 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 87 of the Complaint and therefore deny those allegations.

88. The document cited in Paragraph 88 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 88 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 88 of the Complaint and therefore deny those allegations.

89. The document cited in Paragraph 89 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 89 purporting to summarize that document to the extent they are inconsistent with that document.

90. The document cited in Paragraph 90 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 90 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that GSI supported the work

described in Exhibit 25. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC.

91. Defendants deny that, as of the priority date for the Patents-in-Suit, no one expected a TDF/FTC regimen to be effective as a PrEP regimen. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 91 of the Complaint and therefore deny those allegations.

92. Defendants deny that no researchers focused on two-drug regimens for PrEP studies before the CDC performed its macaque study. Defendants lack sufficient knowledge or information to form a belief as to the first sentence of Paragraph 92 of the Complaint and therefore deny those allegations. Defendants deny the remaining allegations in Paragraph 92 of the Complaint.

2. *Research Leading to CDC's Innovative FTC/Tenofovir Prodrug Regimens*

93. Defendants admit the allegations in Paragraph 93 of the Complaint.

94. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 94 of the Complaint and therefore deny those allegations.

95. Defendants deny that CDC researchers were the first to design a study using FTC/TDF to prevent HIV infection. Defendants lack sufficient knowledge or information to form a belief as to the allegations in the first sentence of Paragraph 95 of the Complaint and therefore deny those allegations. Defendants deny the allegations in the second sentence of Paragraph 95 of the Complaint.

3. *CDC's Animal Modeling Techniques*

96. Defendants deny that the CDC alone provided any “breakthrough work” on PrEP. Defendants deny that the animal model described in Paragraph 96 of the Complaint was “new.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 96 of the Complaint and therefore deny those allegations.

97. Defendants admit that animal research methodologies that focused on large single doses of SIV or SHIV at mucosal surfaces did not accurately represent typical repeat, low-dose mucosal exposures experienced by humans with the sexual transmission of HIV. Defendants admit that such inaccuracies could underestimate the efficacy of potential treatments. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 97 of the Complaint and therefore deny those allegations.

98. Defendants deny that the CDC’s methodology was “new.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 98 of the Complaint and therefore deny those allegations.

4. *CDC's Determination of Proper Dosing*

99. On the basis that GSI researchers provided data and assistance with applicable dosing experiments, Defendants deny that the named inventors were solely responsible for the “prior determination of the proper doses of FTC and TDF used in their study.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 99 of the Complaint and therefore deny those allegations.

100. Defendants deny that “no literature or other studies suggested that the therapeutic doses of TDF and FTC available in Truvada[®] would also constitute effective preventive doses for a PrEP regimen.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 100 of the Complaint and therefore deny those allegations.

101. Defendants admit that, to control for species differences in the elimination of drugs, GSI and CDC researchers collaborated on pharmacokinetic studies to determine what doses in macaques would approximate appropriate blood and cellular levels of FTC and TDF in humans. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 101 of the Complaint and therefore deny those allegations.

5. CDC's Determination of Appropriate FTC Dose

102. The document cited in Paragraph 102 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 102 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that GSI employees Drs. Michael Miller and Howard Jaffe participated in the email exchange reflected in Exhibit 28. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 102 of the Complaint and therefore deny those allegations.

103. Defendants admit that GSI and the CDC entered into a Material Transfer Agreement (MTA) that the CDC executed on December 28, 2004, and that GSI executed on January 31, 2005. The document cited in Paragraph 103 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 103 purporting to summarize that document to the extent they are inconsistent with that document. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 103 of the Complaint and therefore deny those allegations.

104. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 104 of the Complaint and therefore deny those allegations.

105. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 105 of the Complaint and therefore deny those allegations.

6. CDC's Determination of Appropriate TDF Dose

106. Defendants admit that the CDC conducted pharmacokinetic research, in collaboration with GSI, to ensure proper dosing. Defendants deny that this research was CDC's "own" or exclusive research. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 106 of the Complaint and therefore deny those allegations.

107. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 107 of the Complaint and therefore deny those allegations.

108. The document cited in Paragraph 108 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 108 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 108 of the Complaint and therefore deny those allegations.

109. The document cited in Paragraph 109 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 109 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 109 of the Complaint and therefore deny those allegations.

7. *CDC's PrEP Experiments*

110. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 110 of the Complaint and therefore deny those allegations.

111. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 111 of the Complaint and therefore deny those allegations.

112. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 112 of the Complaint and therefore deny those allegations.

113. Defendants deny that the CDC's modeling techniques were "newly-developed." Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 113 of the Complaint and therefore deny those allegations.

114. The document cited in Paragraph 114 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 114 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 114 of the Complaint and therefore deny those allegations.

8. *Results of CDC's PrEP Experiments*

115. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 115 of the Complaint and therefore deny those allegations.

116. The document cited in Paragraph 116 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 116 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 116 of the Complaint and therefore deny those allegations.

117. Defendants deny that the results referred to in Paragraph 117 of the Complaint “demonstrated” definitively that “a person at risk for HIV infection could be effectively protected against HIV infection by regular prophylactic doses of FTC and tenofovir or FTC and a tenofovir prodrug.” Defendants further deny that the results permitted the CDC researchers to “conclude” definitively that the identified dosing levels would be “highly effective in adult humans.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 117 of the Complaint and therefore deny those allegations.

118. Defendants deny the allegations in Paragraph 118 of the Complaint.

J. Gilead’s Contribution Limited to Drug Donations

119. Defendants deny the allegations in Paragraph 119 of the Complaint.

120. Defendants admit GSI executed MTAs and amendments to MTAs with CDC between 2004 and 2008 under which GSI agreed to provide, and did provide, CDC with FTC, TDF, and tenofovir. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 120 of the Complaint and therefore deny those allegations.

121. Defendants admit that an MTA related to the research leading to the Patents-in-Suit was signed in December 2004 by Dr. Heneine, and later by Dr. Mick Hitchcock, GSI’s then–Vice President of Medical Affairs, in response to Dr. Heneine’s email request for a cost-free transfer of FTC to CDC. Defendants deny that this MTA was the earliest MTA related to the research leading to the Patents-in-Suit. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC.

122. Defendants admit that GSI entered into at least three other MTAs, as well as several MTA amendments, with the CDC, as well as amendments to these agreements. The documents discussed in Paragraph 122 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 122 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants deny the remaining allegations in Paragraph 122 of the Complaint.

123. The document cited in Paragraph 123 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 123 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that the CDC agreed to provide GSI with prompt notice of any applications for intellectual property based on material provided under the terms of the MTA. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC.

124. The document cited and the other documents discussed in Paragraph 124 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 124 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC.

125. Defendants deny the allegations in Paragraph 125 of the Complaint.

126. The document cited in Paragraph 126 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 126 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny that "[o]ther than the provision

of the study drugs, Gilead provided no substantive input into the protocol and methods used in CDC research.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 126 of the Complaint and therefore deny those allegations.

127. The document cited in Paragraph 127 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 127 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny the remaining allegations in Paragraph 127 of the Complaint.

K. Patent Applications Covering CDC’s Invention and Disclosure to Gilead

128. Defendants admit that U.S. non-provisional patent application number 11/669,547 was filed on January 31, 2007, and was published by the PTO on November 15, 2007. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 128 of the Complaint and therefore deny those allegations.

129. Defendants admit that PCT Application No. US2007/002926 was published on August 16, 2007. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 129 of the Complaint and therefore deny those allegations.

130. The document cited in Paragraph 130 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 130 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 130 of the Complaint and therefore deny those allegations.

131. Defendants admit that GSI received a draft copy of the referenced article prior to its publication. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants lack sufficient knowledge or

information to form a belief as to the remaining allegations in Paragraph 131 of the Complaint and therefore deny those allegations.

132. Defendants admit that some later papers relating to the CDC's PrEP research were made available to employees of GSI before publication. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the vague allegations in Paragraph 132 of the Complaint and therefore deny those allegations.

133. The documents referenced in Paragraph 133 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 133 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 133 of the Complaint and therefore deny those allegations.

134. Defendants deny the allegations in Paragraph 134 of the Complaint.

L. Immediate Impact of CDC's Innovative Regimens on Clinical Research

135. The document cited in Paragraph 135 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 135 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 135 of the Complaint and therefore deny those allegations.

136. The document cited in Paragraph 136 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 136 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or

information to form a belief as to the remaining allegations in Paragraph 136 of the Complaint and therefore deny those allegations.

137. The document cited in Paragraph 137 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 137 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 137 of the Complaint and therefore deny those allegations.

138. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 138 of the Complaint and therefore deny those allegations.

139. Defendants admit that the methodology of the PrEP trial in Botswana was changed, at least in part, due to research published by the CDC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 139 of the Complaint and therefore deny those allegations.

140. Defendants admit that the methodology of the PrEP trial in Botswana was changed, at least in part, due to research published by the CDC. Defendants admit that the planned methodology of the iPrEx trial was changed after the CDC's findings were presented, but Defendants deny that, after the iPrEx screening began in 2008, there was a change to FTC/TDF from TDF only. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 140 of the Complaint and therefore deny those allegations.

141. The document cited in Paragraph 141 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 141 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or

information to form a belief as to the remaining allegations in Paragraph 141 of the Complaint and therefore deny those allegations.

142. The document cited in Paragraph 142 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 142 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 142 of the Complaint and therefore deny those allegations.

143. Defendants deny the allegations in Paragraph 143 of the Complaint.

M. Numerous Subsequent Clinical Studies Confirming the Groundbreaking Efficacy of CDC's Inventive FTC/TDF Regimen

144. Defendants admit that FTC/TDF, when taken in adherence to a prescribed PrEP regimen, has been estimated to reduce the risk of contracting HIV from sex with an effectiveness of about 99 percent. However, due to the vagueness of these allegations, including those concerning the terms “a number of human studies” and “confirmed,” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 144 of the Complaint and therefore deny those allegations.

145. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 145 of the Complaint and therefore deny those allegations.

146. Defendants deny the allegations in Paragraph 146 of the Complaint.

1. *iPrEx Study*

147. Defendants admit that NIH was a sponsor of clinical trial NCT00458393, which is known by the name iPrEx and which ran from 2007 through 2014, including 2007 to 2011. Defendants further admit that the iPrEx trial was a randomized, double-blind, placebo-controlled

multinational study evaluating Truvada® in 2,499 HIV-seronegative men or transgender women who have sex with men and with evidence of high-risk behavior for HIV-1 infection.

148. The document cited in Paragraph 148 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 148 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny that iPrEx was the first published human study showing the clinical efficacy of PrEP. Defendants admit that the iPrEx trial showed that, at the end of treatment, emergent HIV-1 seroconversion was observed in 131 subjects, of which 48 occurred in the Truvada® group and 83 occurred in the placebo group, indicating a 42% reduction in risk; the iPrEx trial also showed that efficacy was strongly correlated with adherence. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 148 of the Complaint and therefore deny those allegations.

149. The documents cited in Paragraph 149 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 149 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 149 of the Complaint and therefore deny those allegations.

150. The document cited in Paragraph 150 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 150 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that the planned methodology of the iPrEx trial changed after the CDC's findings were presented, but Defendants deny that, after the iPrEx screening began in 2008, there was a change to FTC/TDF from TDF only.

151. Defendants admit that, in his testimony before the United States House Committee on Oversight and Reform (House Oversight Committee) in May 2019, current GSI CEO Daniel O'Day offered the following testimony in response to a question by Congressman Jim Jordan:

Rep. Jordan: And earlier, Dr. Grant said Gilead did not provide leadership or funding for PrEP in the studies at CDC. Is that true?

Mr. O'Day: No, that's not true. I mean, we have nine scientists that were involved in the iPrEx trial itself. It was one of the two trials that went to the FDA to seek approval. And of those, we have two scientists, both who are still with the company actually, that were authors in the primary New England Journal article that is the iPrEx study.

And to be an author on the New England Journal of Medicine article, you must -- you must have involvement in the trial, in addition to the free medicine we provided and the know-how.

152. The document cited in Paragraph 152 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 152 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny the remaining allegations in Paragraph 152.

153. The document cited in Paragraph 153 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 153 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny that GSI has been "a hesitant partner on PrEP research"; deny that GSI "did not provide leadership, innovation, or funding for PrEP research"; and deny that GSI limited its involvement in PrEP research "to donating study drug and placebos." Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC.

154. The document cited in Paragraph 154 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 154 purporting to summarize that document to the

extent they are inconsistent with that document. Defendants admit that GSI provided medication for the iPrEx study but did not provide monetary funding. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 154 of the Complaint and therefore deny those allegations.

2. *Partners PrEP Study*

155. Defendants admit that clinical trial NCT00557245, which is known by the name Partners PrEP, was initiated in 2007 with a study start date in 2008. Defendants further admit that the Partners PrEP trial was a randomized, double-blind, placebo-controlled 3-arm trial conducted in 4,758 HIV-1 serodiscordant heterosexual couples in Kenya and Uganda to evaluate the efficacy and safety of TDF (N=1,589) and FTC/TDF (N=1,583) versus (parallel comparison) placebo (N=1,586) in preventing HIV-1 acquisition by the uninfected partner. The document cited in Paragraph 155 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 155 purporting to summarize that document to the extent they are inconsistent with that document.

156. The document cited in Paragraph 156 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 156 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that the Partners PrEP trial showed that the risk reduction for Truvada[®] relative to placebo was 75% and that efficacy was strongly correlated with adherence. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 156 of the Complaint and therefore deny those allegations.

157. The document cited in Paragraph 157 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 157 purporting to summarize that document to the extent they are inconsistent with that document.

158. The documents cited in Paragraph 158 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 158 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants admit that GSI provided medication for the Partners PrEP study but did not provide monetary funding. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 158 of the Complaint and therefore deny those allegations.

159. The document cited in Paragraph 159 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 159 purporting to summarize that document to the extent they are inconsistent with that document.

3. *TDF2 Study*

160. The document cited in Paragraph 160 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 160 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 160 of the Complaint and therefore deny those allegations.

161. The document cited in Paragraph 161 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 161 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or

information to form a belief as to the remaining allegations in Paragraph 161 of the Complaint and therefore deny those allegations.

162. The document cited in Paragraph 162 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 162 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 162 of the Complaint and therefore deny those allegations.

4. *PROUD Study*

163. Defendants admit that studies started after iPrEx, Partners PrEP, and TDF2 found a daily Truvada® regimen to have higher efficacy than reported in the iPrEx, Partners PrEP, and TDF2 trials in some circumstances. To the extent there are further allegations in Paragraph 163 of the Complaint, Defendants lack sufficient knowledge or information to form a belief as to those allegations and therefore deny those allegations.

164. The document cited in Paragraph 164 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 164 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that GSI provided financial and in-kind support, including the Truvada® drug product and a grant for diagnostic testing, for the PROUD study. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 164 of the Complaint and therefore deny those allegations.

165. The documents cited in Paragraph 165 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 165 purporting to summarize those documents to

the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 165 of the Complaint and therefore deny those allegations.

5. *ANRS-IPERGAY Study*

166. The document cited in Paragraph 166 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 166 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that GSI provided financial and in-kind support, including medications and funding, for the IPERGAY study. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 166 of the Complaint and therefore deny those allegations.

167. The documents cited in Paragraph 167 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 167 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 167 of the Complaint and therefore deny those allegations.

6. *CDC's Methodology Now "Gold Standard" For Clinical Researchers*

168. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 168 of the Complaint and therefore deny those allegations.

169. Defendants deny that macaque modeling and testing are always necessary prior to the use of ARVs in human clinical trials for PrEP. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 169 of the Complaint and therefore deny those allegations.

N. Approval and Sales of Truvada[®] and Quick Approval of Descovy[®] That Followed from CDC's Inventive Work

170. Defendants admit that in July 2012, FDA approved the Truvada[®] drug product, which was invented by GSI researchers, for use as PrEP and that GSI owns a U.S. trademark registration for Truvada for PrEP. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants deny the remaining allegations in Paragraph 170 of the Complaint.

171. Defendants admit that GSI's application for FDA approval of Truvada[®] for the PrEP indication cited the iPrEx and Partners PrEP studies, among other studies. Defendants deny that, other than donating drugs, GSI did not support any of the clinical efforts leading to FDA approval of Truvada[®] for the PrEP indication. Defendants deny that GSI openly expressed skepticism regarding PrEP. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. The document cited in Paragraph 171 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 171 purporting to summarize that document to the extent they are inconsistent with that document.

172. Defendants admit that, following FDA approval of Truvada[®] for the PrEP indication, GSI developed and supported educational initiatives and demonstration projects designed to identify at-risk persons who could benefit from PrEP. Defendants deny the remaining allegations in Paragraph 172 of the Complaint.

173. The document cited in Paragraph 173 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 173 purporting to summarize that document to the extent they are inconsistent with that document.

174. Defendants admit that, as of January 1, 2013, the annualized wholesale acquisition cost (“WAC”) for Truvada[®] was approximately \$14,883.61 in the United States, although the cost varied depending on the specific payor. The documents cited in Paragraph 174 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 174 purporting to summarize those documents to the extent they are inconsistent with those documents.

175. The document cited in Paragraph 175 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 175 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 175 of the Complaint and therefore deny those allegations.

176. The document cited in Paragraph 176 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 176 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 176 of the Complaint and therefore deny those allegations.

177. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 177 of the Complaint and therefore deny those allegations.

178. Defendants admit that, as of November 2019, the wholesale acquisition cost (WAC) of a bottle containing 30 tablets of Truvada[®] was \$1757.90. Defendants admit that GSI has increased the U.S. WAC for Truvada[®]. Defendants admit that Defendants’ global revenues for Truvada[®] in 2018 were \$2.997 billion. Defendants admit that GSI’s domestic sales of Truvada[®] for the PrEP indication contributed to Defendants’ collective overall revenues for Truvada[®]. Defendants admit that Defendants are committed to ensuring that people who are at high risk for

HIV infection have access to prevention options, including Truvada® and Descovy®, where available. Defendants admit that GSI maintains patient-assistance programs and has taken a leadership position in ensuring patients have access to life-saving medications through a variety of programs and partnerships, including GSI's co-pay coupon program for eligible people with commercial insurance and its Truvada for PrEP® Medication Assistance Program for people who lack insurance coverage. Defendants admit that GSI's recent commitment to the CDC to provide up to 2.4 million bottles of Truvada® or Descovy® annually free of charge will support a greatly accelerated effort to reach uninsured Americans at risk for HIV. Further, Defendants admit that a CDC analysis found that of the estimated 1.2 million people in the U.S. eligible for PrEP, less than 1 percent do not have financial assistance to pay for PrEP medication and care. *See* Smith et al., "Estimated coverage to address financial barriers to HIV preexposure prophylaxis among persons with indications for its use, United States, 2015," *J. Acquir. Immune Defic. Syndr.* 2017 December 15; 76(5): 465–472. The documents cited in Paragraph 178 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 178 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 178 of the Complaint and therefore deny those allegations.

179. Defendants admit that GSI submitted a supplemental new drug application to FDA on April 5, 2019, seeking approval to market Descovy® for, among other things, use in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex, provided that such individuals have a negative HIV-1 test immediately prior to

initiating Descovy® for HIV-1 PrEP. Defendants deny the remaining allegations in Paragraph 179 of the Complaint.

180. Defendants admit the allegations in Paragraph 180 of the Complaint.

181. The document cited in Paragraph 181 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 181 purporting to summarize that document to the extent they are inconsistent with that document. Specifically, Defendants deny that Exhibit 9 includes the quote in Paragraph 181 of the Complaint, but Defendants admit that Exhibit 9 says “Descovy is not indicated in individuals at risk of HIV-1 infection from receptive vaginal sex because the effectiveness in this population has not been evaluated.” Defendants admit that, on October 3, 2019, FDA approved GSI’s supplemental NDA to market Descovy® for use in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex, provided that such individuals have a negative HIV-1 test immediately prior to initiating Descovy® for HIV-1 PrEP. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 181 of the Complaint and therefore deny those allegations.

O. PrEP as Critical Component of Effort to End HIV Epidemic

182. The documents cited in Paragraph 182 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 182 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 182 of the Complaint and therefore deny those allegations.

183. The document cited in Paragraph 183 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 183 purporting to summarize that document to the

extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 183 of the Complaint and therefore deny those allegations.

184. Defendants admit that efforts to administer Truvada® for PrEP in identified geographic areas, or “hot spots,” in the United States could be helpful to certain communities. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 184 of the Complaint and therefore deny those allegations.

185. Defendants admit that efforts to reach marginalized and hard-to-reach communities at high risk for HIV infections can be hindered by stigma associated with PrEP use. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 185 of the Complaint and therefore deny those allegations.

186. Defendants deny that the cost of the Truvada® drug product is a critical barrier to increasing access to PrEP in the United States. Defendants deny that the cost of the Truvada® drug product is a major reason that many at risk of HIV infection in the United States are not currently taking Truvada® for the PrEP indication. Defendants admit that Defendants are committed to ensuring that people who are at high risk for HIV infection have access to prevention options, including Truvada® and Descovy®, where available. Defendants admit that GSI maintains patient-assistance programs and has taken a leadership position in ensuring patients have access to GSI’s medications through a variety of programs and partnerships, including GSI’s co-pay coupon program for eligible people with commercial insurance and its Truvada for PrEP® Medication Assistance Program for people who lack insurance coverage. Defendants admit that GSI’s recent commitment to the CDC to provide up to 2.4 million bottles of Truvada® or Descovy® annually free of charge will support a greatly accelerated effort to reach uninsured Americans at risk for

HIV. Further, Defendants admit that a CDC analysis found that of the estimated 1.2 million people in the U.S. eligible for PrEP, less than 1 percent do not have financial assistance to pay for PrEP medication and care. *See* Smith et al., “Estimated coverage to address financial barriers to HIV preexposure prophylaxis among persons with indications for its use, United States, 2015,” *J. Acquir. Immune Defic. Syndr.* 2017 December 15; 76(5): 465–472. Defendants admit that, in the United States, Truvada® is currently sold only by GSI, which has substantial rights in patents covering that product. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 186 of the Complaint and therefore deny those allegations.

187. The documents cited in Paragraph 187 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 187 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants admit that some activists have criticized the pricing of Truvada® in the United States. Defendants admit that the pricing of Truvada® in the United States was a topic during a House Oversight Committee hearing in May 2019. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 187 of the Complaint and therefore deny those allegations.

188. The documents cited in Paragraph 188 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 188 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 188 of the Complaint and therefore deny those allegations.

P. Teva Settlement Announcement

189. Defendants admit that GSI has taken actions regarding access to Truvada®. Defendants deny the remaining allegations in Paragraph 189 of the Complaint.

190. Defendants admit that GSI disclosed the following in a May 8, 2019 Form 10-Q securities filing: “Pursuant to a settlement agreement relating to patents that protect Truvada and Atripla, Teva Pharmaceuticals will be able to launch generic fixed-dose combinations of emtricitabine and TDF and generic fixed-dose combinations of emtricitabine, TDF and efavirenz in the United States on September 30, 2020.” Defendants admit that this settlement took place in 2014. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants deny the remaining allegations in Paragraph 190 of the Complaint.

191. Defendants admit that Douglas M. Brooks, GSI’s Executive Director for Community Engagement, sent an email to several individuals on May 8, 2019, stating that:

There has been significant speculation, and some misinformation, in recent months related to the Truvada patents and the timing of a generic version of the drug into the market.

Gilead reached an agreement with Teva Pharmaceuticals in 2014 to allow the early launch of a generic version of Truvada into the market in 2020, a year earlier than required.

For background, a generic version of Truvada is not currently available. The patents and exclusivity for tenofovir disoproxil fumarate (TDF), one component of Truvada, have expired. The patent for emtricitabine, the other component of Truvada, expires in September of 2021.

Pursuant to a settlement agreement reached in 2014 relating to patents that protect Truvada as well as Atripla (emtricitabine/TDF/efavirenz), Teva will be able to launch generic fixed-dose combinations of emtricitabine and TDF and generic

fixed-dose combinations of emtricitabine, TDF and efavirenz in the United States on September 30, 2020.

This agreement is not related to current discussions with the U.S. government to broaden access to Truvada for PrEP for vulnerable populations and support the federal plan to end the HIV epidemic. Those discussions are ongoing.

Defendants deny the allegations of Paragraph 191 to the extent they are inconsistent with the text above.

192. Defendants deny the allegations in Paragraph 192 of the Complaint.

193. The document cited in Paragraph 193 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 193 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 193 of the Complaint and therefore deny those allegations.

194. The document cited in Paragraph 194 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 194 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 194 of the Complaint and therefore deny those allegations.

195. Defendants admit that the launch of the Descovy[®] PrEP indication has preceded the availability of any generic equivalent of Truvada[®] in the United States. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 195 of the Complaint and therefore deny those allegations.

V. CDC's Patents

196. Paragraph 196 of the Complaint contains conclusions of law purporting to summarize the scope of the claims of the Patents-in-Suit, to which no response is required. To the

extent a response to those conclusions of law is required, Defendants deny those allegations. The patents referenced in Paragraph 196 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 196 purporting to summarize those patents to the extent they are inconsistent with those patents. Defendants deny that the patents referenced in Paragraph 196 are valid. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 196 of the Complaint and therefore deny those allegations.

A. The '509 Patent

197. Defendants admit that the '509 Patent is entitled “Inhibition of HIV Infection through Chemoprophylaxis” and bears an issuance date of June 2, 2015. Defendants admit that the '509 Patent states that it “claims priority of U.S. Provisional Patent Application Ser. No. 60/764,811 filed Feb. 3, 2006.” Defendants deny that the '509 Patent was validly issued.

198. Defendants admit that the '509 Patent lists Walid M. Heneine, Thomas M. Folks, Robert Janssen, Ronald Otten, and Jose Gerardo García Lerma as inventors on its face. Defendants deny that the '509 Patent is valid.

199. Paragraph 199 of the Complaint contains conclusions of law to which no response is required. To the extent a response to those conclusions of law is required, Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 199 of the Complaint and therefore deny those allegations.

200. Paragraph 200 of the Complaint contains conclusions of law to which no response is required. To the extent a response is required, the '509 Patent speaks for itself, and Defendants deny the allegations of Paragraph 200 purporting to summarize that patent to the extent they are inconsistent with that patent.

201. Paragraph 201 of the Complaint contains conclusions of law to which no response is required. To the extent an answer is required, the '509 Patent speaks for itself, and Defendants

deny the allegations of Paragraph 201 purporting to summarize that patent to the extent they are inconsistent with that patent. Defendants admit that HHS canceled Claim 12 via statutory disclaimer after being faced with GSI's invalidity positions in IPR2019-01453. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 201 of the Complaint and therefore deny those allegations.

202. Defendants admit that TDF is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester prodrug of tenofovir. Defendants deny that TAF is a tenofovir ester. To the extent that Paragraph 202 of the Complaint includes allegations about the scope of the claim term "tenofovir ester," Paragraph 202 of the Complaint contains conclusions of law to which no response is required.

203. Paragraph 203 of the Complaint contains conclusions of law to which no response is required. To the extent a response is required, the '509 Patent speaks for itself, and Defendants deny the allegations of Paragraph 203 purporting to summarize that patent to the extent they are inconsistent with that patent.

204. Paragraph 204 of the Complaint contains conclusions of law to which no response is required.

205. The patents referenced in Paragraph 205 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 205 purporting to summarize those patents to the extent they are inconsistent with those patents. Defendants admit that HHS has canceled Claims 12 and 14-18 via statutory disclaimer after being faced with GSI's invalidity positions in IPR2019-01453. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 205 of the Complaint and therefore deny those allegations.

B. The '333 Patent

206. Defendants admit that the '333 Patent bears an issuance date of February 28, 2017. Defendants deny that the '333 Patent was validly issued.

207. Paragraph 207 of the Complaint contains conclusions of law to which no response is required. To the extent a response to those conclusions of law is required, Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 207 of the Complaint and therefore deny those allegations.

208. Paragraph 208 of the Complaint contains conclusions of law to which no response is required. To the extent an answer is required, Defendants admit that HHS has canceled Claims 12 and 14-17 via statutory disclaimer after being faced with GSI's invalidity positions in IPR2019-01454. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 208 of the Complaint and therefore deny those allegations.

209. The '333 Patent speaks for itself, and Defendants deny the allegations of Paragraph 209 purporting to summarize that patent to the extent they are inconsistent with that patent.

210. The '333 Patent speaks for itself, and Defendants deny the allegations of Paragraph 210 purporting to summarize that patent to the extent they are inconsistent with that patent. Defendants admit that HHS has canceled Claim 12 via statutory disclaimer after being faced with GSI's invalidity positions in IPR2019-01454. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 210 of the Complaint and therefore deny those allegations.

211. Paragraph 211 of the Complaint contains conclusions of law to which no response is required. To the extent a response is required, the '333 Patent speaks for itself, and Defendants deny the allegations of Paragraph 211 purporting to summarize that patent to the extent they are inconsistent with that patent.

C. The '191 Patent

212. Defendants admit that the '191 Patent bears an issuance date of April 10, 2018. Defendants deny that the '191 Patent was validly issued.

213. Paragraph 213 of the Complaint contains conclusions of law to which no response is required. To the extent a response to those conclusions of law is required, Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 213 of the Complaint and therefore deny those allegations.

214. Paragraph 214 of the Complaint contains conclusions of law to which no response is required.

215. The '191 Patent speaks for itself, and Defendants deny the allegations of Paragraph 215 purporting to summarize that patent to the extent they are inconsistent with that patent.

216. The '191 Patent speaks for itself, and Defendants deny the allegations of Paragraph 216 purporting to summarize that patent to the extent they are inconsistent with that patent.

D. The '423 Patent

217. Defendants admit that the '423 Patent bears an issuance date of July 2, 2019. Defendants deny that the '423 Patent was validly issued.

218. Paragraph 218 of the Complaint contains conclusions of law to which no response is required. To the extent a response to those conclusions of law is required, Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 218 of the Complaint and therefore deny those allegations.

219. Paragraph 219 of the Complaint contains conclusions of law to which no response is required.

220. The '423 Patent speaks for itself, and Defendants deny the allegations of Paragraph 220 purporting to summarize that patent to the extent they are inconsistent with that patent.

221. The '423 Patent speaks for itself, and Defendants deny the allegations of Paragraph 221 purporting to summarize that patent to the extent they are inconsistent with that patent.

222. Defendants admit that both TDF and TAF are prodrugs metabolized in the body to form the active metabolite tenofovir diphosphate. To the extent that Paragraph 222 of the Complaint includes allegations about the scope of the claim term “tenofovir prodrug,” Paragraph 222 of the Complaint contains conclusions of law to which no response is required.

223. Paragraph 223 of the Complaint contains conclusions of law to which no response is required. Defendants admit that the '333, '191, and '423 Patents share the same title and list the same inventors as the '509 Patent.

VI. CDC'S EFFORTS TO LICENSE THE PATENTS-IN-SUIT

A. CDC's Licensing of Its Patented Work Outside the United States

224. Defendants admit that GSI has substantial rights in the patents listed for all strengths of Truvada® in the FDA's *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, including, but not limited to, rights associated with being a licensee of those patents and the right to sue for infringement of those patents. Defendants further admit that GSI is the assignee of additional patents listed in the *Orange Book* for the 200 mg FTC, 300 mg TDF strengths of Truvada®. Whether these patents that are held or licensed by GSI would prevent the sale by others of pharmaceutical combinations of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) in the United States is a conclusion of law to which no response is required. Defendants further admit that generic forms of FTC/TDF fixed-dose tablets are now on the market in some non-U.S. countries where Defendants' patent protections have expired. Defendants deny the remaining allegations of Paragraph 224 of the Complaint.

225. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 225 of the Complaint and therefore deny those allegations.

226. Defendants admit that Mylan challenged European Patent No. 2,015,753, making only allegations based on documents examined during prosecution and making no arguments citing the prior art cited by GSI in its IPR petitions, Nos. IPR2019-01453, -01454, -01455, and -01456. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 226 of the Complaint and therefore deny those allegations.

227. Defendants deny that the claims of CDC's European patent are valid. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 227 of the Complaint and therefore deny those allegations.

228. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 228 of the Complaint and therefore deny those allegations.

229. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 229 of the Complaint and therefore deny those allegations.

230. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 230 of the Complaint and therefore deny those allegations.

231. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 231 of the Complaint and therefore deny those allegations.

232. Defendants admit that GSI has sold the Truvada[®] drug product, which contains an indication for PrEP, in the United States without paying any royalties to CDC. Defendants further admit that one or more corporate affiliates of GSI has sold Truvada[®] in certain non-U.S. jurisdictions where Truvada[®] is indicated for PrEP without paying any royalties to CDC. Defendants deny that CDC is entitled to any royalties from the sale of Truvada[®] for PrEP. Defendants deny the remaining allegations in Paragraph 232 of the Complaint.

B. Gilead's Refusal to Take a License to CDC's Patents

233. Defendants lack sufficient knowledge or information to form a belief as to the vague allegations in Paragraph 233 of the Complaint and therefore deny those allegations.

234. Defendants admit that Dr. Jay Parrish, who was a member of GSI's Corporate Development Team, received the email shown in Exhibit 78 from Laura T. Prestia, Technology Transfer Fellow-CDC Unit, Office of Technology Transfer, National Institutes of Health, on or around October 23, 2014. Defendants further admit that Dr. Linda Higgins, who was GSI's Vice-President of Biology, received an email substantially similar to the email shown in Exhibit 78 from Laura T. Prestia, Technology Transfer Fellow-CDC Unit, Office of Technology Transfer, National Institutes of Health, on or around October 23, 2014. Defendants deny that these communications constituted notice of the patented technology or alleged inventions. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 234 of the Complaint and therefore deny those allegations.

235. The document cited in Paragraph 235 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 235 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny that these communications constituted notice of the patented technology.

236. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 236 of the Complaint and therefore deny those allegations.

237. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 237 of the Complaint and therefore deny those allegations.

238. Defendants admit that Jay Parrish, an employee of GSI, received an email from Tara Kirby, Ph.D., CDC Team Supervisor, Technology Transfer and Intellectual Property Office, National Institute of Allergy and Infectious Diseases, on or around March 11, 2016, that stated, among other things, “The matter I wanted to discuss with you is an invention from CDC’s Division of HIV/Aids Prevention Surveillance and Epidemiology, our reference number E-195-2013/0. We have recently obtained issued patents for this invention in a number of jurisdictions, including the United States (USPN 9,044,509), and we believe that your marketed drug, Truvada, may be covered by these patents. For your ease of reference, I have attached a copy of the issued U.S. patent, as well as a listing of our patent filings relating to this invention. We would be happy to discuss an amicable resolution to this matter. This invention is available for licensing on a non-exclusive basis, so I have attached a copy of our standard license application form for your review and consideration.” Defendants further admit that this email attached a copy of the ’509 Patent, a document purporting to show a listing of CDC’s patent filings related to the alleged invention, and a document purporting to be a standard license application form. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. To the extent there are remaining allegations in Paragraph 238 of the Complaint, Defendants deny them.

239. Defendants admit that Defendants’ outside counsel, WilmerHale LLP, spoke with Dr. Kirby by telephone in April 2016. Defendants deny the remaining allegations in Paragraph 239 of the Complaint.

240. Defendants admit that individuals from GSI and HHS engaged in two confidential conferences in 2017 and continued to correspond and communicate in 2018. Defendants admit

that the parties were unable to resolve the dispute and admit they did not enter into a licensing agreement. Defendants deny the remaining allegations in Paragraph 240 of the Complaint.

241. Defendants admit that GSI has publicly and repeatedly stated its position that the Patents-in-Suit are invalid, including in the testimony of GSI's CEO Daniel O'Day before the House Oversight Committee in May 2019. Defendants deny that they infringe the Patents-in-Suit. Defendants further admit that an invalid patent cannot be infringed. Defendants deny the remaining allegations in Paragraph 241 of the Complaint.

242. Defendants admit the allegations in Paragraph 242 of the Complaint.

243. Defendants admit that GSI challenged the validity of all claims of the four Patents-in-Suit by petitioning for *inter partes* review (IPR) at the PTO. Defendants further admit that GSI filed petitions on August 21, 2019, challenging the validity of all claims of the '509 and '333 Patents, in Patent Trial and Appeal Board ("PTAB") docket numbers IPR2019-01453 and IPR2019-01454, respectively; and on August 23, 2019, challenging the validity of all claims of the '191 and '423 patents, in PTAB docket numbers IPR2019-01455 and IPR2019-01456, respectively. Defendants deny the remaining allegations in Paragraph 243 of the Complaint.

C. CDC's Efforts to License Generic Products in United States

244. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 244 of the Complaint and therefore deny those allegations.

245. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 245 of the Complaint and therefore deny those allegations.

246. Defendants deny that Teva or any other generic manufacturer will launch a product branded as Truvada[®]. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 246 of the Complaint and therefore deny those allegations.

247. Defendants admit the allegations in Paragraph 247 of the Complaint.

248. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 248 of the Complaint and therefore deny those allegations.

D. Gilead's Intellectual Property Relating to CDC's Inventive Regimens

249. Defendants admit that GSI has pursued trademark protection relating to Truvada[®] for PrEP and GSIUC has pursued trademark protection relating to Descovy[®] for PrEP. Defendants admit that Defendants have not taken a license to the Patents-in-Suit. Defendants deny that the Government has any valid intellectual property rights in PrEP and therefore that Defendants have any obligation to license or acknowledge such rights. Defendants deny the remaining allegations in Paragraph 249 of the Complaint.

250. Defendants admit the allegations in Paragraph 250 of the Complaint to the extent that "Gilead" refers to GSI. The allegations in this paragraph are denied to the extent that "Gilead" refers to GSIUC.

251. Defendants admit that GSIUC applied for a trademark in the United States for exclusive use of the mark, DESCOVY FOR PREP, and that GSIUC's application for the mark was filed on January 17, 2019 as U.S. Ser. No. 88,266,226. Defendants admit that GSIUC applied for trademark registration of Descovy for PrEP's logo as U.S. Ser. No. 88,615,918. The allegations in this paragraph are denied to the extent that "Gilead" refers to GSI. Defendants deny the remaining allegations in Paragraph 251 of the Complaint.

252. Defendants admit that GSI filed the trademark applications referenced in Paragraph 250 of the Complaint after Plaintiff proposed a license to the '509 Patent. Defendants deny that GSI filed the trademark applications referenced in Paragraph 250 of the Complaint after Plaintiff identified the remaining Patents-in-Suit because, among other things, the remaining Patents-in-Suit had not issued as of the referenced trademark application dates. Defendants further admit that GSIUC filed the trademark application referenced in Paragraph 251 of the Complaint after Plaintiff

proposed a license to at least the '509 Patent. Defendants deny that GSIUC filed trademark application U.S. Ser. No. 88,266,226 referenced in Paragraph 251 of the Complaint after Plaintiff identified at least the '423 Patent because, among other things, the '423 Patent had not issued as of January 17, 2019. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 252 of the Complaint and therefore deny those allegations.

VII. GILEAD'S WILLFUL INFRINGEMENT OF CDC'S PATENTS

A. Inducement of PrEP Regimens Through Sales of Truvada®

253. Defendants admit that, since, 2012, GSI has marketed and sold bottles of Truvada® in the United States for all indications on its label, including its PrEP-related indication. Defendants deny any remaining allegations in Paragraph 253 of the Complaint.

254. Defendants admit that Truvada® has been Defendants' top-selling HIV medication by revenue worldwide over the full period from its launch in 2004 through the end of Defendants' fiscal year 2018. Defendants deny, however, that Truvada® has been Defendants' top-selling HIV medication by revenue worldwide in each year during that period; for example, Defendants deny that Truvada® was Defendants' top-selling HIV medication by revenue worldwide in fiscal years 2017 or 2018. Defendants admit that Defendants' collective worldwide revenue from Truvada® was approximately 20.5% of their collective worldwide revenue from HIV products and approximately 13.8% of their collective worldwide revenue from all products in fiscal year 2018, but Defendants state that these percentages have varied based on the fiscal year and market considered. Defendants lack sufficient knowledge or information to form a belief as to the remaining vague allegations in Paragraph 254 of the Complaint and therefore deny those allegations.

255. Defendants admit that the percentage of Truvada® sales attributable to the PrEP indication has fluctuated over time. Defendants admit that Defendants estimate that more than

60% of demand for Truvada[®] in the first quarter of 2019 was attributable to use for the PrEP indication. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 255 of the Complaint and therefore deny those allegations.

256. Defendants admit that GSI has educated healthcare providers and patients on administration of Truvada[®] for the PrEP indication via the FDA-approved package insert for Truvada[®], the FDA-approved packaging for Truvada[®], and promotional messaging consistent with these FDA-approved messages. Defendants' investigation is ongoing, and based on the information currently known to Defendants, Defendants deny the remaining allegations of Paragraph 256 of the Complaint.

257. Defendants admit that Truvada[®] tablets are formulated with FTC and TDF in four dosage combinations, one of which is 200 mg FTC and 300 mg TDF. The document cited in Paragraph 257 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 257 purporting to summarize that document to the extent they are inconsistent with that document.

258. The document cited in Paragraph 258 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 258 purporting to summarize that document to the extent they are inconsistent with that document.

259. Defendants admit that GSI has promoted Truvada[®] for PrEP and has made available a pamphlet entitled "TRUVADA for a Pre-Exposure Prophylaxis (PrEP) indication." Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that

“Gilead” refers to GSIUC. Defendants deny the remaining allegations in Paragraph 259 of the Complaint.

260. Defendants admit that GSI provides the document cited in Paragraph 260 for prescribing healthcare providers and patients to sign prior to initiating Truvada[®] for PrEP. The document cited in Paragraph 260 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 260 purporting to summarize that document to the extent they are inconsistent with that document. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants deny the remaining allegations in Paragraph 260 of the Complaint.

261. Defendants admit that GSI obtained a U.S. trademark registration for Truvada for PrEP[®] and applied for a U.S. trademark registration for the phrase “Step Up. PrEP Up” for “promoting public awareness of prevention, treatment, and diagnosis of HIV and AIDS.” Compl. Ex. 86 at 1. Defendants further admit that GSI has obtained a U.S. trademark registration for “a three-dimensional configuration of an oblong tablet, combined with the color blue as applied to the entire surface of the tablet” for “pharmaceutical preparations, namely, pre-exposure prophylaxis (PrEP) preparations for prevention and risk mitigation of contracting HIV.” Compl. Ex. 87 at 1-2. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants deny the remaining allegations in Paragraph 261 of the Complaint.

B. Gilead’s Clinical Trials to Obtain FDA Approval of Descovy[®] for PrEP

262. Defendants admit that GSI conducted a clinical trial as part of the FDA approval process for Descovy[®] for the PrEP indication. Defendants’ investigation is ongoing, and based on

the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining vague allegations in Paragraph 262 of the Complaint and therefore deny those allegations.

263. Defendants admit that the DISCOVER trial is titled “Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection (DISCOVER).” Defendants admit that GSI is the sole sponsor of this trial and that this trial was intended to support GSI’s supplemental new drug application seeking FDA approval to market Descovy[®] for the PrEP indication. Defendants admit that GSI did not enlist any Government support or funding for the DISCOVER trial and that the Government did not directly support or fund the DISCOVER trial. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 263 of the Complaint and therefore deny those allegations.

264. Defendants admit that the DISCOVER trial consists of three experimental arms: a) an experimental arm in which the subject is given FTC/TAF (200/25 mg tablet) and an FTC/TDF placebo, each administered orally once daily for at least 96 weeks; b) an experimental arm in which the subject is given FTC/TDF (200/300 mg tablet) and an FTC/TAF placebo, each administered orally once daily for at least 96 weeks; c) an open-label extension experimental arm wherein, once all participants have been on blinded treatment for at least 96 weeks, the study will be unblinded and participants will be offered the option to continue on open-label FTC/TAF treatment for pre-

exposure prophylaxis in the open-label extension for 48 weeks, where the open label FTC/TAF (200/25 mg tablet) regimen is administered orally once daily. The allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants deny any remaining allegations in Paragraph 264 of the Complaint.

265. The documents cited in Paragraph 265 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 265 purporting to summarize those documents to the extent they are inconsistent with those documents.

266. The document cited in Paragraph 266 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 266 purporting to summarize that document to the extent they are inconsistent with that document.

267. Defendants admit that GSI submitted a supplemental new drug application to FDA on April 5, 2019, seeking approval to market Descovy® for, among other things, use in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex, provided that such individuals have a negative HIV-1 test immediately prior to initiating DESCOVY for HIV-1 PrEP. Defendants further admit that FDA approved GSI’s sNDA for this indication on October 3, 2019. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. To the extent Paragraph 267 of the Complaint contains additional allegations, Defendants deny them.

268. Defendants admit that all participants on the DISCOVER trial were required to roll over to the open label phase by July 31, 2019. Defendants admit that the DISCOVER open label phase will be ongoing until Descovy® for PrEP is commercially available in participants’

respective countries. Defendants admit that the open label phase for participants in the United States will end by October 2020. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 268 of the Complaint and therefore deny those allegations.

C. Inducement of PrEP Regimens Through Sales of Descovy®

269. Defendants admit that GSI is now marketing and selling Descovy® for all of its indications, including its indication for PrEP in certain patient populations. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants deny the remaining allegations in Paragraph 269 of the Complaint.

270. Defendants admit that GSI holds U.S. patents relating to Descovy®. Defendants admit that there are no generic versions of Descovy® currently on the market in the United States. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 270 of the Complaint and therefore deny those allegations.

271. Defendants deny the allegations in Paragraph 271 of the Complaint.

272. Defendants admit that GSI has educated healthcare providers and patients on administration of Descovy® for PrEP via the FDA-approved package insert for Descovy®, the FDA-approved packaging for Descovy®, and promotional messaging consistent with these FDA-approved messages. Defendants deny the remaining allegations of Paragraph 272 of the Complaint.

273. The document cited in Paragraph 273 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 273 purporting to summarize that document to the extent they are inconsistent with that document.

274. Defendants admit that GSIUC applied for a trademark in the United States for exclusive use of the mark, DESCOVY FOR PREP. The documents cited in Paragraph 274 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 274 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants deny the remaining allegations of Paragraph 274 of the Complaint.

D. Willfulness and Deliberateness of Gilead's Activities

275. Defendants deny the allegations in Paragraph 275 of the Complaint.

276. Defendants deny that they have not contended that the marketing and selling of Truvada® for PrEP and Descovy® for PrEP do not infringe the Patents-in-Suit. Defendants admit that they have not made such a contention in testimony before Congress.

277. Defendants admit that GSI has asserted that the Patents-in-Suit are invalid in public statements. Defendants deny the remaining allegations in Paragraph 277 of the Complaint.

278. Defendants deny the allegations in Paragraph 278 of the Complaint.

279. Paragraph 279 of the Complaint contains conclusions of law to which no response is required. To the extent there are any factual allegations in Paragraph 279 of the Complaint, Defendants deny them.

COUNT I:
**GILEAD'S WILLFUL INFRINGEMENT OF THE '509 PATENT
BASED ON TRUVADA FOR PREP® AND DESCOVY® FOR PREP**

280. Defendants repeat and incorporate the admissions and denials in the preceding paragraphs as though fully set forth herein.

281. Defendants admit that the '509 Patent bears an issuance date of June 2, 2015. Defendants admit that the '509 Patent lists the United States of America as the assignee on its face. Defendants deny that the '509 Patent was validly issued. The remainder of Paragraph 281 of the Complaint contains conclusions of law to which no response is required.

282. Defendants deny the allegations in Paragraph 282 of the Complaint.

283. Defendants deny the allegations in Paragraph 283 of the Complaint.

284. Defendants deny the allegations in Paragraph 284 of the Complaint.

285. Defendants deny the allegations in Paragraph 285 of the Complaint.

286. Defendants deny the allegations in Paragraph 286 of the Complaint.

287. Defendants deny the allegations in Paragraph 287 of the Complaint.

288. Defendants deny the allegations in Paragraph 288 of the Complaint.

COUNT II:
GILEAD'S WILLFUL INFRINGEMENT OF THE '333 PATENT
BASED ON TRUVADA FOR PREP®

289. Defendants repeat and incorporate the admissions and denials in the preceding paragraphs as though fully set forth herein.

290. Defendants deny that the '333 Patent was issued on June 2, 2015. Defendants admit that the '333 Patent lists the United States of America as the assignee on its face. Defendants deny that the '333 Patent was validly issued. The remainder of Paragraph 290 of the Complaint contains conclusions of law to which no response is required.

291. Defendants deny the allegations in Paragraph 291 of the Complaint.

292. Defendants deny the allegations in Paragraph 292 of the Complaint.

293. Defendants deny the allegations in Paragraph 293 of the Complaint.

294. Defendants deny the allegations in Paragraph 294 of the Complaint.

295. Defendants deny the allegations in Paragraph 295 of the Complaint.

296. Defendants deny the allegations in Paragraph 296 of the Complaint.

COUNT III:
GILEAD'S WILLFUL INFRINGEMENT OF THE '191 PATENT
BASED ON TRUVADA FOR PREP®

297. Defendants repeat and incorporate the admissions and denials in the preceding paragraphs as though fully set forth herein.

298. Defendants deny that the '191 Patent was issued on June 2, 2015. Defendants admit that the '191 Patent lists the United States of America as the assignee on its face. Defendants deny that the '191 Patent was validly issued. The remainder of Paragraph 298 of the Complaint contains conclusions of law to which no response is required.

299. Defendants deny the allegations in Paragraph 299 of the Complaint.

300. Defendants deny the allegations in Paragraph 300 of the Complaint.

301. Defendants deny the allegations in Paragraph 301 of the Complaint.

302. Defendants deny the allegations in Paragraph 302 of the Complaint.

303. Defendants deny the allegations in Paragraph 303 of the Complaint.

304. Defendants deny the allegations in Paragraph 304 of the Complaint.

COUNT IV:
GILEAD'S WILLFUL INFRINGEMENT OF THE '423 PATENT
BASED ON TRUVADA FOR PREP® AND DESCOVY® FOR PREP

305. Defendants repeat and incorporate the admissions and denials in the preceding paragraphs as though fully set forth herein.

306. Defendants deny that the '423 Patent was issued on June 2, 2015. Defendants admit that the '423 Patent lists the United States of America as the assignee on its face. Defendants deny

that the '423 Patent was validly issued. The remainder of Paragraph 306 of the Complaint contains conclusions of law to which no response is required.

307. Defendants deny the allegations in Paragraph 307 of the Complaint.

308. Defendants deny the allegations in Paragraph 308 of the Complaint.

309. Defendants deny the allegations in Paragraph 309 of the Complaint.

310. Defendants deny the allegations in Paragraph 310 of the Complaint.

311. Defendants deny the allegations in Paragraph 311 of the Complaint.

312. Defendants deny the allegations in Paragraph 312 of the Complaint.

313. Defendants deny the allegations in Paragraph 313 of the Complaint.

RESPONSE TO PRAYER FOR RELIEF

The remainder of the Complaint recites a prayer for relief to which no response is required. To the extent any response is required, Defendants deny that the Government is entitled to any remedy or relief.

AFFIRMATIVE DEFENSES

Without any admission as to the burden of proof, burden of persuasion, or truth of any allegation in the Complaint, Defendants assert the following defenses:

FIRST AFFIRMATIVE DEFENSE (FAILURE TO STATE A CLAIM FOR RELIEF)

1. Plaintiff's Complaint fails to state a claim upon which relief can be granted. To the extent Plaintiff's Complaint states any claim as to GSI, it fails to state a claim upon which relief can be granted as to GSIUC.

**SECOND AFFIRMATIVE DEFENSE
(NON-INFRINGEMENT)**

2. Defendants do not infringe and have not infringed (either directly, contributorily, or by inducement) any valid and enforceable claim of the '509, '333, '191, or '423 Patents, either literally or under the doctrine of equivalents.

**THIRD AFFIRMATIVE DEFENSE
(INVALIDITY)**

3. One or more claims of the '509, '333, '191, and '423 Patents are invalid for failure to satisfy one or more requirements of patentability under 35 U.S.C. § 101 *et seq.*, including without limitation §§ 101, 102, 103, 112, and/or any judicially created doctrine of invalidity, including obviousness-type double patenting.

**FOURTH AFFIRMATIVE DEFENSE
(UNCLEAN HANDS)**

4. The claims of the Patents-in-Suit are unenforceable against Defendants because of the equitable doctrine of unclean hands.

5. For example, the Government has demonstrated unclean hands through its encouragement of both the public use and the prescription of Truvada[®] for PrEP purposes—including in CDC guidelines published even before the Truvada[®] PrEP indication had been approved by the FDA in 2012. For example, the CDC's January 28, 2011 guidelines—issued more than one year before the FDA's approval of the PrEP indication for Truvada[®]—identified “[p]rescrib[ing] 1 tablet of Truvada[®] (TDF [300 mg] plus FTC [200 mg]) daily” as part of “[b]eginning [a] PrEP medication regimen.” Ex. A (January 28, 2011 Interim Guidance) at 68. Furthermore, the Government requested that GSI provide TDF/FTC for use in preclinical and clinical studies concerning PrEP, and the Government (including the FDA) actively encouraged GSI to seek FDA approval for the PrEP indication for Truvada[®]. The Government's promotion

of the use of Truvada[®] for the indication that it now alleges infringes the Patents-in-Suit bars the Government under the doctrine of unclean hands from recovering royalties on sales of Truvada[®].

6. Furthermore, the Government has demonstrated unclean hands because it breached its obligations under at least four Material Transfer Agreements by failing to provide GSI with prompt notice of the alleged inventions or the patent applications that resulted in the Patents-in-Suit. Had the Government performed its contractual obligation under those agreements to promptly notify GSI of the purported invention(s) described in the applications that led to the HHS Patents, GSI would have had the opportunity to consider its options, including providing CDC and/or the PTO with information showing why any such patent would be invalid. Furthermore, the Government has demonstrated unclean hands because its applications for the HHS Patents violated the clear terms of a Clinical Trial Agreement with GSI. That agreement expressly provided that “CDC agrees not to seek patent protection in connection with any inventions that derive from the use of the Study Drug” in a clinical trial that, on information and belief, formed the basis for the Government’s decisions concerning the prosecution of the applications leading to the HHS Patents.

7. Throughout its history and continuing through today, GSI has collaborated in good faith with CDC on various research studies relating to the use of antiretroviral agents for prevention of HIV-1. As part of these collaborations, Gilead scientists have shared their significant expertise in the field of HIV with CDC researchers, including by providing ideas and guidance, and Gilead has provided CDC with millions of dollars of pharmaceuticals—at no cost to CDC—to further the scientific community’s efforts to end the HIV epidemic. During these collaborations, GSI and the Government, acting through the CDC, entered into at least four

material transfer agreements related to the research that resulted in the alleged inventions described in the HHS Patents.

8. On June 21, 2004, GSI and the Government, acting through the CDC, entered into a material transfer agreement bearing CDC Reference Number NCHSTP-V043072 (the “’072 MTA,” Ex. B).

9. Under the ’072 MTA, GSI provided significant quantities of two GSI drugs, tenofovir (“TFV”) and TDF, to CDC at no cost to be used in HIV-1 research conducted at CDC. Specifically, GSI provided the material to be used by CDC in a study that generally involved administering TDF to male Rhesus macaques either daily or weekly and exposing the macaques to simian-human immunodeficiency virus (“SHIV”), a relative of HIV-1, either weekly or shortly after the treatment dose via a low-dose rectal challenge model. The MTA also discussed an in vitro study using tenofovir.

10. In exchange for the drugs that GSI supplied under the ’072 MTA, among other things, CDC “agree[d] to promptly notify” GSI of “any Inventions” under the ’072 MTA, which the ’072 MTA defined as “any inventions, discoveries and ideas that are made, conceived or reduced to practice.” Ex. B (’072 MTA) § 8. The U.S. Public Health Service (“PHS”) likewise agreed “to give serious and reasonable consideration to [GSI’s] request for a non-exclusive or exclusive license on commercially reasonable terms under PHS’s intellectual property rights in or to any Inventions.” *Id.*

11. GSI performed its obligations under the ’072 MTA and delivered the TFV and TDF to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

12. On or around January 24, 2005, GSI and CDC executed an amendment to the '072 MTA whereby GSI would supply CDC with additional TDF at no cost.

13. GSI performed its obligations under the amendment to the '072 MTA and delivered the TDF to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

14. On January 7, 2005, GSI and the Government, acting through CDC, entered into a material transfer agreement bearing CDC Reference Number NCHSTP-V053433 (the "'433 MTA," Ex. C).

15. Under the '433 MTA, GSI provided significant quantities of a GSI drug, TFV, to CDC at no cost to be used in HIV-1 research conducted at CDC. Specifically, GSI provided the material to be used by CDC in a study that generally involved "determin[ing] the effective concentration [of TFV] in mucosal tissues to prevent HIV-1/SHIV infection." Ex. C ('433 MTA) at 7. The '433 MTA expressly stated that the information generated from the study would "be used ... in conjunction with [CDC's] PrEP work being conducted in non-human primates." *Id.*

16. The '433 MTA identified Thomas Folks as a co-investigator of the study described in the '433 MTA. Ex. C ('433 MTA) at 5. Thomas Folks is one of the individuals identified as an inventor on the face of the HHS Patents.

17. In exchange for the drugs that GSI supplied under the '433 MTA, among other things, CDC "agree[d] to promptly notify" GSI of "any Inventions" under the '433 MTA, which the '433 MTA defined as "any inventions, discoveries and ideas that are made, conceived or reduced to practice." Ex. C ('433 MTA) § 8. PHS likewise agreed "to give serious and reasonable consideration to [GSI's] request for a non-exclusive or exclusive license on

commercially reasonable terms under PHS's intellectual property rights in or to any Inventions.”

Id.

18. GSI performed its obligations under the '433 MTA and delivered the TFV to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

19. On January 31, 2005, GSI and the Government, acting through CDC, entered into a material transfer agreement bearing CDC Reference Number NCHSTP-V053471 (the “'471 MTA,” Ex. D).

20. Under the '471 MTA, GSI provided significant quantities of a GSI drug, FTC, to CDC at no cost to be used in HIV-1 research conducted at CDC. Specifically, GSI provided the material to be used by CDC in a study that generally involved administering a combination consisting of TFV and FTC to female Rhesus macaques daily and exposing the macaques to SHIV weekly via a low-dose vaginal challenge model.

21. In exchange for the drugs that GSI supplied under the '471 MTA, among other things, CDC “agree[d] to promptly notify” GSI of “any Inventions” under the '471 MTA, which the '471 MTA defined as “any inventions, discoveries and ideas that are made, conceived or reduced to practice.” Ex. D ('471 MTA) § 8. PHS likewise agreed “to give serious and reasonable consideration to [GSI's] request for a non-exclusive or exclusive license on commercially reasonable terms under PHS's intellectual property rights in or to any Inventions.”

Id.

22. GSI performed its obligations under the '471 MTA and delivered the FTC to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

23. On information and belief, in or around February 2006, GSI and CDC executed a first amendment to the '471 MTA whereby GSI would supply CDC with additional FTC at no cost.

24. GSI performed its obligations under the first amendment to the '471 MTA and delivered the FTC to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

25. On or about March 6, 2006, GSI and CDC executed a second amendment to the '471 MTA whereby GSI would supply CDC with additional TDF at no cost.

26. GSI performed its obligations under the second amendment to the '471 MTA and delivered the TDF to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

27. On April 25, 2005, GSI and the Government, acting through CDC, entered into a material transfer agreement bearing CDC Reference Number NCHSTP-V053649 (the "'649 MTA," Ex. E).

28. Under the '649 MTA, GSI provided significant quantities of a GSI drug, TFV (which was described in the '649 MTA by its alternative names, PMPA and (*R*)-9-(2-phosphonylmethoxypropyl)adenine), to CDC at no cost to be used in HIV-1 research conducted at CDC. Specifically, GSI provided the material to be used by CDC in a study that involved, among other things, administering a combination consisting of TFV and FTC to Rhesus macaques and exposing the macaques to SHIV via a low-dose rectal challenge model.

29. In exchange for the drugs that GSI supplied under the '649 MTA, among other things, CDC "agree[d] to promptly notify" GSI of "any Inventions" under the '649 MTA, which the '649 MTA defined as "any inventions, discoveries and ideas that are made, conceived or

reduced to practice.” Ex. E (’649 MTA) § 8. PHS likewise agreed “to give serious and reasonable consideration to [GSI’s] request for a non-exclusive or exclusive license on commercially reasonable terms under PHS’s intellectual property rights in or to any Inventions.” *Id.*

30. GSI performed its obligations under the ’649 MTA and delivered the FTV to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

31. Between April 30, 2008, and August 4, 2014, GSI and CDC executed five amendments to the ’649 MTA whereby GSI would supply CDC with additional medication at no cost.

32. GSI performed its obligations under the amendments to the ’649 MTA and delivered the medication to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

33. On February 3, 2006, CDC filed U.S. Provisional Patent Application No. 60/764,811 (the “’811 Provisional,” Ex. F), with the U.S. Patent and Trademark Office (“PTO”) related to purported inventions that CDC made in the course of the research conducted under the ’072 MTA, ’433 MTA, the ’471 MTA, and/or the ’649 MTA (collectively, the “MTAs”) and using the medications that GSI provided under the MTAs. On January 31, 2007, CDC filed U.S. non-provisional patent Application No. 11/669,547 (the “’547 Application,” Ex. G), claiming priority to the ’811 Provisional. The ’509 Patent issued from the ’547 Application on June 2, 2015, and the remaining HHS Patents have since issued and claim priority to the same provisional and non-provisional applications. On information and belief, the HHS Patents are

owned by the Government, represented by the U.S. Department of Health and Human Services (“HHS”).

34. The ’811 Provisional described the results of a study in which a group of six Rhesus macaques were injected subcutaneously with 22 mg/kg TFV and 20 mg/kg FTC, which is another GSI drug, once daily. Ex. F (’811 Provisional) at 6. The macaques were also subjected to weekly rectal exposures with a low dose of SHIV. The study found that the subcutaneous TFV/FTC combination provides a high level of protection against repeated virus challenges; the authors therefore concluded that “chemoprophylaxis with potent antiretrovirals is an effective strategy for preventing sexual HIV transmission.” *Id.* A presentation slide submitted as part of the ’811 Provisional reported that “Macaque models show that tenofovir [alone] can provide substantial protection against ... mucosal virus exposures,” like the rectal exposures used in the study. *Id.* at 8. On information and belief, the studies reported in the ’811 Provisional were performed by CDC researchers.

35. The ’547 Application disclosed several studies in the originally filed version of its specification. In one of those studies, a group of six macaques were given oral doses of a combination of TDF (22 mg/kg) and FTC (20 mg/kg) once daily. The macaques were also subjected to weekly rectal exposures with a low dose of SHIV. The study found that the oral TDF/FTC combination reduced infection in these macaques 7.8-fold versus an untreated control group. Ex. G (’547 Application) at [0040]-[0042].

36. On information and belief, the alleged discoveries and ideas and any purported inventions disclosed in the ’811 Provisional and/or the ’547 Application were made, conceived, or reduced to practice as a result of the studies described in the MTAs—*i.e.*, the studies for which GSI provided significant quantities of its proprietary drugs to CDC free of charge. *See*,

e.g., Compl. ¶ 121 (“The earliest MTA *related to the research leading to the Patents-in-Suit* was signed in December 2004 by Dr. Heneine, and later by Dr. Mick Hitchcock, Gilead’s then Vice President of Medical Affairs, in response to Dr. Heneine’s email request for a transfer of FTC to CDC.” (emphasis added)); *id.* ¶ 120 (“Under several MTAs with CDC, signed during the period from 2004 to 2008, Gilead provided the FTC, TDF, and tenofovir used in CDC’s research.”); *id.* ¶ 122 (“Ultimately, several additional MTAs were signed relating to transfers of drugs used in CDC’s patented research.”).

37. Furthermore, GSI and the Government, acting through CDC, also entered into a Clinical Trial Agreement (“CTA”) with an effective date of November 18, 2004. Ex. S. This agreement set forth the terms under which GSI would provide antiviral products free of charge for a clinical trial about HIV prevention in Botswana. The Government agreed, among other things, “to put the results of the Trial, patentable or otherwise, in the public domain for all to use without obligation or compensation to CDC.” “For clarity,” the CTA provided, “CDC agrees not to seek patent protection in connection with any inventions that derive from the use of the Study Drug in the Trial.” In compliance with its obligations under the CTA, GSI provided to CDC compounds and placebos at no cost. On information and belief, CDC utilized the compounds that GSI provided in the Botswana trial contemplated by the CTA. On information and belief, CDC relied on information derived from the Botswana clinical trial to make decisions concerning the prosecution of the ’547 Application.

38. In spite of the express terms of the MTAs requiring CDC to “promptly notify” Gilead of any claimed “Inventions” arising out of the research conducted under the MTAs and the clear term of the CTA expressly providing that “CDC agrees not to seek patent protection in connection with any inventions that derive from the use of the Study Drug in the Trial,” CDC not

only filed patent applications seeking patent protection for purported “Inventions” derived from the use of the compounds Gilead supplied under the MTAs and CTA, but also failed to disclose to Gilead the purported invention(s) claimed in the ’811 Provisional, the ’547 Application, and in the later applications that resulted in the HHS Patents. Instead, CDC and the Government waited several years—until October 2014 at the earliest—to provide the contractually required notice to GSI, and another two years, until March 11, 2016, to assert that Gilead required a license under the HHS Patents in order to continue marketing Truvada® for PrEP.

39. In the interim, in 2012, and with the encouragement and support of the Government (including the FDA), GSI obtained approval from the FDA to market Truvada®, which contains TDF and FTC—the medications that GSI provided to CDC under the MTAs—for HIV-1 PrEP. By the time that the Government first communicated with GSI concerning the purported invention(s) described in the ’811 Provisional or the ’547 Application in October 2014, GSI had already invested substantial amounts in educating at-risk patient populations about the potential benefits of Truvada® for PrEP, and some of those at-risk patient populations had already come to rely on Truvada® for prophylaxis to attempt to minimize their potential for contracting HIV-1.

40. Had CDC fulfilled its contractual obligations to promptly notify GSI of the purported invention(s) described in the ’811 Provisional and in the applications that resulted in the HHS Patents, GSI would have had the opportunity to consider its options, including providing CDC and/or the PTO with information showing why any such patent would be invalid.

41. Even after 2006, because of the Government’s continuing failure to promptly notify GSI of the purported invention(s) described in the ’811 Provisional, the ’547 Application, and in the later applications that resulted in the HHS Patents, GSI was further denied the

opportunity to consider its options, including: providing CDC and/or the PTO with information showing why any such patent would be invalid; changing its application for FDA approval to market Truvada® for PrEP; or indicating the role of GSI scientists in the work that led to the alleged inventions before developing and marketing Truvada® for PrEP and Descovy® for PrEP.

42. Because the Government failed to fulfill its contractual obligations to GSI under the MTAs and the CTA, the Government brings its infringement claims against GSI with unclean hands, and the HHS patents are therefore unenforceable against Defendants.

FIFTH AFFIRMATIVE DEFENSE (INEQUITABLE CONDUCT)

43. The claims of the Patents-in-Suit are unenforceable because of the doctrine of inequitable conduct.

44. Specifically, during prosecution of the HHS Patents, the Government failed to provide material information to the Patent Office relating to the inventiveness of the claimed inventions. On information and belief, these omissions were knowing and willful, made with an intent to deceive the Patent Office.

45. On August 21, 2019, GSI filed a Petition for *Inter Partes* Review of claims 1-18 of the '509 Patent before the Patent Trial and Appeal Board, *see* Ex. H, Petition, Case No. IPR2019-01453 (P.T.A.B. Aug. 21, 2019), and a Petition for *Inter Partes* Review of claims 1-17 of the '333 Patent before the Patent Trial and Appeal Board, *see* Ex. I, Petition, Case No. IPR2019-01454 (P.T.A.B. Aug. 21, 2019) (the "IPR Petitions"). These Petitions are incorporated by reference into these affirmative defenses as if fully set forth herein.

46. Among the prior art asserted in the IPR Petitions were the CDC's own Post-Exposure Prophylaxis guidelines ("CDC-PEP," Ex. J), which were published and made available to the public on January 21, 2005, in Volume 54, No. RR-2 of the CDC periodical *Morbidity and*

Mortality Weekly Report Recommendations and Reports (MMWR-RR). The CDC-PEP publication identified five authors affiliated with the CDC (including the first named author, Dr. Dawn K. Smith), as well as three authors affiliated with the National Institutes of Health, one author affiliated with the FDA, and two authors affiliated with the Health Resources and Services Administration. Ex. J (CDC-PEP) at 1. Furthermore, two of the named inventors of the four HHS Patents, Robert Janssen and Ronald Otten, were identified as “federal consultants” for the CDC-PEP guidelines. *Id.* at 20.

47. CDC-PEP describes a regimen of daily administrations of combinations of antiretroviral agents for an extended period following an HIV exposure to prevent an HIV infection. CDC-PEP identifies TDF+FTC as one of two “preferred” backbone combinations to use in post-exposure prophylaxis (“PEP”), and notes that Truvada[®] is an oral formulation containing 300 mg of TDF and 200 mg of FTC. Ex. J (CDC-PEP) at 8, 9 tbl.2, 10.

48. The January 21, 2005 publication date of CDC-PEP preceded the critical date of February 3, 2005—one year before the earliest priority date claimed by the ’509 Patent or ’333 Patent. Therefore, CDC-PEP constitutes prior art to both the ’509 Patent and ’333 Patent under 35 U.S.C. § 102(b).

49. By virtue of the CDC’s publication of CDC-PEP, that document was in the CDC’s possession prior to the CDC’s filing of the ’811 Provisional on February 3, 2006, or the filing of the ’547 Application on January 31, 2007—the applications that together led to the issuance of each of the HHS Patents, including the ’509 Patent and ’333 Patent.

50. On information and belief, the Government was aware of the CDC-PEP reference during the prosecution of the ’509 Patent and ’333 Patent, including by virtue of its possession and publication of that reference on or before January 21, 2005. As evidence thereof, and as

noted above, two of the named inventors of the four HHS Patents, Robert Janssen and Ronald Otten, were identified as “federal consultants” for the CDC-PEP guidelines and were therefore aware of that document and the findings therein.

51. However, during prosecution of the ’509 Patent and ’333 Patent, the Government did not disclose the CDC-PEP reference to the Patent Office, notwithstanding the duty to disclose material prior art, and notwithstanding the named inventors’ oaths concerning inventorship. Nor did the examiner consider that reference during her evaluation of the applications leading to issuance of those patents.

52. As set forth in the IPR Petitions, which are incorporated herein by reference, claims 12-18 of the ’509 Patent and claims 12-17 of the ’333 Patent are anticipated by the CDC-PEP reference under 35 U.S.C. § 102(b). Similarly, and as set forth in the aforementioned IPR Petitions, the prior art—including CDC-PEP—also renders all challenged claims of the ’509 Patent and ’333 Patent obvious under 35 U.S.C. § 103.

53. Unlike claim 1 of the ’509 Patent, which specifies administration “prior to an exposure” to an immunodeficiency retrovirus, claim 12 and dependent claims 14-18 of the ’509 Patent did not specify administration prior to an actual or potential exposure.

54. Unlike claim 1 of the ’333 Patent, which specifies administration “prior to the exposure” to an immunodeficiency retrovirus, claim 12 and dependent claims 14-17 of the ’333 Patent did not specify administration prior to an actual or potential exposure.

55. On December 2, 2019—after GSI filed its Petition in Case No. IPR2019-01453—the Government disclaimed claims 12 and 14-18 of the ’509 Patent. Ex. K (Disclaimer in Patent Under 37 C.F.R. § 1.321(a), U.S. Patent No. 9,044,509).

56. Likewise, on December 2, 2019, after GSI filed its Petition in Case No. IPR2019-01454, the Government disclaimed claims 12 and 14-17 of the '333 Patent. Ex. L (Disclaimer in Patent Under 37 C.F.R. § 1.321(a), U.S. Patent No. 9,579,333).

57. On information and belief, the Government's disclaimer of claims 12 and 14-18 of the '509 Patent and claims 12 and 14-17 of the '333 Patent was prompted by its recognition that CDC-PEP anticipated each of these claims.

58. The Government also did not disclose the CDC-PEP reference in its original filings on January 13, 2017 for Application No. 15,406,344, which later issued as the '191 Patent. Application No. 15,406,344, as originally filed, include at least one independent claim directed to the use of FTC and TFV or a TFV prodrug for PEP (original claim 12), but the Government failed to disclose CDC-PEP with its January 2017 filing. *See* Ex. M (Application No. 15406344, filed Jan. 13, 2017) at 23 (claim 12); *id.* at 32-36 (initial Information Disclosure Statement). The Government eventually disclosed CDC-PEP to the examiner during that prosecution on March 7, 2017, but did not alert the examiner to its materiality. *See* Ex. N (subsequent Information Disclosure Statement, filed March 7, 2017). The examiner subsequently relied upon CDC-PEP in issuing a non-final rejection of claims 1-19 for obviousness under 35 U.S.C. § 103(a). Ex. O (Aug. 8, 2017 Non-Final Rejection) at 4-5, ¶¶ 5-10 (relying on "Smith et al.," *i.e.*, CDC-PEP). Rather than overcome that rejection directly, the Government canceled several claims, added several claims, and simply amended the remaining claims "to correspond with the claims of U.S. Patent No. 9,044,509." Ex. P (Amendment and Response) at 7. The amended claims included independent claim 12 (issued as claim 13), to which the Government included the limitation that the claimed combination must be

“administered prior to a potential exposure of the human to the human immunodeficiency retrovirus.” *Id.* at 3.

59. On information and belief, the Government’s failure to disclose the CDC-PEP reference materially affected the prosecution of the ’509 and ’333 Patents because at least some claims of those patents would not have been allowed if the CDC-PEP reference had been disclosed during prosecution. This materiality is evidenced by the fact that CDC-PEP anticipates and/or renders obvious all claims of the ’509 and ’333 Patents, including for the reasons set forth in GSI’s IPR Petitions relating to those patents, which are incorporated by reference into these affirmative defenses as if set forth fully herein. *See* Ex. H, Petition, Case No. IPR2019-01453 (P.T.A.B. Aug. 21, 2019) (’509 Patent); Ex. I, Petition, Case No. IPR2019-01454 (P.T.A.B. Aug. 21, 2019) (’333 Patent). This materiality is also evidenced by the Government’s subsequent disclaimer of claims 12 and 14-18 of the ’509 Patent and claims 12 and 14-17 of the ’333 Patent after the CDC-PEP was asserted as prior art in GSI’s IPR Petitions.

60. Furthermore, the materiality of the CDC-PEP reference is also supported by the record in the subsequent prosecution of the ’191 Patent. After the Government’s belated disclosure of CDC-PEP during the prosecution of the ’191 Patent, the examiner rejected claims in reliance on that reference, noting that CDC-PEP disclosed the use of Truvada[®] for PEP purposes and that it would have been obvious to treat uninfected individuals “who are exposed to or at risk of exposure to HIV” with Truvada[®]. Ex. O (Aug. 8, 2017 Non-Final Rejection) at 5-6, ¶ 9. This rejection prompted an amendment to include an explicit limitation confining claim 12 (allowed as claim 13) to pre-exposure administration. Ex. P (Amendment and Response) at 3.

61. Furthermore, individuals with a duty to disclose material information during prosecution—including the named inventors and prosecuting attorneys—failed to disclose the

CDC-PEP reference to the examiner during prosecution of the '509 and '333 Patents. On information and belief, at least some of these individuals failed to disclose this reference despite knowing of that reference and its materiality. On information and belief, the withholding of the CDC-PEP reference by those individuals was done with the intent to deceive the Patent Office. This intent is supported by the but-for materiality of the CDC-PEP reference to the prosecution of the '509 and '333 Patents; the individuals' possession and knowledge of that reference, including based on the involvement of at least two of the named inventors, Robert Janssen and Ronald Otten; and the individuals' knowledge of that reference's materiality to the inventiveness of the pending claims. The individuals' knowledge and intent is further supported by the Government's subsequent, belated disclosure of this reference during its prosecution of the '191 Patent.

62. The Government's failure to disclose the CDC-PEP reference during the prosecution of the '509 and '333 Patents constitutes inequitable conduct, rendering all claims of the '509 Patent and '333 Patent unenforceable.

63. The Government's inequitable conduct during the prosecution of the '509 and '333 Patents also constitutes inequitable conduct with respect to the '191 and '423 Patents, which are continuations of the '509 and '333 Patents. As confirmed by the examiner's findings during prosecution, as well as the Government's terminal disclaimers, the allowed claims of the '191 and '423 Patents are not patentably distinct from those of the '509 and '333 Patents. Furthermore, in allowing the claims of the '191 and '429 Patents, the examiner relied substantially on the previous allowance of the claims of the '509 and '333 Patents.

64. During the prosecution of the '191 and '423 Patents, the Government did not cure its earlier inequitable conduct. The Government did not disclose the CDC-PEP reference with

the initial application for the '191 Patent and disclosed it only later during prosecution. *Compare* Ex. M at 32-36 (initial Information Disclosure Statement for '191 application), *with* Ex. N (subsequent Information Disclosure Statement, filed March 7, 2017). During the prosecution of the '191 and '423 Patents, the Government provided only a bare disclosure of CDC-PEP and did not alert the examiner to the materiality of the CDC-PEP reference. When the examiner relied on her prior allowance of the claims of the '509 Patent to support the patentability of the '191 and '423 Patents, *see, e.g.*, Ex. Q ('191 Notice of Allowance) at 2, ¶ 5, and found the claims of the '191 Patent to be “not patentably distinct” from those in the '509 or '333 Patents, Ex. O (Aug. 8, 2017 Non-Final Rejection) at 3, ¶¶ 2-3, the Government did not alert the examiner to the fact that the Government had not disclosed the material CDC-PEP reference during the prosecution of the '509 and '333 Patents. On the contrary, in amending the claims for the '191 Patent, the Government noted that its amendments were made “to correspond to with the claims of U.S. Patent No. 9,044,509.” Ex. P (Amendment and Response) at 7. Similarly, after the examiner noted that the claims of the '423 Patent were “not patentably distinct” from those in the parent applications and were “allowable over prior art for reasons as set forth in [the] parent applications,” Ex. R (Jan. 23, 2019 Non-Final Rejection) at 3-4, ¶¶ 3-5, the Government did not alert the examiner to the fact that the CDC-PEP reference was not disclosed during the prosecution of the '509 or '333 Patents.

65. The Government's subsequent disclaimer of claims 12 and 14-18 of the '509 Patent and claims 12 and 14-17 of the '333 Patent cannot cure its inequitable conduct during prosecution. The Government's subsequent disclosure of the CDC-PEP reference during prosecution of the '191 and '423 Patents also cannot cure its inequitable conduct with respect to any of the HHS Patents.

**SIXTH AFFIRMATIVE DEFENSE
(DERIVATION)**

66. The Patents-in-Suit are invalid because the alleged invention(s) were derived and/or misappropriated from the true inventor(s).

**SEVENTH AFFIRMATIVE DEFENSE
(SAFE HARBOR)**

67. Defendants are exempt from liability under the safe harbor of 35 U.S.C. § 271(e)(1), at least to the extent the Government claims that uses related to the clinical trials to obtain FDA approval of Descovy[®] for PrEP are acts of infringement.

**EIGHTH AFFIRMATIVE DEFENSE
(ACQUIESCENCE AND/OR ESTOPPEL)**

68. The Government's Complaint, and each of its purported causes of action, is barred in whole or in part by the doctrines of acquiescence and/or estoppel.

69. As set forth above, the Government has encouraged both the public use and the prescription of Truvada[®] for PrEP purposes—including in CDC guidelines published even before the PrEP indication had been approved by the FDA in 2012. For example, the CDC's January 28, 2011 guidelines—issued more than one year before the FDA's approval of the PrEP indication for Truvada[®]—identified “[p]rescrib[ing] 1 tablet of Truvada[®] (TDF [300 mg] plus FTC [200 mg]) daily” as part of “[b]eginning [a] PrEP medication regimen.” Ex. A (January 28, 2011 Interim Guidance) at 68. Furthermore, the Government requested that GSI provide TDF/FTC for use in preclinical and clinical studies concerning PrEP, and the Government (including the FDA) actively encouraged GSI to seek FDA approval for the PrEP indication for Truvada[®]. The Government's promotion of the use of Truvada[®] for the indication that it now alleges infringes the Patents-in-Suit indicates that its Complaint, and each of its purported causes of action, is barred in whole or in part by the of acquiescence and/or estoppel.

**NINTH AFFIRMATIVE DEFENSE
(IMPLIED WAIVER)**

70. The Government's Complaint, and each of its purported causes of action, is barred in whole or in part by the equitable doctrine of implied waiver.

71. For example, the Government has demonstrated implied waiver by seeking patent protection for the use of Truvada[®] for PrEP purposes, failing to disclose to Defendants that the Government was seeking such patent protection, and encouraging GSI to market Truvada[®] for PrEP purposes.

72. The Government filed the '811 Provisional (Ex. F) on February 3, 2006, followed by the '547 Application (Ex. G) on January 31, 2007, which claimed priority to the '811 Provisional. The '509 Patent issued from the '547 Application on June 2, 2015, and the remaining HHS Patents have since issued and claim priority to the same provisional and nonprovisional applications. The Government alleges that the administration of Truvada[®] for PrEP purposes infringes the issued claims of the HHS Patents and that Defendants induce infringement of the HHS Patents through sales of Truvada[®] for PrEP purposes. *E.g.*, Compl. ¶¶ 282-283, 285, 291-293, 299-301, 307-308, 310.

73. However, the Government failed to provide adequate or timely notice to Defendants that the Government had sought patent protection for the subject matter claimed in the HHS Patents. The CDC and the Government waited several years—until October 2014 at the earliest—to provide notice to either Defendant concerning the existence of the HHS Patents. *See* Aff. Defenses ¶ 38. The Government's failure to provide such notice violated the terms of several MTAs between GSI and the CDC. *See id.* ¶¶ 6-42 (incorporated herein by reference).

74. Despite this lack of notice to Defendants, the Government extensively encouraged both the public use and the prescription of Truvada[®] for PrEP purposes—including in CDC

guidelines published even before the Truvada[®] PrEP indication had been approved by the FDA in 2012. For example, the CDC’s January 28, 2011 guidelines—issued more than one year before the FDA’s approval of the PrEP indication for Truvada[®]—identified “[p]rescrib[ing] 1 tablet of Truvada[®] (TDF [300 mg] plus FTC [200 mg]) daily” as part of “[b]eginning [a] PrEP medication regimen.” Ex. A (January 28, 2011 Interim Guidance) at 68. Furthermore, the Government requested that GSI provide TDF/FTC for use in preclinical and clinical studies concerning PrEP. Furthermore, the Government (including the FDA) actively encouraged GSI to seek FDA approval for the PrEP indication for Truvada[®], which was approved in August 2012.

75. The Government’s conduct—including its failure to provide timely notice to Defendants of the applications that resulted in the HHS Patents, its promotion of the use of Truvada[®] for the indication that it now alleges infringes the Patents-in-Suit, and its encouragement of GSI to seek FDA approval for the for the PrEP indication for Truvada[®]—is “so inconsistent with an intent to enforce its rights as to induce a reasonable belief that such right has been relinquished.” *Core Wireless Licensing S.A.R.L. v. Apple Inc.*, 899 F.3d 1356, 1365 (Fed. Cir. 2018) (quoting *Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1348 (Fed. Cir. 2011)) (internal quotation mark omitted). For this reason, the Government is barred under the doctrine of implied waiver from enforcing the HHS Patents against Gilead.

**TENTH AFFIRMATIVE DEFENSE
(NO WILLFULNESS)**

76. Defendants have not willfully infringed any claim of the Patents-in-Suit.

**ELEVENTH AFFIRMATIVE DEFENSE
(NO EXCEPTIONAL CASE)**

77. Defendants’ actions in defending this case do not give rise to an exceptional case under 35 U.S.C. § 285.

**TWELFTH AFFIRMATIVE DEFENSE
(NO RECOVERY OF COSTS)**

78. The Government is barred by 35 U.S.C. § 288 from recovering any costs associated with this action.

**THIRTEENTH AFFIRMATIVE DEFENSE
(FAILURE TO MITIGATE)**

79. The Government has failed to mitigate the harm it claims to have sustained, if any.

**FOURTEENTH AFFIRMATIVE DEFENSE
(NO STANDING)**

80. The Government lacks standing to assert one or more of the Patents-in-Suit.

**FIFTEENTH AFFIRMATIVE DEFENSE
(NO CONSTITUTIONAL AUTHORITY)**

81. The Government lacks authority under the United States Constitution, including the Intellectual Property Clause thereof (art. I, § 8, cl. 8), to own or assert the four Patents-in-Suit.

RESERVATION OF DEFENSES

As Defendants' investigation is ongoing and discovery has not yet been completed, Defendants are without complete information regarding the existence or non-existence of other facts or acts that would constitute a defense to the purported causes of action in the Government's Complaint. Accordingly, Defendants reserve the right to assert any other defenses that discovery may reveal.

GSI'S FIRST AMENDED COUNTERCLAIMS

Without admitting any of the Government's allegations other than those expressly admitted herein, and without prejudice of the rights of Defendant/Counterclaim-Plaintiff Gilead Sciences, Inc. ("GSI") to plead additional Counterclaims as the facts of the matter warrant, Defendant/Counterclaim-Plaintiff GSI hereby asserts the following Counterclaims against the Government. Defendants contend that Defendant Gilead Sciences Ireland UC is not a proper party to this action; however, if Gilead Sciences Ireland UC is deemed to be a proper party or otherwise remains in this action, Gilead Sciences Ireland UC reserves the right to bring or seek to bring counterclaims on its own behalf at a later stage in the case.

For its Counterclaims against the Government, Defendant/Counterclaim-Plaintiff GSI states as follows:

THE PARTIES

1. Counterclaim-Plaintiff Gilead Sciences, Inc. ("GSI") is a corporation organized under the laws of the State of Delaware, having its principal place of business at 333 Lakeside Drive, Foster City, California 94404.

2. Counterclaim-Defendant alleges in its Complaint that it is acting on behalf of the Department of Health and Human Services (HHS) and is headquartered at 200 Independence Avenue, S.W., Washington, D.C. 20201.

JURISDICTION & VENUE

3. Defendant/Counterclaim-Plaintiff GSI brings these Counterclaims under the Patent Laws of the United States, 35 U.S.C. §§ 1 *et seq.*, for a declaratory judgment pursuant to 28 U.S.C. §§ 2201-2202 that U.S. Patent Nos. 9,044,509 (the "'509 Patent"), 9,579,333 (the "'333 Patent"), 9,937,191 (the "'191 Patent"), and 10,335,423 (the "'423 Patent") (collectively, the "HHS

Patents”) have not been infringed and are not being infringed by Defendant/Counterclaim-Plaintiff GSI, that the HHS Patents are invalid, and that the HHS Patents are unenforceable.

4. This Court has subject matter jurisdiction over Defendant’s Counterclaims under 28 U.S.C. §§ 1331 and 1338. The Government’s sovereign immunity does not bar GSI’s counterclaims. *See, e.g., U.S. Dep’t of Health & Human Servs. v. Mylan Pharms., Inc.*, No. 10-cv-5956-WHW, 2011 WL 13238650 (D.N.J. July 13, 2011) (holding that because “Defendants’ counterclaims [for declaratory judgment of noninfringement and invalidity] are ... of the same kind or nature as the Government’s claims, as the declaratory judgment sought by defendants is a mirror-image of the judgment sought by the Government,” *id.* at *3, the federal government “is subject to adjudication of defendants’ compulsory counterclaims properly sounding in recoupment,” *id.* at *4); *Delano Farms Co. v. California Table Grape Comm’n*, 655 F.3d 1337, 1343-1344, 1349 & n.6 (Fed. Cir. 2011) (holding that 5 U.S.C. § 702 “waives sovereign immunity for non-monetary claims against federal agencies,” *id.* at 1344, including “declaratory judgment claims under the Patent Act,” *id.* at 1349).

5. This Court has personal jurisdiction over Plaintiff/Counterclaim-Defendant. Plaintiff/Counterclaim-Defendant has subjected itself to personal jurisdiction by maintaining its lawsuit against Defendant/Counterclaim-Plaintiff GSI in this District.

6. Venue in this case is proper in this District by virtue of the Government’s filing of the Complaint in this District, which gave rise to these Counterclaims. The Government contends in its Complaint that venue is proper in this District.

THE HHS PATENTS

7. The ’509 Patent, titled “Inhibition of HIV Infection through Chemoprophylaxis,” issued on June 2, 2015. The Government alleges that it owns the ’509 Patent. The earliest possible

priority date for the '509 Patent is February 3, 2006. The Government alleges that the '509 Patent expires on May 12, 2031.

8. The '333 Patent, titled "Inhibition of HIV Infection through Chemoprophylaxis," issued on February 28, 2017. The Government alleges that it owns the '333 Patent. The earliest possible priority date for the '333 Patent is February 3, 2006. The Government alleges that the '333 Patent expires on January 31, 2027.

9. The '191 Patent, titled "Inhibition of HIV Infection through Chemoprophylaxis," issued on April 10, 2018. The Government alleges that it owns the '191 Patent. The earliest possible priority date for the '191 Patent is February 3, 2006. The Government alleges that the '191 Patent expires on January 31, 2027.

10. The '423 Patent, titled "Inhibition of HIV Infection through Chemoprophylaxis," issued on July 2, 2019. The Government alleges that it owns the '423 Patent. The earliest possible priority date for the '423 Patent is February 3, 2006. The Government alleges that the '423 Patent expires on January 31, 2027.

FACTUAL BACKGROUND

11. GSI is the holder of New Drug Application ("NDA") No. 21-752, which relates to tablets containing emtricitabine ("FTC") and tenofovir disoproxil fumarate ("TDF"). On August 2, 2004, the United States Food and Drug Administration ("FDA") approved the use of the tablets described in NDA No. 21-752 for the treatment of HIV-1 infection in adults. These tablets are prescribed and sold in the United States under the trademark Truvada®. Truvada® was originally available in one dosage form: 200 mg FTC and 300 mg TDF.

12. On July 16, 2012, FDA approved Truvada® for use in combination with safer sex practices for pre-exposure prophylaxis ("PrEP") to reduce the risk of sexually acquired human

immunodeficiency virus 1 (“HIV-1”) in adults at high risk. GSI promotes this indication under the trademark Truvada for PrEP®. Only the original dosage form of Truvada®, 200 mg FTC and 300 mg TDF, is indicated for use in Truvada for PrEP®.

13. GSI is also the holder of NDA No. 208215, which relates to tablets containing FTC and TAF. On April 4, 2016, FDA approved the use of the tablets described in NDA No. 208215 for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age or older. These tablets are prescribed and sold in the United States under the trademark Descovy®. Descovy® is available in one dosage form: 200 mg FTC and 25 mg TAF.

14. On October 3, 2019, FDA approved Descovy® for use in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex, and provided that individuals must have a negative HIV-1 test immediately prior to initiating Descovy® for HIV-1 PrEP. GSI promotes this indication under the trademark Descovy for PrEP®.

15. In its Complaint, the Government asserts that Defendants have induced infringement of certain claims of the HHS Patents by, among other things, selling Truvada® and instructing doctors and patients on how to administer Truvada® for PrEP. The Government further asserts that Defendants have induced infringement of certain claims of the ’509 Patent and the ’423 Patent by, among other things, selling Descovy® and instructing doctors and patients on how to administer Descovy® for PrEP.

16. The HHS Patents are invalid and/or have not been and will not be infringed by Defendants, either directly or indirectly, literally or under the doctrine of equivalents.

COUNT I:
DECLARATORY JUDGMENT OF NON-INFRINGEMENT
OF U.S. PATENT NO. 9,044,509

17. Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-16 above as if fully set forth herein.

18. The Government has alleged that it is the owner of all right, title, and interest in the '509 Patent.

19. A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '509 Patent.

20. Counterclaim-Plaintiff GSI has not infringed, and does not infringe, directly or indirectly, any valid or enforceable claim of the '509 Patent.

21. The controversy between the parties is amenable to specific relief through a decree of conclusive character.

22. Counterclaim-Plaintiff GSI is entitled to a judicial declaration that Counterclaim-Plaintiff GSI has not and will not infringe, directly or indirectly, any valid and enforceable claim of the '509 Patent. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT II:
DECLARATORY JUDGMENT OF INVALIDITY
OF U.S. PATENT NO. 9,044,509

23. Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-16 above as if fully set forth herein.

24. The Government has alleged that it is the owner of all right, title, and interest in the '509 Patent.

25. A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '509 Patent.

26. One or more claims of the '509 Patent are invalid for failure to satisfy one or more requirements of patentability under 35 U.S.C. § 101 *et seq.*, including without limitation §§ 101, 102, 103, 112, and/or any judicially created doctrine of invalidity, including obviousness-type double patenting.

27. The controversy between the parties is amenable to specific relief through a decree of conclusive character.

28. Counterclaim-Plaintiff GSI is entitled to a judicial declaration that one or more claims of the '509 Patent are invalid. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT III:
DECLARATORY JUDGMENT OF NON-INFRINGEMENT
OF U.S. PATENT NO. 9,579,333

29. Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-16 above as if fully set forth herein.

30. The Government has alleged that it is the owner of all right, title, and interest in the '333 Patent.

31. A case or controversy exists because the Government has alleged that Defendants have infringed and will infringe one or more claims of the '333 Patent.

32. Counterclaim-Plaintiff GSI has not infringed, and does not infringe, directly or indirectly, any valid or enforceable claim of the '333 Patent.

33. The controversy between the parties is amenable to specific relief through a decree of conclusive character.

34. Counterclaim-Plaintiff GSI is entitled to a judicial declaration that Counterclaim-Plaintiff GSI has not and will not infringe, directly or indirectly, any valid and enforceable claim of the '333 Patent. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT IV:
DECLARATORY JUDGMENT OF INVALIDITY
OF U.S. PATENT NO. 9,579,333

35. Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-16 above as if fully set forth herein.

36. The Government has alleged that it is the owner of all right, title, and interest in the '333 Patent.

37. A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '333 Patent.

38. One or more claims of the '333 Patent are invalid for failure to satisfy one or more requirements of patentability under 35 U.S.C. § 101 *et seq.*, including without limitation §§ 101, 102, 103, 112, and/or any judicially created doctrine of invalidity, including obviousness-type double patenting.

39. The controversy between the parties is amenable to specific relief through a decree of conclusive character.

40. Counterclaim-Plaintiff GSI is entitled to a judicial declaration that one or more claims of the '333 Patent are invalid. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT V:
DECLARATORY JUDGMENT OF NON-INFRINGEMENT
OF U.S. PATENT NO. 9,937,191

41. Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-16 above as if fully set forth herein.

42. The Government has alleged that it is the owner of all right, title, and interest in the '191 Patent.

43. A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '191 Patent.

44. Counterclaim-Plaintiff GSI has not infringed, and does not infringe, directly or indirectly, any valid or enforceable claim of the '191 Patent.

45. The controversy between the parties is amenable to specific relief through a decree of conclusive character.

46. Counterclaim-Plaintiff GSI is entitled to a judicial declaration that Counterclaim-Plaintiff GSI has not and will not infringe, directly or indirectly, any valid and enforceable claim of the '191 Patent. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT VI:
DECLARATORY JUDGMENT OF INVALIDITY
OF U.S. PATENT NO. 9,937,191

47. Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-16 above as if fully set forth herein.

48. The Government has alleged that it is the owner of all right, title, and interest in the '191 Patent.

49. A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '191 Patent.

50. One or more claims of the '191 Patent are invalid for failure to satisfy one or more requirements of patentability under 35 U.S.C. § 101 *et seq.*, including without limitation §§ 101, 102, 103, 112, and/or any judicially created doctrine of invalidity, including obviousness-type double patenting.

51. The controversy between the parties is amenable to specific relief through a decree of conclusive character.

52. Counterclaim-Plaintiff GSI is entitled to a judicial declaration that one or more claims of the '191 Patent are invalid. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT VII:
DECLARATORY JUDGMENT OF NON-INFRINGEMENT
OF U.S. PATENT NO. 10,335,423

53. Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-16 above as if fully set forth herein.

54. The Government has alleged that it is the owner of all right, title, and interest in the '423 Patent.

55. A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '423 Patent.

56. Counterclaim-Plaintiff GSI has not infringed, and does not infringe, directly or indirectly, any valid or enforceable claim of the '423 Patent.

57. The controversy between the parties is amenable to specific relief through a decree of conclusive character.

58. Counterclaim-Plaintiff GSI is entitled to a judicial declaration that Counterclaim-Plaintiff GSI has not and will not infringe, directly or indirectly, any valid and enforceable claim of the '423 Patent. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT VIII:
DECLARATORY JUDGMENT OF INVALIDITY
OF U.S. PATENT NO. 10,335,423

59. Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-16 above as if fully set forth herein.

60. The Government has alleged that it is the owner of all right, title, and interest in the '423 Patent.

61. A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '423 Patent.

62. One or more claims of the '423 Patent are invalid for failure to satisfy one or more requirements of patentability under 35 U.S.C. § 101 *et seq.*, including without limitation §§ 101, 102, 103, 112, and/or any judicially created doctrine of invalidity, including obviousness-type double patenting.

63. The controversy between the parties is amenable to specific relief through a decree of conclusive character.

64. Counterclaim-Plaintiff GSI is entitled to a judicial declaration that one or more claims of the '423 Patent are invalid. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

PRAYER FOR RELIEF

WHEREFORE, Counterclaim-Plaintiff GSI respectfully requests that this Court enter judgment in its favor against the Government and grant the following relief:

- (a) Adjudge and decree that the Government be denied all forms of relief requested in its Complaint;
- (b) Dismiss the Complaint in its entirety with prejudice;
- (c) Declare that Counterclaim-Plaintiff GSI has not, does not, and will not infringe any valid and enforceable claim of U.S. Patent Nos. 9,044,509, 9,579,333, 9,937,191, or 10,335,423;
- (d) Declare that one or more claims of U.S. Patent Nos. 9,044,509, 9,579,333, 9,937,191, and 10,335,423 are invalid;
- (e) Declare that this is an exceptional case in favor of Counterclaim-Plaintiff GSI and award Counterclaim-Plaintiff its reasonable attorneys' fees pursuant to 35 U.S.C. § 285;
- (f) Award Counterclaim-Plaintiff GSI costs and expenses; and
- (g) Award any and all such other relief as the Court determines to be just and proper.

Dated: March 27, 2020

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**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

THE UNITED STATES OF AMERICA,

Plaintiff & Counterclaim-Defendant,

v.

GILEAD SCIENCES, INC. and
GILEAD SCIENCES IRELAND UC,

Defendants & Counterclaim-Plaintiff.

C.A. No. 19-02103-MN

**DEFENDANTS' FIRST AMENDED ANSWER AND AFFIRMATIVE DEFENSES
AND DEFENDANT GILEAD SCIENCES, INC.'S
FIRST AMENDED COUNTERCLAIMS**

Pursuant to Federal Rules of Civil Procedure 13 and 15(a), Defendant Gilead Sciences, Inc. (“GSI”) and Gilead Sciences Ireland UC (“GSIUC”) (collectively, “Defendants”) hereby file Defendants’ First Amended Answer and Affirmative Defenses and Defendant GSI’s First Amended Counterclaims in response to the Complaint of the United States of America (the “Government” or “Plaintiff”). This filing supersedes Defendants’ Answer and Affirmative Defenses and GSI’s Counterclaims, filed on January 23, 2020 (D.I. 7).

ANSWER

Defendants Gilead Sciences, Inc. (“GSI”) and Gilead Sciences Ireland UC (“GSIUC”) (collectively, “Defendants”) hereby respond to the Complaint of the United States of America (the “Government” or “Plaintiff”) as follows. Defendants deny each and every allegation contained in the Government’s Complaint that is not expressly admitted below. To the extent any factual allegation below is admitted, it is admitted only as to the specific admitted facts, not as to any purported conclusions, characterizations, implications, or speculations that arguably may follow from the admitted facts. No admission below should be construed as an admission or concession regarding the relevance of any allegation to any cause of action identified in the Complaint. No admission below should be construed as an admission concerning the accuracy, authenticity, admissibility, or relevance of any documents cited or referenced in the Complaint. No admission below with respect to GSI should be construed as an admission with respect to GSIUC, nor should any admission below with respect to GSIUC be construed as an admission with respect to GSI. Defendants deny that the Government is entitled to the relief requested in the Complaint or to any other relief.

1. Defendants admit that HIV is the cause of AIDS. Defendants admit that researchers, including Defendants’ researchers, have made and continue to make extensive efforts to develop treatments to prevent the spread and effects of HIV and AIDS. Defendants admit that millions of people are living with HIV and that millions have died due to AIDS. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 1 of the Complaint and therefore deny those allegations.

2. Defendants deny that CDC researchers “succeeded where others had not” and “conceived of and developed” the use of emtricitabine and “tenofovir or a tenofovir prodrug” as

pre-exposure prophylaxis, or PrEP. Defendants deny that CDC researchers used “new” and “precise” animal modeling methods. Defendants deny that the two-drug regimens described in Paragraph 2 were “innovative” as of the mid-2000s. Defendants admit that Truvada[®] (tenofovir disoproxil fumarate and emtricitabine) is indicated in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 2 of the Complaint and therefore deny those allegations.

3. Defendants admit that, as of 2006, at least some scientists and community advocates expressed concerns that PrEP could promote unsafe sexual practices and consequently increase the number of sexually transmitted diseases and questioned whether some patients would adhere to the PrEP regimen. Defendants deny the remaining allegations in Paragraph 3 of the Complaint.

4. Defendants deny that the CDC’s efforts constituted a “breakthrough” or that the CDC developed “new PrEP regimens.” Defendants admit that, following the CDC macaque research, researchers changed the methodology of at least one human PrEP trial. Defendants deny that the human PrEP trials used or demonstrated the efficacy of “CDC’s new PrEP regimens.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 4 of the Complaint and therefore deny those allegations.

5. Defendants deny that the four patents asserted in this case reflect any “innovative regimens” developed by the CDC. Defendants deny that the CDC is entitled to a “reasonable royalty.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 5 of the Complaint and therefore deny those allegations.

6. Defendants admit that one or both of GSI and GSIUC manufactures, markets, and sells Truvada[®] and Descovy[®], either in the United States or elsewhere in the world. Defendants admit that these products include a combination of (i) FTC and (ii) a tenofovir prodrug. Defendants admit that, when used as directed as part of a PrEP regimen and safe sex practices, these products are effective at reducing the risk of sexually transmitted HIV infection. Defendants admit that GSI received FDA approval for use of these products in treating HIV infections in combination with other medications. Defendants admit that GSI subsequently received FDA approval for the use of Truvada[®] and Descovy[®] as part of PrEP regimens. Defendants deny that the use of Truvada[®] and Descovy[®] as part of PrEP regimens is claimed and protected by CDC's patents. Defendants deny that the CDC's PrEP research was "groundbreaking." Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants deny that GSIUC has FDA approval to sell Truvada[®] or Descovy[®], including for use as PrEP regimens. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 6 of the Complaint and therefore deny those allegations.

7. Defendants admit that GSI markets and sells Truvada[®] and Descovy[®] in the United States for all of their indications, including their PrEP indications. Defendants deny that the PrEP regimens for which Truvada[®] and Descovy[®] are indicated are "protected by CDC's patents." Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to

form a belief as to the remaining allegations in Paragraph 7 of the Complaint and therefore deny those allegations.

8. Defendants deny the allegations in Paragraph 8 of the Complaint.

9. Defendants admit that they have not obtained a license from the CDC for any of the four patents asserted in the Complaint, which Defendants contend are invalid. Defendants admit that they have earned revenues from the sale of Truvada[®] and Descovy[®], either in the United States or elsewhere, and that Defendants have not paid and have no obligation to pay royalties to the CDC based on those sales revenues. Defendants lack sufficient knowledge or information to form a belief as to the vague allegation concerning “research funded by hundreds of millions of taxpayer dollars” and therefore deny that allegation. Defendants deny the remaining allegations in Paragraph 9 of the Complaint.

I. Nature of the Action¹

10. Paragraph 10 contains conclusions of law to which no response is required. To the extent a response is required, Defendants admit that Plaintiff has alleged that Defendants have infringed U.S. Patent Nos. 9,044,509 (the “’509 Patent”), 9,579,333 (the “’333 Patent”), 9,937,191 (the “’191 Patent”), and 10,335,423 (the “’423 Patent”) (collectively, the “Patents-in-Suit”) under 35 U.S.C. § 271 *et seq.* Defendants deny that they have infringed any valid and enforceable claim of the Patents-in-Suit.

II. Parties

11. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 11 of the Complaint and therefore deny those allegations.

¹ Defendants’ inclusion of the headings from the Government’s Complaint is for purposes of convenience only and should not be construed as an admission or concession regarding the accuracy, implications, or relevance of those headings.

12. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 12 of the Complaint and therefore deny those allegations.

13. Defendants admit the allegations in Paragraph 13 of the Complaint.

14. Defendants admit that Defendant GSIUC (formerly known as Gilead Sciences Limited) is an unlimited liability company formed under the laws of Ireland, with a principal place of business at IDA Business & Technology Park, Carrigtohill, County Cork, Ireland. Defendants admit that GSIUC is a wholly owned, indirect subsidiary of GSI. Defendants deny that GSIUC markets or sells Truvada[®] and Descovy[®] for PrEP in the United States or for the U.S. market. Defendants' investigation is ongoing, and based on the information currently known to Defendants, Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 14 and therefore deny those allegations.

15. Paragraph 15 of the Complaint contains conclusions of law to which no response is required.

III. Jurisdiction and Venue

16. Paragraph 16 of the Complaint contains conclusions of law to which no response is required.

17. Paragraph 17 of the Complaint contains conclusions of law to which no response is required. To the extent a response is required, Defendants admit that GSI is a Delaware corporation. Defendants admit that GSI and Emory University filed a complaint against Aurobindo Pharma Ltd. and Aurobindo Pharma USA, Inc. in Case No. 1:18-cv-00765 in the District of Delaware on May 18, 2018. Defendants admit that GSI and Emory University filed a complaint against Amneal Pharmaceuticals LLC in Case No. 1:17-cv-00943 in the District of Delaware on July 13, 2017.

18. Paragraph 18 of the Complaint contains conclusions of law to which no response is required. To the extent a response is required, Defendants admit that GSIUC has manufactured Truvada[®] and Descovy[®] products, at least for non-U.S. markets, and that Truvada[®] and Descovy[®] products have been labeled, marketed, distributed, and sold to residents of Delaware. Defendants admit that Janssen Pharmaceutica, N.V., Janssen Sciences Ireland UC, GSI, and GSIUC filed a complaint against Mylan Pharmaceuticals, Inc. and Mylan Inc. in Case No. 1:15-cv-00760 in the District of Delaware on August 31, 2015. Defendants admit that GSI and GSIUC filed a complaint against AbbVie, Inc. in Case No. 1:15-cv-00399 in the District of Delaware on May 19, 2015. Defendants' investigation is ongoing, and based on the information currently known to Defendants, Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 18 and therefore deny those allegations.

19. Paragraph 19 of the Complaint contains conclusions of law to which no response is required.

20. Defendants admit that GSI has earned revenues from the sale of Truvada[®] for PrEP and Descovy[®] for PrEP in the United States. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants deny the remaining allegations in Paragraph 20 of the Complaint.

21. Paragraph 21 of the Complaint contains conclusions of law to which no response is required.

IV. Technical and Historical Background

A. The Human Immunodeficiency Virus

22. Defendants admit the allegations in Paragraph 22 of the Complaint.

23. Defendants admit the allegations in Paragraph 23 of the Complaint.

24. Defendants admit that HIV infects human CD4⁺ cells (among others), uses those cells to replicate the virus, and kills CD4⁺ cells. HIV infection of CD4⁺ cells and HIV replication are complicated and involve numerous chemical and biological reactions. Defendants admit the basic steps outlined in Paragraph 24 of the Complaint, except to the extent that the description is overly simplistic and omits critical details in the infection and replication process.

25. Defendants admit that, over time, an HIV infection can lead to acquired immune deficiency syndrome (“AIDS”). Defendants likewise admit that AIDS is diagnosed when a person’s CD4⁺ T cell count falls below 200 cells/mm³ or the person has an AIDS-defining illness. Defendants further admit that a person diagnosed with AIDS often has opportunistic illnesses due to a weakened immune system. To the extent there are other allegations in Paragraph 25 of the Complaint, Defendants deny the allegations as being overly simplistic and omitting critical details.

26. Defendants admit the basic principles outlined in Paragraph 26, except to the extent that the description is overly simplistic and omits critical details in the infection process.

27. Defendants admit that HIV-1 and HIV-2 are the major types of HIV; that HIV-1 and HIV-2 can both lead to a weakening of an infected person’s immune system; that HIV-1 and HIV-2 are genetically distinct; that the recommended antiretroviral treatments may be different for patients infected with HIV-1 versus HIV-2; and that HIV-1 is the more predominant type of HIV found in human infections worldwide. To the extent there are other allegations in this paragraph, Defendants deny the allegations as being overly simplistic and omitting critical details.

28. Defendants admit the allegations in Paragraph 28 of the Complaint.

29. Defendants admit the allegations in Paragraph 29 of the Complaint.

B. The HIV/AIDS Epidemic

30. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 30 of the Complaint and therefore deny those allegations.

31. Defendants admit the allegations in Paragraph 31 of the Complaint, except to the extent that the efficacy of ART regimens can vary based on the type of therapy, patient compliance, and other factors.

32. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 32 of the Complaint and therefore deny those allegations.

33. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 33 of the Complaint and therefore deny those allegations.

34. Defendants admit the allegations in Paragraph 34 of the Complaint.

C. Treatment of HIV Infections

35. Defendants admit that current FDA-approved treatments for HIV are highly effective but not curative, and that these treatments can help people with HIV live longer, healthier lives but do not eliminate the virus from the human body or prevent reemergence of the virus when treatment is discontinued. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 35 of the Complaint and therefore deny those allegations.

36. Defendants admit the basic statements in Paragraph 36, except to the extent that the description is overly simplistic and omits critical details in the drug-resistance process.

37. Defendants admit that the current standard of care for HIV infection is the administration of three or more antiretroviral drugs from at least two different drug classes. Defendants further admit that the goal of this treatment strategy is to keep a patient's viral load (a measure of the amount of virus in the bloodstream) below detectable levels. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 37 of the Complaint and therefore deny those allegations.

38. Defendants admit that (i) nucleoside reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs), (ii) nonnucleoside reverse transcriptase inhibitors (NNRTIs), (iii) protease inhibitors (PIs), (iv) integrase inhibitors, and (v) entry or fusion inhibitors are different classes of antiretroviral drugs that can be used to treat HIV infections.

39. Defendants admit the basic statements in Paragraph 39 of the Complaint, except to the extent that the description is overly simplistic and omits critical details about the functioning of NRTIs and NtRTIs.

40. Defendants lack sufficient knowledge or information to form a belief as to the vague and overbroad allegations in Paragraph 40 of the Complaint and therefore deny those allegations.

41. Defendants lack sufficient knowledge or information to form a belief as to the vague and overbroad allegations in Paragraph 41 of the Complaint and therefore deny those allegations.

42. Defendants admit that, under the current standard of care for HIV infection, a standard ART regimen may include two NRTI/NtRTIs and one integrase inhibitor, NNRTI, or PI; however, the current standard of care also allows for treatment with other drug combinations. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 42 of the Complaint and therefore deny those allegations.

43. The document cited in Paragraph 43 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 43 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 43 of the Complaint and therefore deny those allegations.

44. The document cited in Paragraph 44 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 44 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 44 of the Complaint and therefore deny those allegations.

45. Defendants admit the allegations in Paragraph 45 of the Complaint.

46. Defendants admit that, using antiretroviral drugs currently approved by the FDA, a patient infected with HIV must use ART therapy for the remainder of the patient's life; otherwise, the patient's viral load of HIV may rise and the patient may transmit HIV to others. Defendants deny that a patient must adhere to one single ART treatment regimen continuously for the remainder of the patient's life. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 46 of the Complaint and therefore deny those allegations.

D. Truvada®

47. Defendants admit Truvada® is a registered trademark and is the proprietary name for a fixed-dose combination therapy that was invented and developed by GSI researchers for the treatment of HIV and later for the prevention of HIV infection, and that Truvada® consists of emtricitabine and tenofovir disoproxil fumarate.

48. Defendants admit that the Truvada® drug product, which was invented by GSI researchers, is a fixed-dose, two-drug combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) that is available in four strengths: (i) 200 mg FTC with 300 mg TDF, (ii) 167 mg FTC with 250 mg TDF, (iii) 133 mg FTC with 200 mg TDF, and (iv) 100 mg FTC with 150 mg TDF. Defendants further admit that the current package insert for Truvada® instructs the administration of only the strength containing 200 mg FTC with 300 mg TDF for adult use.

Defendants further admit that Truvada[®] was approved for sale by the FDA in 2004 for the treatment of HIV-1 infection in adults when used in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors). To the extent Paragraph 48 of the Complaint contains any additional allegations, Defendants deny them.

49. Defendants admit that TDF is a tenofovir prodrug; that TDF is enzymatically and/or chemically converted by metabolic processes in the body into tenofovir; and that tenofovir—which cannot be administered orally—is an NtRTI that was first discovered in the 1980s. To the extent Paragraph 49 of the Complaint contains any additional allegations, Defendants deny them.

50. Defendants admit that they developed tenofovir disoproxil fumarate, which is specifically designed to require initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Defendants further admit that tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase. To the extent that Paragraph 50 of the Complaint contains any additional allegations, Defendants deny them.

51. The document cited in Paragraph 51 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 51 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that FTC was discovered in the mid-1990s and is an NRTI that has been used in ART regimens at least since FDA's approval of Emtriva[®] in 2003. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 51 of the Complaint and therefore deny those allegations.

52. Defendants admit that Truvada[®], which was invented by GSI researchers, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg. Defendants further admit that, under current

guidelines, Truvada[®] may be used in an ART regimen in combination with an integrase inhibitor (for example, DTG or RAL); however, other combinations including Truvada[®] are also consistent with current treatment guidelines. Defendants further admit that Atripla[®], Complera[®], and Stribild[®] are the proprietary names for Defendants' products that contain FTC and TDF, among other components, and that these products may be administered as once-daily ART regimens. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 52 of the Complaint and therefore deny those allegations.

53. Defendants admit that GSI received FDA approval in 2012 to sell Truvada[®], which was invented by GSI researchers, as a tablet consisting of 200 mg FTC and 300 mg TDF for pre-exposure prophylaxis (PrEP), in combination with safer sex practices, to reduce the risk of sexually acquired HIV-1 in adults at high risk. Defendants deny that GSIUC has FDA approval to sell Truvada[®]. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC.

E. Descovy[®]

54. Defendants admit that Defendants manufacture, distribute, and sell the Descovy[®] drug product, either in the United States or elsewhere in the world. Defendants further admit that Descovy[®] is the proprietary name of a fixed-dose antiretroviral drug combination that includes FTC and tenofovir alafenamide, which is a phosphoramidate prodrug of tenofovir invented by GSI researchers.

55. Defendants admit that the Descovy[®] drug product does not contain TDF but does contain TAF, ~~which stands for~~ TAF is used to refer to tenofovir alafenamide. ~~Defendants deny that "TAF" stands for "~~the free base. The form of tenofovir ~~alafenamide fumarate" or that~~ in the Descovy[®] drug product ~~contains "~~is tenofovir alafenamide ~~fumarate."~~ (TAF) hemi-fumarate.

Defendants deny that TAF is an ester of tenofovir. Defendants admit that the introduction of TAF in blood plasma allows for permeation into cells. TAF is designed to intracellularly convert to tenofovir primarily through hydrolysis by cathepsin A followed by additional hydrolysis steps. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate.

56. Defendants admit that the FDA approved the Descovy[®] drug product, which was invented by GSI researchers, in April 2016 for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older in combination with other antiretroviral agents. Defendants further admit that Descovy[®] tablets approved by the FDA are available in one strength, a combination that includes 200 mg of FTC and 25 mg of TAF.

57. The document cited in Paragraph 57 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 57 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that, on October 3, 2019, GSI received FDA approval to sell Descovy[®] as a tablet consisting of 200 mg of FTC and 25 mg of TAF for the following indication: “DESCOVY is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating DESCOVY for HIV-1 PrEP.” Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. To the extent Paragraph 57 of the Complaint contains other allegations, they are denied.

F. Efforts to Develop Regimens to Prevent HIV Transmission

58. Defendants admit that patients whose HIV is fully suppressed by ART receive a clinical benefit and that poor adherence to the ART regimen reduces that benefit. Defendants further admit that persons living with HIV not receiving ART or who are unaware of their HIV-positive status can spread HIV. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 58 of the Complaint and therefore deny those allegations.

59. Defendants admit that vaccines, post-exposure prophylaxis, and pre-exposure prophylaxis are being pursued as separate and distinct strategies in an effort to protect HIV-negative persons from infection, among other potential strategies for preventing transmission to HIV-negative persons, such as treatment of people living with HIV through ART. Defendants lack sufficient knowledge or information to form a belief as to the remainder of the allegations in Paragraph 59 of the Complaint and therefore deny those allegations.

G. Decades of Unsuccessful Attempts to Create an HIV Vaccine

60. Defendants admit the allegations in Paragraph 60 of the Complaint.

61. The document cited in Paragraph 61 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 61 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 61 of the Complaint and therefore deny those allegations.

62. The document cited in Paragraph 62 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 62 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or

information to form a belief as to the remaining allegations in Paragraph 62 of the Complaint and therefore deny those allegations.

63. Defendants admit that there has been extensive research into an effective HIV vaccine. Defendants further admit that they are unaware of the existence of any effective HIV vaccine, although promising vaccines are currently being studied, including through collaborations with Defendants. To the extent that Paragraph 63 contains any additional allegations, Defendants lack sufficient knowledge or information to form a belief as to those allegations and therefore deny them.

H. Post-Exposure Prophylaxis (PEP) Regimens Based on Empirical Data

64. Defendants admit that post-exposure prophylaxis, or PEP, is a known type of HIV-prevention regimen. Defendants admit that PEP involves taking antiretroviral medication shortly after a potential exposure that presents a risk for HIV infection. The document cited in Paragraph 64 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 64 purporting to summarize that document to the extent they are inconsistent with that document.

65. The document cited in Paragraph 65 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 65 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 65 of the Complaint and therefore deny those allegations.

66. The document cited in Paragraph 66 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 66 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 66 of the Complaint and therefore deny those allegations.

67. The document cited in Paragraph 67 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 67 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 67 of the Complaint and therefore deny those allegations.

1. *Early Data Regarding Tenofovir Alone for PEP*

68. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 68 of the Complaint and therefore deny those allegations.

69. The document cited in Paragraph 69 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 69 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 69 of the Complaint and therefore deny those allegations.

2. *PEP Guidelines*

70. Defendants admit the allegations in Paragraph 70 of the Complaint.

71. The document discussed in Paragraph 71 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 71 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that the use of the Truvada[®] drug product for PEP, as described in the document discussed in Paragraph 71, anticipates claims 12 and 14-18 of the '509 Patent and claims 12 and 14-17 of the '333 Patent, all of which were disclaimed by the Government after the filing of this lawsuit. Defendants admit that neither the CDC nor HHS invented the use of Truvada[®] for PEP or PrEP. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 71 of the Complaint and therefore deny those allegations.

72. The document cited in Paragraph 72 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 72 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 72 of the Complaint and therefore deny those allegations.

73. The document cited in Paragraph 73 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 73 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 73 of the Complaint and therefore deny those allegations.

74. The document discussed in Paragraph 74 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 74 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 74 of the Complaint and therefore deny those allegations.

75. The document cited in Paragraph 75 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 75 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 75 of the Complaint and therefore deny those allegations.

76. The document cited in Paragraph 76 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 76 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or

information to form a belief as to the remaining allegations in Paragraph 76 of the Complaint and therefore deny those allegations.

I. Pre-Exposure Prophylaxis (PrEP)

77. Defendants admit that pre-exposure prophylaxis (PrEP) refers to a regimen including oral medications that, when taken on a regular basis prior to exposure, prevent the spread of HIV. Defendants admit that PrEP research has been undertaken by multiple research groups, including Defendants. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 77 of the Complaint and therefore deny those allegations.

78. The document cited in Paragraph 78 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 78 purporting to summarize that document to the extent they are inconsistent with that document. For example, Defendants deny that the cited source identifies PEP as a “28-course of antiretroviral therapy.”

79. Defendants admit that the applications for PrEP regimens for Truvada® and Descovy® that the FDA and foreign regulatory authorities have approved included animal data and data from randomized human clinical trials. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 79 of the Complaint and therefore deny those allegations.

80. The documents cited in Paragraph 80 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 80 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants admit that FTC/TDF and FTC/TAF, when taken in adherence to a prescribed PrEP regimen, have been estimated to reduce the risk of contracting HIV from sex with an effectiveness

of about 99 percent. However, due to the vagueness of these allegations, including those concerning “effectiveness” and “evidence from several large clinical trials and observational studies of at-risk populations,” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 80 of the Complaint and therefore deny those allegations.

1. *Early PrEP Efforts*

81. Defendants deny that the CDC established “effective daily PrEP regimens in the mid-2000s.” Defendants admit that prior to the mid-2000s, concerns existed regarding, among other things, the sociological considerations surrounding PrEP’s overall efficacy, “risk compensation,” a person’s ability to adhere to a daily PrEP regimen, the safety and burden of a daily PrEP regimen for otherwise healthy people, and the potential for developing resistant HIV strains if PrEP fails. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 81 of the Complaint and therefore deny those allegations.

82. The document cited in Paragraph 82 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 82 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 82 of the Complaint and therefore deny those allegations.

83. The documents cited in Paragraph 83 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 83 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 83 of the Complaint and therefore deny those allegations.

84. The document cited in Paragraph 84 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 84 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that TDF received FDA approval in 2001 and that TAF was also known as GS-7340. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 84 of the Complaint and therefore deny those allegations.

85. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 85 of the Complaint and therefore deny those allegations.

86. The document cited in Paragraph 86 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 86 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 86 of the Complaint and therefore deny those allegations.

87. The document cited in Paragraph 87 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 87 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 87 of the Complaint and therefore deny those allegations.

88. The document cited in Paragraph 88 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 88 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 88 of the Complaint and therefore deny those allegations.

89. The document cited in Paragraph 89 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 89 purporting to summarize that document to the extent they are inconsistent with that document.

90. The document cited in Paragraph 90 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 90 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that GSI supported the work described in Exhibit 25. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC.

91. Defendants deny that, as of the priority date for the Patents-in-Suit, no one expected a TDF/FTC regimen to be effective as a PrEP regimen. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 91 of the Complaint and therefore deny those allegations.

92. Defendants deny that no researchers focused on two-drug regimens for PrEP studies before the CDC performed its macaque study. Defendants lack sufficient knowledge or information to form a belief as to the first sentence of Paragraph 92 of the Complaint and therefore deny those allegations. Defendants deny the remaining allegations in Paragraph 92 of the Complaint.

2. *Research Leading to CDC's Innovative FTC/Tenofovir Prodrug Regimens*

93. Defendants admit the allegations in Paragraph 93 of the Complaint.

94. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 94 of the Complaint and therefore deny those allegations.

95. Defendants deny that CDC researchers were the first to design a study using FTC/TDF to prevent HIV infection. Defendants lack sufficient knowledge or information to form a belief as to the allegations in the first sentence of Paragraph 95 of the Complaint and therefore deny those allegations. Defendants deny the allegations in the second sentence of Paragraph 95 of the Complaint.

3. *CDC's Animal Modeling Techniques*

96. Defendants deny that the CDC alone provided any “breakthrough work” on PrEP. Defendants deny that the animal model described in Paragraph 96 of the Complaint was “new.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 96 of the Complaint and therefore deny those allegations.

97. Defendants admit that animal research methodologies that focused on large single doses of SIV or SHIV at mucosal surfaces did not accurately represent typical repeat, low-dose mucosal exposures experienced by humans with the sexual transmission of HIV. Defendants admit that such inaccuracies could underestimate the efficacy of potential treatments. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 97 of the Complaint and therefore deny those allegations.

98. Defendants deny that the CDC’s methodology was “new.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 98 of the Complaint and therefore deny those allegations.

4. *CDC's Determination of Proper Dosing*

99. On the basis that GSI researchers provided data and assistance with applicable dosing experiments, Defendants deny that the named inventors were solely responsible for the “prior determination of the proper doses of FTC and TDF used in their study.” Defendants lack

sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 99 of the Complaint and therefore deny those allegations.

100. Defendants deny that “no literature or other studies suggested that the therapeutic doses of TDF and FTC available in Truvada[®] would also constitute effective preventive doses for a PrEP regimen.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 100 of the Complaint and therefore deny those allegations.

101. Defendants admit that, to control for species differences in the elimination of drugs, GSI and CDC researchers collaborated on pharmacokinetic studies to determine what doses in macaques would approximate appropriate blood and cellular levels of FTC and TDF in humans. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 101 of the Complaint and therefore deny those allegations.

5. CDC’s *Determination of Appropriate FTC Dose*

102. The document cited in Paragraph 102 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 102 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that GSI employees Drs. Michael Miller and Howard Jaffe participated in the email exchange reflected in Exhibit 28. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 102 of the Complaint and therefore deny those allegations.

103. Defendants admit that GSI and the CDC entered into a Material Transfer Agreement (MTA) that the CDC executed on December 28, 2004, and that GSI executed on January 31, 2005. The document cited in Paragraph 103 of the Complaint speaks for itself, and

Defendants deny the allegations of Paragraph 103 purporting to summarize that document to the extent they are inconsistent with that document. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 103 of the Complaint and therefore deny those allegations.

104. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 104 of the Complaint and therefore deny those allegations.

105. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 105 of the Complaint and therefore deny those allegations.

6. CDC's Determination of Appropriate TDF Dose

106. Defendants admit that the CDC conducted pharmacokinetic research, in collaboration with GSI, to ensure proper dosing. Defendants deny that this research was CDC's "own" or exclusive research. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 106 of the Complaint and therefore deny those allegations.

107. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 107 of the Complaint and therefore deny those allegations.

108. The document cited in Paragraph 108 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 108 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 108 of the Complaint and therefore deny those allegations.

109. The document cited in Paragraph 109 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 109 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 109 of the Complaint and therefore deny those allegations.

7. CDC's PrEP Experiments

110. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 110 of the Complaint and therefore deny those allegations.

111. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 111 of the Complaint and therefore deny those allegations.

112. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 112 of the Complaint and therefore deny those allegations.

113. Defendants deny that the CDC's modeling techniques were "newly-developed." Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 113 of the Complaint and therefore deny those allegations.

114. The document cited in Paragraph 114 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 114 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 114 of the Complaint and therefore deny those allegations.

8. Results of CDC's PrEP Experiments

115. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 115 of the Complaint and therefore deny those allegations.

116. The document cited in Paragraph 116 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 116 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 116 of the Complaint and therefore deny those allegations.

117. Defendants deny that the results referred to in Paragraph 117 of the Complaint “demonstrated” definitively that “a person at risk for HIV infection could be effectively protected against HIV infection by regular prophylactic doses of FTC and tenofovir or FTC and a tenofovir prodrug.” Defendants further deny that the results permitted the CDC researchers to “conclude” definitively that the identified dosing levels would be “highly effective in adult humans.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 117 of the Complaint and therefore deny those allegations.

118. Defendants deny the allegations in Paragraph 118 of the Complaint.

J. Gilead’s Contribution Limited to Drug Donations

119. Defendants deny the allegations in Paragraph 119 of the Complaint.

120. Defendants admit GSI executed MTAs and amendments to MTAs with CDC between 2004 and 2008 under which GSI agreed to provide, and did provide, CDC with FTC, TDF, and tenofovir. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 120 of the Complaint and therefore deny those allegations.

121. Defendants admit that an MTA related to the research leading to the Patents-in-Suit was signed in December 2004 by Dr. Heneine, and later by Dr. Mick Hitchcock, GSI’s then–Vice

President of Medical Affairs, in response to Dr. Heneine's email request for a cost-free transfer of FTC to CDC. Defendants deny that this MTA was the earliest MTA related to the research leading to the Patents-in-Suit. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC.

122. Defendants admit that GSI entered into at least three other MTAs, as well as several MTA amendments, with the CDC, as well as amendments to these agreements. The documents discussed in Paragraph 122 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 122 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants deny the remaining allegations in Paragraph 122 of the Complaint.

123. The document cited in Paragraph 123 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 123 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that the CDC agreed to provide GSI with prompt notice of any applications for intellectual property based on material provided under the terms of the MTA. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC.

124. The document cited and the other documents discussed in Paragraph 124 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 124 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants' investigation is ongoing, and based on the information currently known to

Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC.

125. Defendants deny the allegations in Paragraph 125 of the Complaint.

126. The document cited in Paragraph 126 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 126 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny that “[o]ther than the provision of the study drugs, Gilead provided no substantive input into the protocol and methods used in CDC research.” Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 126 of the Complaint and therefore deny those allegations.

127. The document cited in Paragraph 127 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 127 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny the remaining allegations in Paragraph 127 of the Complaint.

K. Patent Applications Covering CDC’s Invention and Disclosure to Gilead

128. Defendants admit that U.S. non-provisional patent application number 11/669,547 was filed on January 31, 2007, and was published by the PTO on November 15, 2007. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 128 of the Complaint and therefore deny those allegations.

129. Defendants admit that PCT Application No. US2007/002926 was published on August 16, 2007. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 129 of the Complaint and therefore deny those allegations.

130. The document cited in Paragraph 130 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 130 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or

information to form a belief as to the remaining allegations in Paragraph 130 of the Complaint and therefore deny those allegations.

131. Defendants admit that GSI received a draft copy of the referenced article prior to its publication. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 131 of the Complaint and therefore deny those allegations.

132. Defendants admit that some later papers relating to the CDC's PrEP research were made available to employees of GSI before publication. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the vague allegations in Paragraph 132 of the Complaint and therefore deny those allegations.

133. The documents referenced in Paragraph 133 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 133 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 133 of the Complaint and therefore deny those allegations.

134. Defendants deny the allegations in Paragraph 134 of the Complaint.

L. Immediate Impact of CDC's Innovative Regimens on Clinical Research

135. The document cited in Paragraph 135 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 135 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or

information to form a belief as to the remaining allegations in Paragraph 135 of the Complaint and therefore deny those allegations.

136. The document cited in Paragraph 136 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 136 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 136 of the Complaint and therefore deny those allegations.

137. The document cited in Paragraph 137 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 137 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 137 of the Complaint and therefore deny those allegations.

138. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 138 of the Complaint and therefore deny those allegations.

139. Defendants admit that the methodology of the PrEP trial in Botswana was changed, at least in part, due to research published by the CDC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 139 of the Complaint and therefore deny those allegations.

140. Defendants admit that the methodology of the PrEP trial in Botswana was changed, at least in part, due to research published by the CDC. Defendants admit that the planned methodology of the iPrEx trial was changed after the CDC's findings were presented, but Defendants deny that, after the iPrEx screening began in 2008, there was a change to FTC/TDF

from TDF only. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 140 of the Complaint and therefore deny those allegations.

141. The document cited in Paragraph 141 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 141 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 141 of the Complaint and therefore deny those allegations.

142. The document cited in Paragraph 142 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 142 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 142 of the Complaint and therefore deny those allegations.

143. Defendants deny the allegations in Paragraph 143 of the Complaint.

M. Numerous Subsequent Clinical Studies Confirming the Groundbreaking Efficacy of CDC's Inventive FTC/TDF Regimen

144. Defendants admit that FTC/TDF, when taken in adherence to a prescribed PrEP regimen, has been estimated to reduce the risk of contracting HIV from sex with an effectiveness of about 99 percent. However, due to the vagueness of these allegations, including those concerning the terms "a number of human studies" and "confirmed," Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 144 of the Complaint and therefore deny those allegations.

145. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 145 of the Complaint and therefore deny those allegations.

146. Defendants deny the allegations in Paragraph 146 of the Complaint.

1. *iPrEx Study*

147. Defendants admit that NIH was a sponsor of clinical trial NCT00458393, which is known by the name iPrEx and which ran from 2007 through 2014, including 2007 to 2011. Defendants further admit that the iPrEx trial was a randomized, double-blind, placebo-controlled multinational study evaluating Truvada[®] in 2,499 HIV-seronegative men or transgender women who have sex with men and with evidence of high-risk behavior for HIV-1 infection.

148. The document cited in Paragraph 148 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 148 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny that iPrEx was the first published human study showing the clinical efficacy of PrEP. Defendants admit that the iPrEx trial showed that, at the end of treatment, emergent HIV-1 seroconversion was observed in 131 subjects, of which 48 occurred in the Truvada[®] group and 83 occurred in the placebo group, indicating a 42% reduction in risk; the iPrEx trial also showed that efficacy was strongly correlated with adherence. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 148 of the Complaint and therefore deny those allegations.

149. The documents cited in Paragraph 149 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 149 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 149 of the Complaint and therefore deny those allegations.

150. The document cited in Paragraph 150 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 150 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that the planned methodology

of the iPrEx trial changed after the CDC's findings were presented, but Defendants deny that, after the iPrEx screening began in 2008, there was a change to FTC/TDF from TDF only.

151. Defendants admit that, in his testimony before the United States House Committee on Oversight and Reform (House Oversight Committee) in May 2019, current GSI CEO Daniel O'Day offered the following testimony in response to a question by Congressman Jim Jordan:

Rep. Jordan: And earlier, Dr. Grant said Gilead did not provide leadership or funding for PrEP in the studies at CDC. Is that true?

Mr. O'Day: No, that's not true. I mean, we have nine scientists that were involved in the iPrEx trial itself. It was one of the two trials that went to the FDA to seek approval. And of those, we have two scientists, both who are still with the company actually, that were authors in the primary New England Journal article that is the iPrEx study.

And to be an author on the New England Journal of Medicine article, you must -- you must have involvement in the trial, in addition to the free medicine we provided and the know-how.

152. The document cited in Paragraph 152 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 152 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny the remaining allegations in Paragraph 152.

153. The document cited in Paragraph 153 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 153 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny that GSI has been "a hesitant partner on PrEP research"; deny that GSI "did not provide leadership, innovation, or funding for PrEP research"; and deny that GSI limited its involvement in PrEP research "to donating study drug and placebos." Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC.

154. The document cited in Paragraph 154 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 154 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that GSI provided medication for the iPrEx study but did not provide monetary funding. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 154 of the Complaint and therefore deny those allegations.

2. *Partners PrEP Study*

155. Defendants admit that clinical trial NCT00557245, which is known by the name Partners PrEP, was initiated in 2007 with a study start date in 2008. Defendants further admit that the Partners PrEP trial was a randomized, double-blind, placebo-controlled 3-arm trial conducted in 4,758 HIV-1 serodiscordant heterosexual couples in Kenya and Uganda to evaluate the efficacy and safety of TDF (N=1,589) and FTC/TDF (N=1,583) versus (parallel comparison) placebo (N=1,586) in preventing HIV-1 acquisition by the uninfected partner. The document cited in Paragraph 155 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 155 purporting to summarize that document to the extent they are inconsistent with that document.

156. The document cited in Paragraph 156 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 156 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that the Partners PrEP trial showed that the risk reduction for Truvada® relative to placebo was 75% and that efficacy was strongly correlated with adherence. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 156 of the Complaint and therefore deny those allegations.

157. The document cited in Paragraph 157 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 157 purporting to summarize that document to the extent they are inconsistent with that document.

158. The documents cited in Paragraph 158 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 158 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants admit that GSI provided medication for the Partners PrEP study but did not provide monetary funding. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 158 of the Complaint and therefore deny those allegations.

159. The document cited in Paragraph 159 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 159 purporting to summarize that document to the extent they are inconsistent with that document.

3. *TDF2 Study*

160. The document cited in Paragraph 160 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 160 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 160 of the Complaint and therefore deny those allegations.

161. The document cited in Paragraph 161 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 161 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or

information to form a belief as to the remaining allegations in Paragraph 161 of the Complaint and therefore deny those allegations.

162. The document cited in Paragraph 162 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 162 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 162 of the Complaint and therefore deny those allegations.

4. *PROUD Study*

163. Defendants admit that studies started after iPrEx, Partners PrEP, and TDF2 found a daily Truvada® regimen to have higher efficacy than reported in the iPrEx, Partners PrEP, and TDF2 trials in some circumstances. To the extent there are further allegations in Paragraph 163 of the Complaint, Defendants lack sufficient knowledge or information to form a belief as to those allegations and therefore deny those allegations.

164. The document cited in Paragraph 164 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 164 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that GSI provided financial and in-kind support, including the Truvada® drug product and a grant for diagnostic testing, for the PROUD study. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 164 of the Complaint and therefore deny those allegations.

165. The documents cited in Paragraph 165 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 165 purporting to summarize those documents to

the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 165 of the Complaint and therefore deny those allegations.

5. *ANRS-IPERGAY Study*

166. The document cited in Paragraph 166 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 166 purporting to summarize that document to the extent they are inconsistent with that document. Defendants admit that GSI provided financial and in-kind support, including medications and funding, for the IPERGAY study. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 166 of the Complaint and therefore deny those allegations.

167. The documents cited in Paragraph 167 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 167 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 167 of the Complaint and therefore deny those allegations.

6. *CDC's Methodology Now "Gold Standard" For Clinical Researchers*

168. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 168 of the Complaint and therefore deny those allegations.

169. Defendants deny that macaque modeling and testing are always necessary prior to the use of ARVs in human clinical trials for PrEP. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 169 of the Complaint and therefore deny those allegations.

N. Approval and Sales of Truvada[®] and Quick Approval of Descovy[®] That Followed from CDC's Inventive Work

170. Defendants admit that in July 2012, FDA approved the Truvada[®] drug product, which was invented by GSI researchers, for use as PrEP and that GSI owns a U.S. trademark registration for Truvada for PrEP. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants deny the remaining allegations in Paragraph 170 of the Complaint.

171. Defendants admit that GSI's application for FDA approval of Truvada[®] for the PrEP indication cited the iPrEx and Partners PrEP studies, among other studies. Defendants deny that, other than donating drugs, GSI did not support any of the clinical efforts leading to FDA approval of Truvada[®] for the PrEP indication. Defendants deny that GSI openly expressed skepticism regarding PrEP. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. The document cited in Paragraph 171 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 171 purporting to summarize that document to the extent they are inconsistent with that document.

172. Defendants admit that, following FDA approval of Truvada[®] for the PrEP indication, GSI developed and supported educational initiatives and demonstration projects designed to identify at-risk persons who could benefit from PrEP. Defendants deny the remaining allegations in Paragraph 172 of the Complaint.

173. The document cited in Paragraph 173 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 173 purporting to summarize that document to the extent they are inconsistent with that document.

174. Defendants admit that, as of January 1, 2013, the annualized wholesale acquisition cost (“WAC”) for Truvada[®] was approximately \$14,883.61 in the United States, although the cost varied depending on the specific payor. The documents cited in Paragraph 174 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 174 purporting to summarize those documents to the extent they are inconsistent with those documents.

175. The document cited in Paragraph 175 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 175 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 175 of the Complaint and therefore deny those allegations.

176. The document cited in Paragraph 176 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 176 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 176 of the Complaint and therefore deny those allegations.

177. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 177 of the Complaint and therefore deny those allegations.

178. Defendants admit that, as of November 2019, the wholesale acquisition cost (WAC) of a bottle containing 30 tablets of Truvada[®] was \$1757.90. Defendants admit that GSI has increased the U.S. WAC for Truvada[®]. Defendants admit that Defendants’ global revenues for Truvada[®] in 2018 were \$2.997 billion. Defendants admit that GSI’s domestic sales of Truvada[®] for the PrEP indication contributed to Defendants’ collective overall revenues for Truvada[®]. Defendants admit that Defendants are committed to ensuring that people who are at high risk for

HIV infection have access to prevention options, including Truvada® and Descovy®, where available. Defendants admit that GSI maintains patient-assistance programs and has taken a leadership position in ensuring patients have access to life-saving medications through a variety of programs and partnerships, including GSI's co-pay coupon program for eligible people with commercial insurance and its Truvada for PrEP® Medication Assistance Program for people who lack insurance coverage. Defendants admit that GSI's recent commitment to the CDC to provide up to 2.4 million bottles of Truvada® or Descovy® annually free of charge will support a greatly accelerated effort to reach uninsured Americans at risk for HIV. Further, Defendants admit that a CDC analysis found that of the estimated 1.2 million people in the U.S. eligible for PrEP, less than 1 percent do not have financial assistance to pay for PrEP medication and care. *See* Smith et al., "Estimated coverage to address financial barriers to HIV preexposure prophylaxis among persons with indications for its use, United States, 2015," *J. Acquir. Immune Defic. Syndr.* 2017 December 15; 76(5): 465–472. The documents cited in Paragraph 178 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 178 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 178 of the Complaint and therefore deny those allegations.

179. Defendants admit that GSI submitted a supplemental new drug application to FDA on April 5, 2019, seeking approval to market Descovy® for, among other things, use in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex, provided that such individuals have a negative HIV-1 test immediately prior to

initiating Descovy® for HIV-1 PrEP. Defendants deny the remaining allegations in Paragraph 179 of the Complaint.

180. Defendants admit the allegations in Paragraph 180 of the Complaint.

181. The document cited in Paragraph 181 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 181 purporting to summarize that document to the extent they are inconsistent with that document. Specifically, Defendants deny that Exhibit 9 includes the quote in Paragraph 181 of the Complaint, but Defendants admit that Exhibit 9 says “Descovy is not indicated in individuals at risk of HIV-1 infection from receptive vaginal sex because the effectiveness in this population has not been evaluated.” Defendants admit that, on October 3, 2019, FDA approved GSI’s supplemental NDA to market Descovy® for use in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex, provided that such individuals have a negative HIV-1 test immediately prior to initiating Descovy® for HIV-1 PrEP. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 181 of the Complaint and therefore deny those allegations.

O. PrEP as Critical Component of Effort to End HIV Epidemic

182. The documents cited in Paragraph 182 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 182 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 182 of the Complaint and therefore deny those allegations.

183. The document cited in Paragraph 183 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 183 purporting to summarize that document to the

extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 183 of the Complaint and therefore deny those allegations.

184. Defendants admit that efforts to administer Truvada® for PrEP in identified geographic areas, or “hot spots,” in the United States could be helpful to certain communities. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 184 of the Complaint and therefore deny those allegations.

185. Defendants admit that efforts to reach marginalized and hard-to-reach communities at high risk for HIV infections can be hindered by stigma associated with PrEP use. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 185 of the Complaint and therefore deny those allegations.

186. Defendants deny that the cost of the Truvada® drug product is a critical barrier to increasing access to PrEP in the United States. Defendants deny that the cost of the Truvada® drug product is a major reason that many at risk of HIV infection in the United States are not currently taking Truvada® for the PrEP indication. Defendants admit that Defendants are committed to ensuring that people who are at high risk for HIV infection have access to prevention options, including Truvada® and Descovy®, where available. Defendants admit that GSI maintains patient-assistance programs and has taken a leadership position in ensuring patients have access to GSI’s medications through a variety of programs and partnerships, including GSI’s co-pay coupon program for eligible people with commercial insurance and its Truvada for PrEP® Medication Assistance Program for people who lack insurance coverage. Defendants admit that GSI’s recent commitment to the CDC to provide up to 2.4 million bottles of Truvada® or Descovy® annually free of charge will support a greatly accelerated effort to reach uninsured Americans at risk for

HIV. Further, Defendants admit that a CDC analysis found that of the estimated 1.2 million people in the U.S. eligible for PrEP, less than 1 percent do not have financial assistance to pay for PrEP medication and care. *See* Smith et al., “Estimated coverage to address financial barriers to HIV preexposure prophylaxis among persons with indications for its use, United States, 2015,” *J. Acquir. Immune Defic. Syndr.* 2017 December 15; 76(5): 465–472. Defendants admit that, in the United States, Truvada® is currently sold only by GSI, which has substantial rights in patents covering that product. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 186 of the Complaint and therefore deny those allegations.

187. The documents cited in Paragraph 187 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 187 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants admit that some activists have criticized the pricing of Truvada® in the United States. Defendants admit that the pricing of Truvada® in the United States was a topic during a House Oversight Committee hearing in May 2019. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 187 of the Complaint and therefore deny those allegations.

188. The documents cited in Paragraph 188 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 188 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 188 of the Complaint and therefore deny those allegations.

P. Teva Settlement Announcement

189. Defendants admit that GSI has taken actions regarding access to Truvada®. Defendants deny the remaining allegations in Paragraph 189 of the Complaint.

190. Defendants admit that GSI disclosed the following in a May 8, 2019 Form 10-Q securities filing: “Pursuant to a settlement agreement relating to patents that protect Truvada and Atripla, Teva Pharmaceuticals will be able to launch generic fixed-dose combinations of emtricitabine and TDF and generic fixed-dose combinations of emtricitabine, TDF and efavirenz in the United States on September 30, 2020.” Defendants admit that this settlement took place in 2014. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants deny the remaining allegations in Paragraph 190 of the Complaint.

191. Defendants admit that Douglas M. Brooks, GSI’s Executive Director for Community Engagement, sent an email to several individuals on May 8, 2019, stating that:

There has been significant speculation, and some misinformation, in recent months related to the Truvada patents and the timing of a generic version of the drug into the market.

Gilead reached an agreement with Teva Pharmaceuticals in 2014 to allow the early launch of a generic version of Truvada into the market in 2020, a year earlier than required.

For background, a generic version of Truvada is not currently available. The patents and exclusivity for tenofovir disoproxil fumarate (TDF), one component of Truvada, have expired. The patent for emtricitabine, the other component of Truvada, expires in September of 2021.

Pursuant to a settlement agreement reached in 2014 relating to patents that protect Truvada as well as Atripla (emtricitabine/TDF/efavirenz), Teva will be able to launch generic fixed-dose combinations of emtricitabine and TDF and generic

fixed-dose combinations of emtricitabine, TDF and efavirenz in the United States on September 30, 2020.

This agreement is not related to current discussions with the U.S. government to broaden access to Truvada for PrEP for vulnerable populations and support the federal plan to end the HIV epidemic. Those discussions are ongoing.

Defendants deny the allegations of Paragraph 191 to the extent they are inconsistent with the text above.

192. Defendants deny the allegations in Paragraph 192 of the Complaint.

193. The document cited in Paragraph 193 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 193 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 193 of the Complaint and therefore deny those allegations.

194. The document cited in Paragraph 194 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 194 purporting to summarize that document to the extent they are inconsistent with that document. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 194 of the Complaint and therefore deny those allegations.

195. Defendants admit that the launch of the Descovy[®] PrEP indication has preceded the availability of any generic equivalent of Truvada[®] in the United States. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 195 of the Complaint and therefore deny those allegations.

V. CDC's Patents

196. Paragraph 196 of the Complaint contains conclusions of law purporting to summarize the scope of the claims of the Patents-in-Suit, to which no response is required. To the

extent a response to those conclusions of law is required, Defendants deny those allegations. The patents referenced in Paragraph 196 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 196 purporting to summarize those patents to the extent they are inconsistent with those patents. Defendants deny that the patents referenced in Paragraph 196 are valid. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 196 of the Complaint and therefore deny those allegations.

A. The '509 Patent

197. Defendants admit that the '509 Patent is entitled “Inhibition of HIV Infection through Chemoprophylaxis” and bears an issuance date of June 2, 2015. Defendants admit that the '509 Patent states that it “claims priority of U.S. Provisional Patent Application Ser. No. 60/764,811 filed Feb. 3, 2006.” Defendants deny that the '509 Patent was validly issued.

198. Defendants admit that the '509 Patent lists Walid M. Heneine, Thomas M. Folks, Robert Janssen, Ronald Otten, and Jose Gerardo García Lerma as inventors on its face. Defendants deny that the '509 Patent is valid.

199. Paragraph 199 of the Complaint contains conclusions of law to which no response is required. To the extent a response to those conclusions of law is required, Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 199 of the Complaint and therefore deny those allegations.

200. Paragraph 200 of the Complaint contains conclusions of law to which no response is required. To the extent a response is required, the '509 Patent speaks for itself, and Defendants deny the allegations of Paragraph 200 purporting to summarize that patent to the extent they are inconsistent with that patent.

201. Paragraph 201 of the Complaint contains conclusions of law to which no response is required. To the extent an answer is required, the '509 Patent speaks for itself, and Defendants

deny the allegations of Paragraph 201 purporting to summarize that patent to the extent they are inconsistent with that patent. Defendants admit that HHS ~~has~~ canceled Claim 12 via statutory disclaimer after being faced with GSI's invalidity positions in IPR2019-01453, ~~which is pending before the United States Patent Trial and Appeal Board (PTAB)~~. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 201 of the Complaint and therefore deny those allegations.

202. Defendants admit that TDF is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester prodrug of tenofovir. Defendants deny that TAF is a tenofovir ester. To the extent that Paragraph 202 of the Complaint includes allegations about the scope of the claim term "tenofovir ester," Paragraph 202 of the Complaint contains conclusions of law to which no response is required.

203. Paragraph 203 of the Complaint contains conclusions of law to which no response is required. To the extent a response is required, the '509 Patent speaks for itself, and Defendants deny the allegations of Paragraph 203 purporting to summarize that patent to the extent they are inconsistent with that patent.

204. Paragraph 204 of the Complaint contains conclusions of law to which no response is required.

205. The patents referenced in Paragraph 205 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 205 purporting to summarize those patents to the extent they are inconsistent with those patents. Defendants admit that HHS has canceled Claims 12 and 14-18 via statutory disclaimer after being faced with GSI's invalidity positions in IPR2019-01453, ~~which is pending before the PTAB~~. Defendants lack sufficient knowledge or

information to form a belief as to the remaining allegations in Paragraph 205 of the Complaint and therefore deny those allegations.

B. The '333 Patent

206. Defendants admit that the '333 Patent bears an issuance date of February 28, 2017. Defendants deny that the '333 Patent was validly issued.

207. Paragraph 207 of the Complaint contains conclusions of law to which no response is required. To the extent a response to those conclusions of law is required, Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 207 of the Complaint and therefore deny those allegations.

208. Paragraph 208 of the Complaint contains conclusions of law to which no response is required. To the extent an answer is required, Defendants admit that HHS has canceled Claims 12 and 14-17 via statutory disclaimer after being faced with GSI's invalidity positions in IPR2019-01454, ~~which is pending before the PTAB~~. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 208 of the Complaint and therefore deny those allegations.

209. The '333 Patent speaks for itself, and Defendants deny the allegations of Paragraph 209 purporting to summarize that patent to the extent they are inconsistent with that patent.

210. The '333 Patent speaks for itself, and Defendants deny the allegations of Paragraph 210 purporting to summarize that patent to the extent they are inconsistent with that patent. Defendants admit that HHS has canceled Claim 12 via statutory disclaimer after being faced with GSI's invalidity positions in IPR2019-01454, ~~which is pending before the PTAB~~. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 210 of the Complaint and therefore deny those allegations.

211. Paragraph 211 of the Complaint contains conclusions of law to which no response is required. To the extent a response is required, the '333 Patent speaks for itself, and Defendants deny the allegations of Paragraph 211 purporting to summarize that patent to the extent they are inconsistent with that patent.

C. The '191 Patent

212. Defendants admit that the '191 Patent bears an issuance date of April 10, 2018. Defendants deny that the '191 Patent was validly issued.

213. Paragraph 213 of the Complaint contains conclusions of law to which no response is required. To the extent a response to those conclusions of law is required, Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 213 of the Complaint and therefore deny those allegations.

214. Paragraph 214 of the Complaint contains conclusions of law to which no response is required.

215. The '191 Patent speaks for itself, and Defendants deny the allegations of Paragraph 215 purporting to summarize that patent to the extent they are inconsistent with that patent.

216. The '191 Patent speaks for itself, and Defendants deny the allegations of Paragraph 216 purporting to summarize that patent to the extent they are inconsistent with that patent.

D. The '423 Patent

217. Defendants admit that the '423 Patent bears an issuance date of July 2, 2019. Defendants deny that the '423 Patent was validly issued.

218. Paragraph 218 of the Complaint contains conclusions of law to which no response is required. To the extent a response to those conclusions of law is required, Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 218 of the Complaint and therefore deny those allegations.

219. Paragraph 219 of the Complaint contains conclusions of law to which no response is required.

220. The '423 Patent speaks for itself, and Defendants deny the allegations of Paragraph 220 purporting to summarize that patent to the extent they are inconsistent with that patent.

221. The '423 Patent speaks for itself, and Defendants deny the allegations of Paragraph 221 purporting to summarize that patent to the extent they are inconsistent with that patent.

222. Defendants admit that both TDF and TAF are prodrugs metabolized in the body to form the active metabolite tenofovir diphosphate. To the extent that Paragraph 222 of the Complaint includes allegations about the scope of the claim term “tenofovir prodrug,” Paragraph 222 of the Complaint contains conclusions of law to which no response is required.

223. Paragraph 223 of the Complaint contains conclusions of law to which no response is required. Defendants admit that the '333, '191, and '423 Patents share the same title and list the same inventors as the '509 Patent.

VI. CDC'S EFFORTS TO LICENSE THE PATENTS-IN-SUIT

A. CDC's Licensing of Its Patented Work Outside the United States

224. Defendants admit that GSI has substantial rights in the patents listed for all strengths of Truvada® in the FDA's *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, including, but not limited to, rights associated with being a licensee of those patents and the right to sue for infringement of those patents. Defendants further admit that GSI is the assignee of additional patents listed in the *Orange Book* for the 200 mg FTC, 300 mg TDF strengths of Truvada®. Whether these patents that are held or licensed by GSI would prevent the sale by others of pharmaceutical combinations of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) in the United States is a conclusion of law to which no response is required. Defendants further admit that generic forms of FTC/TDF fixed-dose tablets are now on the market

in some non-U.S. countries where Defendants' patent protections have expired. Defendants deny the remaining allegations of Paragraph 224 of the Complaint.

225. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 225 of the Complaint and therefore deny those allegations.

226. Defendants admit that Mylan challenged European Patent No. 2,015,753, making only allegations based on documents examined during prosecution and making no arguments citing the prior art cited by GSI in its IPR petitions, Nos. IPR2019-01453, -01454, -01455, and -01456. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 226 of the Complaint and therefore deny those allegations.

227. Defendants deny that the claims of CDC's European patent are valid. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 227 of the Complaint and therefore deny those allegations.

228. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 228 of the Complaint and therefore deny those allegations.

229. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 229 of the Complaint and therefore deny those allegations.

230. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 230 of the Complaint and therefore deny those allegations.

231. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 231 of the Complaint and therefore deny those allegations.

232. Defendants admit that GSI has sold the Truvada[®] drug product, which contains an indication for PrEP, in the United States without paying any royalties to CDC. Defendants further admit that one or more corporate affiliates of GSI has sold Truvada[®] in certain non-U.S.

jurisdictions where Truvada[®] is indicated for PrEP without paying any royalties to CDC. Defendants deny that CDC is entitled to any royalties from the sale of Truvada[®] for PrEP. Defendants deny the remaining allegations in Paragraph 232 of the Complaint.

B. Gilead's Refusal to Take a License to CDC's Patents

233. Defendants lack sufficient knowledge or information to form a belief as to the vague allegations in Paragraph 233 of the Complaint and therefore deny those allegations.

234. Defendants admit that Dr. Jay Parrish, who was a member of GSI's Corporate Development Team, received the email shown in Exhibit 78 from Laura T. Prestia, Technology Transfer Fellow-CDC Unit, Office of Technology Transfer, National Institutes of Health, on or around October 23, 2014. Defendants further admit that Dr. Linda Higgins, who was GSI's Vice-President of Biology, received an email substantially similar to the email shown in Exhibit 78 from Laura T. Prestia, Technology Transfer Fellow-CDC Unit, Office of Technology Transfer, National Institutes of Health, on or around October 23, 2014. Defendants deny that these communications constituted notice of the patented technology or alleged inventions. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 234 of the Complaint and therefore deny those allegations.

235. The document cited in Paragraph 235 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 235 purporting to summarize that document to the extent they are inconsistent with that document. Defendants deny that these communications constituted notice of the patented technology.

236. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 236 of the Complaint and therefore deny those allegations.

237. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 237 of the Complaint and therefore deny those allegations.

238. Defendants admit that Jay Parrish, an employee of GSI, received an email from Tara Kirby, Ph.D., CDC Team Supervisor, Technology Transfer and Intellectual Property Office, National Institute of Allergy and Infectious Diseases, on or around March 11, 2016, that stated, among other things, “The matter I wanted to discuss with you is an invention from CDC’s Division of HIV/Aids Prevention Surveillance and Epidemiology, our reference number E-195-2013/0. We have recently obtained issued patents for this invention in a number of jurisdictions, including the United States (USPN 9,044,509), and we believe that your marketed drug, Truvada, may be covered by these patents. For your ease of reference, I have attached a copy of the issued U.S. patent, as well as a listing of our patent filings relating to this invention. We would be happy to discuss an amicable resolution to this matter. This invention is available for licensing on a non-exclusive basis, so I have attached a copy of our standard license application form for your review and consideration.” Defendants further admit that this email attached a copy of the ’509 Patent, a document purporting to show a listing of CDC’s patent filings related to the alleged invention, and a document purporting to be a standard license application form. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. To the extent there are remaining allegations in Paragraph 238 of the Complaint, Defendants deny them.

239. Defendants admit that Defendants’ outside counsel, WilmerHale LLP, spoke with Dr. Kirby by telephone in April 2016. Defendants deny the remaining allegations in Paragraph 239 of the Complaint.

240. Defendants admit that individuals from GSI and HHS engaged in two confidential conferences in 2017 and continued to correspond and communicate in 2018. Defendants admit that the parties were unable to resolve the dispute and admit they did not enter into a licensing agreement. Defendants deny the remaining allegations in Paragraph 240 of the Complaint.

241. Defendants admit that GSI has publicly and repeatedly stated its position that the Patents-in-Suit are invalid, including in the testimony of GSI's CEO Daniel O'Day before the House Oversight Committee in May 2019. Defendants deny that they infringe the Patents-in-Suit. Defendants further admit that an invalid patent cannot be infringed. Defendants deny the remaining allegations in Paragraph 241 of the Complaint.

242. Defendants admit the allegations in Paragraph 242 of the Complaint.

243. Defendants admit that GSI challenged the validity of all claims of the four Patents-in-Suit by petitioning for *inter partes* review (IPR) at the PTO. Defendants further admit that GSI filed petitions on August 21, 2019, challenging the validity of all claims of the '509 and '333 Patents, in [Patent Trial and Appeal Board \("PTAB"\)](#) docket numbers IPR2019-01453 and IPR2019-01454, respectively; and on August 23, 2019, challenging the validity of all claims of the '191 and '423 patents, in PTAB docket numbers IPR2019-01455 and IPR2019-01456, respectively. Defendants deny the remaining allegations in Paragraph 243 of the Complaint.

C. CDC's Efforts to License Generic Products in United States

244. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 244 of the Complaint and therefore deny those allegations.

245. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 245 of the Complaint and therefore deny those allegations.

246. Defendants deny that Teva or any other generic manufacturer will launch a product branded as Truvada[®]. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 246 of the Complaint and therefore deny those allegations.

247. Defendants admit the allegations in Paragraph 247 of the Complaint.

248. Defendants lack sufficient knowledge or information to form a belief as to the allegations in Paragraph 248 of the Complaint and therefore deny those allegations.

D. Gilead's Intellectual Property Relating to CDC's Inventive Regimens

249. Defendants admit that GSI has pursued trademark protection relating to Truvada[®] for PrEP and GSIUC has pursued trademark protection relating to Descovy[®] for PrEP. Defendants admit that Defendants have not taken a license to the Patents-in-Suit. Defendants deny that the Government has any valid intellectual property rights in PrEP and therefore that Defendants have any obligation to license or acknowledge such rights. Defendants deny the remaining allegations in Paragraph 249 of the Complaint.

250. Defendants admit the allegations in Paragraph 250 of the Complaint to the extent that "Gilead" refers to GSI. The allegations in this paragraph are denied to the extent that "Gilead" refers to GSIUC.

251. Defendants admit that GSIUC applied for a trademark in the United States for exclusive use of the mark, DESCOVY FOR PREP, and that GSIUC's application for the mark was filed on January 17, 2019 as U.S. Ser. No. 88,266,226. Defendants admit that GSIUC applied for trademark registration of Descovy for PrEP's logo as U.S. Ser. No. 88,615,918. The allegations in this paragraph are denied to the extent that "Gilead" refers to GSI. Defendants deny the remaining allegations in Paragraph 251 of the Complaint.

252. Defendants admit that GSI filed the trademark applications referenced in Paragraph 250 of the Complaint after Plaintiff proposed a license to the '509 Patent. Defendants deny that

GSI filed the trademark applications referenced in Paragraph 250 of the Complaint after Plaintiff identified the remaining Patents-in-Suit because, among other things, the remaining Patents-in-Suit had not issued as of the referenced trademark application dates. Defendants further admit that GSIUC filed the trademark application referenced in Paragraph 251 of the Complaint after Plaintiff proposed a license to at least the '509 Patent. Defendants deny that GSIUC filed trademark application U.S. Ser. No. 88,266,226 referenced in Paragraph 251 of the Complaint after Plaintiff identified at least the '423 Patent because, among other things, the '423 Patent had not issued as of January 17, 2019. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 252 of the Complaint and therefore deny those allegations.

VII. GILEAD'S WILLFUL INFRINGEMENT OF CDC'S PATENTS

A. Inducement of PrEP Regimens Through Sales of Truvada®

253. Defendants admit that, since, 2012, GSI has marketed and sold bottles of Truvada® in the United States for all indications on its label, including its PrEP-related indication. Defendants deny any remaining allegations in Paragraph 253 of the Complaint.

254. Defendants admit that Truvada® has been Defendants' top-selling HIV medication by revenue worldwide over the full period from its launch in 2004 through the end of Defendants' fiscal year 2018. Defendants deny, however, that Truvada® has been Defendants' top-selling HIV medication by revenue worldwide in each year during that period; for example, Defendants deny that Truvada® was Defendants' top-selling HIV medication by revenue worldwide in fiscal years 2017 or 2018. Defendants admit that Defendants' collective worldwide revenue from Truvada® was approximately 20.5% of their collective worldwide revenue from HIV products and approximately 13.8% of their collective worldwide revenue from all products in fiscal year 2018, but Defendants state that these percentages have varied based on the fiscal year and market considered. Defendants lack sufficient knowledge or information to form a belief as to the

remaining vague allegations in Paragraph 254 of the Complaint and therefore deny those allegations.

255. Defendants admit that the percentage of Truvada[®] sales attributable to the PrEP indication has fluctuated over time. Defendants admit that Defendants estimate that more than 60% of demand for Truvada[®] in the first quarter of 2019 was attributable to use for the PrEP indication. Defendants' investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of "Gilead" are denied to the extent that "Gilead" refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 255 of the Complaint and therefore deny those allegations.

256. Defendants admit that GSI has educated healthcare providers and patients on administration of Truvada[®] for the PrEP indication via the FDA-approved package insert for Truvada[®], the FDA-approved packaging for Truvada[®], and promotional messaging consistent with these FDA-approved messages. Defendants' investigation is ongoing, and based on the information currently known to Defendants, Defendants deny the remaining allegations of Paragraph 256 of the Complaint.

257. Defendants admit that Truvada[®] tablets are formulated with FTC and TDF in four dosage combinations, one of which is 200 mg FTC and 300 mg TDF. The document cited in Paragraph 257 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 257 purporting to summarize that document to the extent they are inconsistent with that document.

258. The document cited in Paragraph 258 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 258 purporting to summarize that document to the extent they are inconsistent with that document.

259. Defendants admit that GSI has promoted Truvada[®] for PrEP and has made available a pamphlet entitled “TRUVADA for a Pre-Exposure Prophylaxis (PrEP) indication.” Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants deny the remaining allegations in Paragraph 259 of the Complaint.

260. Defendants admit that GSI provides the document cited in Paragraph 260 for prescribing healthcare providers and patients to sign prior to initiating Truvada[®] for PrEP. The document cited in Paragraph 260 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 260 purporting to summarize that document to the extent they are inconsistent with that document. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants deny the remaining allegations in Paragraph 260 of the Complaint.

261. Defendants admit that GSI obtained a U.S. trademark registration for Truvada for PrEP[®] and applied for a U.S. trademark registration for the phrase “Step Up. PrEP Up” for “promoting public awareness of prevention, treatment, and diagnosis of HIV and AIDS.” Compl. Ex. 86 at 1. Defendants further admit that GSI has obtained a U.S. trademark registration for “a three-dimensional configuration of an oblong tablet, combined with the color blue as applied to the entire surface of the tablet” for “pharmaceutical preparations, namely, pre-exposure prophylaxis (PrEP) preparations for prevention and risk mitigation of contracting HIV.” Compl. Ex. 87 at 1-2. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to

the extent that “Gilead” refers to GSIUC. Defendants deny the remaining allegations in Paragraph 261 of the Complaint.

B. Gilead’s Clinical Trials to Obtain FDA Approval of Descovy® for PrEP

262. Defendants admit that GSI conducted a clinical trial as part of the FDA approval process for Descovy® for the PrEP indication. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining vague allegations in Paragraph 262 of the Complaint and therefore deny those allegations.

263. Defendants admit that the DISCOVER trial is titled “Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection (DISCOVER).” Defendants admit that GSI is the sole sponsor of this trial and that this trial was intended to support GSI’s supplemental new drug application seeking FDA approval to market Descovy® for the PrEP indication. Defendants admit that GSI did not enlist any Government support or funding for the DISCOVER trial and that the Government did not directly support or fund the DISCOVER trial. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 263 of the Complaint and therefore deny those allegations.

264. Defendants admit that the DISCOVER trial consists of three experimental arms: a) an experimental arm in which the subject is given FTC/TAF (200/25 mg tablet) and an FTC/TDF placebo, each administered orally once daily for at least 96 weeks; b) an experimental arm in which

the subject is given FTC/TDF (200/300 mg tablet) and an FTC/TAF placebo, each administered orally once daily for at least 96 weeks; c) an open-label extension experimental arm wherein, once all participants have been on blinded treatment for at least 96 weeks, the study will be unblinded and participants will be offered the option to continue on open-label FTC/TAF treatment for pre-exposure prophylaxis in the open-label extension for 48 weeks, where the open label FTC/TAF (200/25 mg tablet) regimen is administered orally once daily. The allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants deny any remaining allegations in Paragraph 264 of the Complaint.

265. The documents cited in Paragraph 265 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 265 purporting to summarize those documents to the extent they are inconsistent with those documents.

266. The document cited in Paragraph 266 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 266 purporting to summarize that document to the extent they are inconsistent with that document.

267. Defendants admit that GSI submitted a supplemental new drug application to FDA on April 5, 2019, seeking approval to market Descovy® for, among other things, use in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex, provided that such individuals have a negative HIV-1 test immediately prior to initiating DESCOVY for HIV-1 PrEP. Defendants further admit that FDA approved GSI’s sNDA for this indication on October 3, 2019. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the

activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. To the extent Paragraph 267 of the Complaint contains additional allegations, Defendants deny them.

268. Defendants admit that all participants on the DISCOVER trial were required to roll over to the open label phase by July 31, 2019. Defendants admit that the DISCOVER open label phase will be ongoing until Descovy[®] for PrEP is commercially available in participants’ respective countries. Defendants admit that the open label phase for participants in the United States will end by October 2020. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 268 of the Complaint and therefore deny those allegations.

C. Inducement of PrEP Regimens Through Sales of Descovy[®]

269. Defendants admit that GSI is now marketing and selling Descovy[®] for all of its indications, including its indication for PrEP in certain patient populations. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants deny the remaining allegations in Paragraph 269 of the Complaint.

270. Defendants admit that GSI holds U.S. patents relating to Descovy[®]. Defendants admit that there are no generic versions of Descovy[®] currently on the market in the United States. Defendants’ investigation is ongoing, and based on the information currently known to Defendants, the allegations in this paragraph concerning the activities of “Gilead” are denied to the extent that “Gilead” refers to GSIUC. Defendants lack sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 270 of the Complaint and therefore deny those allegations.

271. Defendants deny the allegations in Paragraph 271 of the Complaint.

272. Defendants admit that GSI has educated healthcare providers and patients on administration of Descovy® for PrEP via the FDA-approved package insert for Descovy®, the FDA-approved packaging for Descovy®, and promotional messaging consistent with these FDA-approved messages. Defendants deny the remaining allegations of Paragraph 272 of the Complaint.

273. The document cited in Paragraph 273 of the Complaint speaks for itself, and Defendants deny the allegations of Paragraph 273 purporting to summarize that document to the extent they are inconsistent with that document.

274. Defendants admit that GSIUC applied for a trademark in the United States for exclusive use of the mark, DESCOVY FOR PREP. The documents cited in Paragraph 274 of the Complaint speak for themselves, and Defendants deny the allegations of Paragraph 274 purporting to summarize those documents to the extent they are inconsistent with those documents. Defendants deny the remaining allegations of Paragraph 274 of the Complaint.

D. Willfulness and Deliberateness of Gilead's Activities

275. Defendants deny the allegations in Paragraph 275 of the Complaint.

276. Defendants deny that they have not contended that the marketing and selling of Truvada® for PrEP and Descovy® for PrEP do not infringe the Patents-in-Suit. Defendants admit that they have not made such a contention in testimony before Congress.

277. Defendants admit that GSI has asserted that the Patents-in-Suit are invalid in public statements. Defendants deny the remaining allegations in Paragraph 277 of the Complaint.

278. Defendants deny the allegations in Paragraph 278 of the Complaint.

279. Paragraph 279 of the Complaint contains conclusions of law to which no response is required. To the extent there are any factual allegations in Paragraph 279 of the Complaint, Defendants deny them.

COUNT I:
**GILEAD'S WILLFUL INFRINGEMENT OF THE '509 PATENT
BASED ON TRUVADA FOR PREP® AND DESCOVY® FOR PREP**

280. Defendants repeat and incorporate the admissions and denials in the preceding paragraphs as though fully set forth herein.

281. Defendants admit that the '509 Patent bears an issuance date of June 2, 2015. Defendants admit that the '509 Patent lists the United States of America as the assignee on its face. Defendants deny that the '509 Patent was validly issued. The remainder of Paragraph 281 of the Complaint contains conclusions of law to which no response is required.

282. Defendants deny the allegations in Paragraph 282 of the Complaint.

283. Defendants deny the allegations in Paragraph 283 of the Complaint.

284. Defendants deny the allegations in Paragraph 284 of the Complaint.

285. Defendants deny the allegations in Paragraph 285 of the Complaint.

286. Defendants deny the allegations in Paragraph 286 of the Complaint.

287. Defendants deny the allegations in Paragraph 287 of the Complaint.

288. Defendants deny the allegations in Paragraph 288 of the Complaint.

COUNT II:
**GILEAD'S WILLFUL INFRINGEMENT OF THE '333 PATENT
BASED ON TRUVADA FOR PREP®**

289. Defendants repeat and incorporate the admissions and denials in the preceding paragraphs as though fully set forth herein.

290. Defendants deny that the '333 Patent was issued on June 2, 2015. Defendants admit that the '333 Patent lists the United States of America as the assignee on its face. Defendants deny that the '333 Patent was validly issued. The remainder of Paragraph 290 of the Complaint contains conclusions of law to which no response is required.

291. Defendants deny the allegations in Paragraph 291 of the Complaint.

292. Defendants deny the allegations in Paragraph 292 of the Complaint.

293. Defendants deny the allegations in Paragraph 293 of the Complaint.

294. Defendants deny the allegations in Paragraph 294 of the Complaint.

295. Defendants deny the allegations in Paragraph 295 of the Complaint.

296. Defendants deny the allegations in Paragraph 296 of the Complaint.

COUNT III:
GILEAD'S WILLFUL INFRINGEMENT OF THE '191 PATENT
BASED ON TRUVADA FOR PREP®

297. Defendants repeat and incorporate the admissions and denials in the preceding paragraphs as though fully set forth herein.

298. Defendants deny that the '191 Patent was issued on June 2, 2015. Defendants admit that the '191 Patent lists the United States of America as the assignee on its face. Defendants deny that the '191 Patent was validly issued. The remainder of Paragraph 298 of the Complaint contains conclusions of law to which no response is required.

299. Defendants deny the allegations in Paragraph 299 of the Complaint.

300. Defendants deny the allegations in Paragraph 300 of the Complaint.

301. Defendants deny the allegations in Paragraph 301 of the Complaint.

302. Defendants deny the allegations in Paragraph 302 of the Complaint.

303. Defendants deny the allegations in Paragraph 303 of the Complaint.

304. Defendants deny the allegations in Paragraph 304 of the Complaint.

COUNT IV:
**GILEAD'S WILLFUL INFRINGEMENT OF THE '423 PATENT
BASED ON TRUVADA FOR PREP® AND DESCOVY® FOR PREP**

305. Defendants repeat and incorporate the admissions and denials in the preceding paragraphs as though fully set forth herein.

306. Defendants deny that the '423 Patent was issued on June 2, 2015. Defendants admit that the '423 Patent lists the United States of America as the assignee on its face. Defendants deny that the '423 Patent was validly issued. The remainder of Paragraph 306 of the Complaint contains conclusions of law to which no response is required.

307. Defendants deny the allegations in Paragraph 307 of the Complaint.

308. Defendants deny the allegations in Paragraph 308 of the Complaint.

309. Defendants deny the allegations in Paragraph 309 of the Complaint.

310. Defendants deny the allegations in Paragraph 310 of the Complaint.

311. Defendants deny the allegations in Paragraph 311 of the Complaint.

312. Defendants deny the allegations in Paragraph 312 of the Complaint.

313. Defendants deny the allegations in Paragraph 313 of the Complaint.

RESPONSE TO PRAYER FOR RELIEF

The remainder of the Complaint recites a prayer for relief to which no response is required. To the extent any response is required, Defendants deny that the Government is entitled to any remedy or relief.

AFFIRMATIVE DEFENSES

Without any admission as to the burden of proof, burden of persuasion, or truth of any allegation in the Complaint, Defendants assert the following defenses:

**FIRST AFFIRMATIVE DEFENSE
(FAILURE TO STATE A CLAIM FOR RELIEF)**

1. Plaintiff's Complaint fails to state a claim upon which relief can be granted. To the extent Plaintiff's Complaint states any claim as to GSI, it fails to state a claim upon which relief can be granted as to GSIUC.

**SECOND AFFIRMATIVE DEFENSE
(NON-INFRINGEMENT)**

2. Defendants do not infringe and have not infringed (either directly, contributorily, or by inducement) any valid and enforceable claim of the '509, '333, '191, or '423 Patents, either literally or under the doctrine of equivalents.

**THIRD AFFIRMATIVE DEFENSE
(INVALIDITY)**

3. One or more claims of the '509, '333, '191, and '423 Patents are invalid for failure to satisfy one or more requirements of patentability under 35 U.S.C. § 101 *et seq.*, including without limitation §§ 101, 102, 103, 112, and/or any judicially created doctrine of invalidity, including obviousness-type double patenting.

**FOURTH AFFIRMATIVE DEFENSE
(UNCLEAN HANDS)**

4. The claims of the Patents-in-Suit are unenforceable against Defendants because of the equitable doctrine of unclean hands.

~~5. For example, the Government breached its obligations under at least four Material Transfer Agreements by failing to provide GSI with prompt notice of the alleged inventions or the patent applications that resulted in the Patents-in-Suit. Due to the Government's failure to provide prompt notice to GSI, Defendants were denied the opportunity to make the Government aware of~~

~~pertinent prior art that was not presented during the examination of one or more of the Patents-in-Suit, or to indicate the role of GSI scientists in the work that led to the alleged inventions.~~

~~5.~~ ~~6. Furthermore~~ For example, the Government has ~~also~~ demonstrated unclean hands through its encouragement of both the public use and the prescription of Truvada[®] for PrEP purposes—including in CDC guidelines published even before the Truvada[®] PrEP indication had been approved by the FDA in 2012. For example, the CDC’s January 28, 2011 guidelines—issued more than one year before the FDA’s approval of the PrEP indication for Truvada[®]—identified “[p]rescrib[ing] 1 tablet of Truvada[®] (TDF [300 mg] plus FTC [200 mg]) daily” as part of “[b]eginning [a] PrEP medication regimen.” Ex. A (January 28, 2011 Interim Guidance) at 68. Furthermore, the Government requested that GSI provide TDF/FTC for use in preclinical and clinical studies concerning PrEP, and the Government (including the FDA) actively encouraged GSI to seek FDA approval for the PrEP indication for Truvada[®]. The Government’s promotion of the use of Truvada[®] for the indication that it now alleges infringes the Patents-in-Suit bars the Government under the doctrine of unclean hands from recovering royalties on sales of Truvada[®].

~~FIFTH AFFIRMATIVE DEFENSE~~ **~~(INEQUITABLE CONDUCT)~~**

~~7. The claims of the Patents-in-Suit are unenforceable because of the doctrine of inequitable conduct, as detailed in the factual allegations in paragraphs 52-73 of GSI’s Counterclaims below, which are expressly incorporated by reference here.~~

~~SIXTH AFFIRMATIVE DEFENSE~~ **~~(DERIVATION)~~**

~~8. The Patents-in-Suit are invalid because the alleged invention(s) were derived and/or misappropriated from the true inventor(s).~~

~~**SEVENTH AFFIRMATIVE DEFENSE
(SAFE HARBOR)**~~

~~9. Defendants are exempt from liability under the safe harbor of 35 U.S.C. § 271(e)(1), at least to the extent the Government claims that uses related to the clinical trials to obtain FDA approval of Descovy[®] for PrEP are acts of infringement.~~

~~**EIGHTH AFFIRMATIVE DEFENSE
(ACQUIESCENCE AND/OR ESTOPPEL)**~~

~~10. The Government's Complaint, and each of its purported causes of action, is barred in whole or in part by the doctrines of acquiescence and/or estoppel.~~

~~11. As set forth above, the Government has encouraged both the public use and the prescription of Truvada[®] for PrEP purposes—including in CDC guidelines published even before the PrEP indication had been approved by the FDA in 2012. For example, the CDC's January 28, 2011 guidelines—issued more than one year before the FDA's approval of the PrEP indication for Truvada[®]—identified “[p]rescrib[ing] 1 tablet of Truvada[®] (TDF [300 mg] plus FTC [200 mg]) daily” as part of “[b]eginning [a] PrEP medication regimen.” Ex. A (January 28, 2011 Interim Guidance) at 68. Furthermore, the Government requested that GSI provide TDF/FTC for use in preclinical and clinical studies concerning PrEP, and the Government actively encouraged GSI to seek FDA approval for the PrEP indication for Truvada[®]. The Government's promotion of the use of Truvada[®] for the indication that it now alleges infringes the Patents-in-Suit indicates that its Complaint, and each of its purported causes of action, is barred in whole or in part by the of acquiescence and/or estoppel.~~

~~**NINTH AFFIRMATIVE DEFENSE
(NO WILLFULNESS)**~~

~~12. Defendants have not willfully infringed any claim of the Patents-in-Suit.~~

~~**TENTH AFFIRMATIVE DEFENSE
(NO EXCEPTIONAL CASE)**~~

~~13. Defendants' actions in defending this case do not give rise to an exceptional case under 35 U.S.C. § 285.~~

~~**ELEVENTH AFFIRMATIVE DEFENSE
(NO RECOVERY OF COSTS)**~~

~~14. The Government is barred by 35 U.S.C. § 288 from recovering any costs associated with this action.~~

~~**TWELFTH AFFIRMATIVE DEFENSE
(FAILURE TO MITIGATE)**~~

~~15. The Government has failed to mitigate the harm it claims to have sustained, if any.~~

~~**THIRTEENTH AFFIRMATIVE DEFENSE
(NO STANDING)**~~

~~16. The Government lacks standing to assert one or more of the Patents in Suit.~~

~~**FOURTEENTH AFFIRMATIVE DEFENSE
(NO CONSTITUTIONAL AUTHORITY)**~~

~~17. The Government lacks authority under the United States Constitution, including the Intellectual Property Clause thereof (art. I, § 8, cl. 8), to own or assert the four Patents in Suit.~~

~~**RESERVATION OF DEFENSES**~~

~~As Defendants' investigation is ongoing and discovery has not yet been completed, Defendants are without complete information regarding the existence or non-existence of other facts or acts that would constitute a defense to the purported causes of action in the Government's Complaint. Accordingly, Defendants reserve the right to assert any other defenses that discovery may reveal.~~

Furthermore, the Government has demonstrated unclean hands because it breached its obligations under at least four Material Transfer Agreements by failing to provide GSI with prompt notice of the alleged inventions or the patent applications that resulted in the Patents-in-Suit. Had the Government performed its contractual obligation under those agreements to promptly notify GSI of the purported invention(s) described in the applications that led to the HHS Patents, GSI would have had the opportunity to consider its options, including providing CDC and/or the PTO with information showing why any such patent would be invalid.. Furthermore, the Government has demonstrated unclean hands because its applications for the HHS Patents violated the clear terms of a Clinical Trial Agreement with GSI. That agreement expressly provided that “CDC agrees not to seek patent protection in connection with any inventions that derive from the use of the Study Drug” in a clinical trial that, on information and belief, formed the basis for the Government’s decisions concerning the prosecution of the applications leading to the HHS Patents.

COUNTERCLAIMS

~~Without admitting any of the Government’s allegations other than those expressly admitted herein, and without prejudice of the rights of Defendant/Counterclaim Plaintiff Gilead Sciences, Inc. (“GSI”) to plead additional Counterclaims as the facts of the matter warrant, Defendant/Counterclaim Plaintiff GSI hereby asserts the following Counterclaims against the Government. Defendants contend that Defendant Gilead Sciences Ireland UC is not a proper party to this action; however, if Gilead Sciences Ireland UC is deemed to be a proper party or otherwise remains in this action, Gilead Sciences Ireland UC reserves the right to bring or seek to bring counterclaims on its own behalf at a later stage in the case.~~

~~Defendant/Counterclaim Plaintiff GSI incorporates herein by reference the admissions, allegations, denials, and Affirmative Defenses contained in the Answer above as if fully set forth~~

~~herein. For its Counterclaims against the Government, Defendant/Counterclaim Plaintiff GSI states as follows:~~

~~THE PARTIES~~

~~1. Counterclaim Plaintiff Gilead Sciences, Inc. (“GSI”) is a corporation organized under the laws of the State of Delaware, having its principal place of business at 333 Lakeside Drive, Foster City, California 94404.~~

~~2. Counterclaim Defendant alleges in its Complaint that it is acting on behalf of the Department of Health and Human Services (HHS) and is headquartered at 200 Independence Avenue, S.W., Washington, D.C. 20201.~~

~~JURISDICTION & VENUE~~

~~3. Defendant/Counterclaim Plaintiff GSI brings these **counterclaims** under the Patent Laws of the United States, 35 U.S.C. §§ 1 *et seq.*, for a declaratory judgment pursuant to 28 U.S.C. §§ 2201-2202 that U.S. Patent Nos. 9,044,509 (the “’509 Patent”), 9,579,333 (the “’333 Patent”), 9,937,191 (the “’191 Patent”), and 10,335,423 (the “’423 Patent”) (collectively, the “HHS Patents”) have not been infringed and are not being infringed by Defendant/Counterclaim Plaintiff GSI, that the HHS Patents are invalid, and that the HHS Patents are unenforceable.~~

~~4. This Court has subject matter jurisdiction over Defendant’s Counterclaims under 28 U.S.C. §§ 1331 and 1338.~~

~~5. This Court has personal jurisdiction over Plaintiff/Counterclaim Defendant. Plaintiff/Counterclaim Defendant has subjected itself to personal jurisdiction by maintaining its lawsuit against Defendant/Counterclaim Plaintiff GSI in this District.~~

~~6. Venue in this case is proper in this District by virtue of the Government's filing of the Complaint in this District, which gave rise to these Counterclaims. The Government contends in its Complaint that venue is proper in this District.~~

~~THE HHS PATENTS~~

~~7. The '509 Patent, titled "Inhibition of HIV Infection through Chemoprophylaxis," issued on June 2, 2015. The Government alleges that it owns the '509 Patent. The earliest possible priority date for the '509 Patent is February 3, 2006. The Government alleges that the '509 Patent expires on May 12, 2031.~~

~~8. The '333 Patent, titled "Inhibition of HIV Infection through Chemoprophylaxis," issued on February 28, 2017. The Government alleges that it owns the '333 Patent. The earliest possible priority date for the '333 Patent is February 3, 2006. The Government alleges that the '333 Patent expires on January 31, 2027.~~

~~9. The '191 Patent, titled "Inhibition of HIV Infection through Chemoprophylaxis," issued on April 10, 2018. The Government alleges that it owns the '191 Patent. The earliest possible priority date for the '191 Patent is February 3, 2006. The Government alleges that the '191 Patent expires on January 31, 2027.~~

~~10. The '423 Patent, titled "Inhibition of HIV Infection through Chemoprophylaxis," issued on July 2, 2019. The Government alleges that it owns the '423 Patent. The earliest possible priority date for the '423 Patent is February 3, 2006. The Government alleges that the '423 Patent expires on January 31, 2027.~~

~~FACTUAL BACKGROUND~~

~~11. GSI is the holder of New Drug Application ("NDA") No. 21-752, which relates to tablets containing emtricitabine ("FTC") and tenofovir disoproxil fumarate ("TDF"). On August~~

~~2, 2004, the United States Food and Drug Administration (“FDA”) approved the use of the tablets described in NDA No. 21-752 for the treatment of HIV-1 infection in adults. These tablets are prescribed and sold in the United States under the trademark Truvada[®]. Truvada[®] was originally available in one dosage form: 200 mg FTC and 300 mg TDF.~~

~~12. On July 16, 2012, FDA approved Truvada[®] for use in combination with safer sex practices for pre-exposure prophylaxis (“PrEP”) to reduce the risk of sexually acquired human immunodeficiency virus 1 (“HIV-1”) in adults at high risk. GSI promotes this indication under the trademark Truvada for PrEP[®]. Only the original dosage form of Truvada[®], 200 mg FTC and 300 mg TDF, is indicated for use in Truvada for PrEP[®].~~

~~13. GSI is also the holder of NDA No. 208215, which relates to tablets containing FTC and tenofovir alafenamide (“TAF”). On April 4, 2016, FDA approved the use of the tablets described in NDA No. 208215 for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age or older. These tablets are prescribed and sold in the United States under the trademark Descovy[®]. Descovy[®] is available in one dosage form: 200 mg FTC and 25 mg TAF.~~

~~14. On October 3, 2019, FDA approved Descovy[®] for use in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex, and provided that individuals must have a negative HIV-1 test immediately prior to initiating Descovy[®] for HIV-1 PrEP. GSI promotes this indication under the trademark Descovy for PrEP[®].~~

~~15. In its Complaint, the Government asserts that Defendants have induced infringement of certain claims of the HHS Patents by, among other things, selling Truvada[®] and instructing doctors and patients on how to administer Truvada[®] for PrEP. The Government further asserts that Defendants have induced infringement of certain claims of the ’509 Patent and the ’423 Patent~~

by, among other things, selling Descovy[®] and instructing doctors and patients on how to administer Descovy[®] for PrEP.

~~16. The HHS Patents are invalid and/or have not been and will not be infringed by Defendants, either directly or indirectly, literally or under the doctrine of equivalents.~~

~~17. The HHS Patents are also unenforceable against Defendants based on the doctrines of unclean hands and inequitable conduct.~~

~~I. The Material Transfer Agreements~~

6. ~~18. In 2005~~ Throughout its history and continuing through today, GSI has collaborated in good faith with CDC on various research studies relating to the use of antiretroviral agents for prevention of HIV-1. As part of these collaborations, Gilead scientists have shared their significant expertise in the field of HIV with CDC researchers, including by providing ideas and guidance, and Gilead has provided CDC with millions of dollars of pharmaceuticals—at no cost to CDC—to further the scientific community’s efforts to end the HIV epidemic. During these collaborations, GSI and the Government, acting through the ~~Centers for Disease Control and Prevention (“CDC”)~~, entered into at least four material transfer agreements related to the research that resulted in the alleged inventions described in the HHS Patents.

~~A. The ’072 MTA~~

7. ~~19.~~ On June 21, 2004, GSI and the Government, acting through the ~~Centers for Disease Control and Prevention (“CDC”)~~, entered into a material transfer agreement bearing CDC Reference Number NCHSTP-V043072 (the “’072 MTA,” Ex. B).

8. ~~20.~~ Under the ’072 MTA, GSI provided significant quantities of two GSI drugs, tenofovir (“TFV”) and TDF, to CDC at no cost to be used in HIV-1 research conducted at CDC. Specifically, GSI provided the material to be used by CDC in a study that generally involved

administering TDF to male Rhesus macaques either daily or weekly and exposing the macaques to simian-human immunodeficiency virus (“SHIV”), a relative of HIV-1, either weekly or shortly after the treatment dose via a low-dose rectal challenge model. The MTA also discussed an in vitro study using tenofovir.

9. ~~21.~~ In exchange for the drugs that GSI supplied under the ’072 MTA, among other things, CDC “agree[d] to promptly notify” GSI of “any Inventions” under the ’072 MTA, which the ’072 MTA defined as “any inventions, discoveries and ideas that are made, conceived or reduced to practice.” Ex. B (’072 MTA) § 8. The U.S. Public Health Service (“PHS”) likewise agreed “to give serious and reasonable consideration to [GSI’s] request for a non-exclusive or exclusive license on commercially reasonable terms under PHS’s intellectual property rights in or to any Inventions.” *Id.*

10. ~~22.~~ GSI performed its obligations under the ’072 MTA and delivered the TFV and TDF to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

11. ~~23.~~ On or around January 24, 2005, GSI and CDC executed an amendment to the ’072 MTA whereby GSI would supply CDC with additional ~~TFV~~TDF at no cost.

12. ~~24.~~ GSI performed its obligations under the amendment to the ’072 MTA and delivered the ~~TFV~~TDF to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

~~B. The ’433 MTA~~

13. ~~25.~~ On January 7, 2005, GSI and the Government, acting through CDC, entered into a material transfer agreement bearing CDC Reference Number NCHSTP-V053433-~~00~~ (the “’433 MTA,” Ex. C).

14. ~~26.~~ Under the '433 MTA, GSI provided significant quantities of a GSI drug, TFV, to CDC at no cost to be used in HIV-1 research conducted at CDC. Specifically, GSI provided the material to be used by CDC in a study that generally involved “determin[ing] the effective concentration [of TFV] in mucosal tissues to prevent HIV-1/SHIV infection.” Ex. C ('433 MTA) at 7. The '433 MTA expressly stated that the information generated from the study would “be used ... in conjunction with [CDC’s] PrEP work being conducted in non-human primates.” *Id.*

15. ~~27.~~ The '433 MTA identified Thomas Folks as a co-investigator of the study described in the '433 MTA. Ex. C ('433 MTA) at 5. Thomas Folks is one of the individuals identified as an inventor on the face of the HHS Patents.

16. ~~28.~~ In exchange for the drugs that GSI supplied under the '433 MTA, among other things, CDC “agree[d] to promptly notify” GSI of “any Inventions” under the '433 MTA, which the '433 MTA defined as “any inventions, discoveries and ideas that are made, conceived or reduced to practice.” Ex. C ('433 MTA) § 8. PHS likewise agreed “to give serious and reasonable consideration to [GSI’s] request for a non-exclusive or exclusive license on commercially reasonable terms under PHS’s intellectual property rights in or to any Inventions.” *Id.*

17. ~~29.~~ GSI performed its obligations under the '433 MTA and delivered the TFV to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

~~C. The '471 MTA~~

18. ~~30.~~ On January 31, 2005, GSI and the Government, acting through CDC, entered into a material transfer agreement bearing CDC Reference Number NCHSTP-V053471 (the “'471 MTA,” Ex. D).

19. ~~31.~~ Under the '471 MTA, GSI provided significant quantities of a GSI drug, FTC, to CDC at no cost to be used in HIV-1 research conducted at CDC. Specifically, GSI provided the material to be used by CDC in a study that generally involved administering a combination consisting of TFV and FTC to female Rhesus macaques daily and exposing the macaques to SHIV weekly via a low-dose vaginal challenge model.

20. ~~32.~~ In exchange for the drugs that GSI supplied under the '471 MTA, among other things, CDC “agree[d] to promptly notify” GSI of “any Inventions” under the '471 MTA, which the '471 MTA defined as “any inventions, discoveries and ideas that are made, conceived or reduced to practice.” Ex. D ('471 MTA) § 8. PHS likewise agreed “to give serious and reasonable consideration to [GSI’s] request for a non-exclusive or exclusive license on commercially reasonable terms under PHS’s intellectual property rights in or to any Inventions.” *Id.*

21. ~~33.~~ GSI performed its obligations under the '471 MTA and delivered the FTC to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

22. ~~34.~~ On information and belief, in or around February 2006, GSI and CDC executed a first amendment to the '471 MTA whereby GSI would supply CDC with additional FTC at no cost.

23. ~~35.~~ GSI performed its obligations under the first amendment to the '471 MTA and delivered the FTC to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

24. ~~36.~~ On or about March 6, 2006, GSI and CDC executed a second amendment to the '471 MTA whereby GSI would supply CDC with additional TDF at no cost.

25. ~~37.~~ GSI performed its obligations under the second amendment to the '471 MTA and delivered the TDF to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

~~D. The '649 MTA~~

26. ~~38.~~ On April 25, 2005, GSI and the Government, acting through CDC, entered into a material transfer agreement bearing CDC Reference Number NCHSTP-V053649 (the "'649 MTA," Ex. E).

27. ~~39.~~ Under the '649 MTA, GSI provided significant quantities of a GSI drug, TFV (which was described in the '649 MTA by its alternative names, PMPA and (*R*)-9-(2-phosphonylmethoxypropyl)adenine), to CDC at no cost to be used in HIV-1 research conducted at CDC. Specifically, GSI provided the material to be used by CDC in a study that involved, among other things, administering a combination consisting of TFV and FTC to Rhesus macaques and exposing the macaques to SHIV via a low-dose rectal challenge model.

28. ~~40.~~ In exchange for the drugs that GSI supplied under the '649 MTA, among other things, CDC "agree[d] to promptly notify" GSI of "any Inventions" under the '649 MTA, which the '649 MTA defined as "any inventions, discoveries and ideas that are made, conceived or reduced to practice." Ex. E ('649 MTA) § 8. PHS likewise agreed "to give serious and reasonable consideration to [GSI's] request for a non-exclusive or exclusive license on commercially reasonable terms under PHS's intellectual property rights in or to any Inventions." *Id.*

29. ~~41.~~ GSI performed its obligations under the '649 MTA and delivered the FTV to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

30. ~~42.~~ Between April 30, 2008, and August 4, 2014, GSI and CDC executed five amendments to the '649 MTA whereby GSI would supply CDC with additional medication at no cost.

31. ~~43.~~ GSI performed its obligations under the amendments to the '649 MTA and delivered the medication to CDC in a timely manner. On information and belief, CDC used these GSI-provided materials in the course of its HIV research.

~~E. The Government's Breach of the MTAs~~

32. ~~44.~~ On February 3, 2006, CDC filed U.S. Provisional Patent Application No. 60/764,811 (the "'811 Provisional," Ex. F), with the U.S. Patent and Trademark Office ("PTO") related to purported inventions that CDC made in the course of the research conducted under the '072 MTA, '433 MTA, the '471 MTA, and/or the '649 MTA (collectively, the "MTAs") and using the medications that GSI provided under the MTAs. On January 31, 2007, CDC filed U.S. non-provisional patent Application No. 11/669,547 (the "'547 Application," Ex. G), claiming priority to the '811 Provisional. The '509 Patent issued from the '547 Application on June 2, 2015, and the remaining HHS Patents have since issued and claim priority to the same provisional and non-provisional applications. On information and belief, the HHS Patents are owned by the Government, represented by the U.S. Department of Health and Human Services ("HHS").

33. ~~45.~~ The '811 Provisional described the results of a study in which a group of six Rhesus macaques were injected subcutaneously with 22 mg/kg TFV and 20 mg/kg FTC, which is another GSI drug, once daily. Ex. F ('811 Provisional) at 6. The macaques were also subjected to weekly rectal exposures with a low dose of SHIV. The study found that the subcutaneous TFV/FTC combination provides a high level of protection against repeated virus challenges; the authors therefore concluded that "chemoprophylaxis with potent antiretrovirals is

an effective strategy for preventing sexual HIV transmission.” *Id.* A presentation slide submitted as part of the ’811 Provisional reported that “Macaque models show that tenofovir [alone] can provide substantial protection against ... mucosal virus exposures,” like the rectal exposures used in the study. *Id.* at 8. On information and belief, the studies reported in the ’811 Provisional were performed by CDC researchers.

34. ~~46.~~ The ’547 Application disclosed several studies in the originally filed version of its specification. In one of those studies, a group of six macaques were given oral doses of a combination of TDF (22 mg/kg) and FTC (20 mg/kg) once daily. The macaques were also subjected to weekly rectal exposures with a low dose of SHIV. The study found that the oral TDF/FTC combination reduced infection in these macaques 7.8-fold versus an untreated control group. Ex. G (’547 Application) at [0040]-[0042].

35. ~~47.~~ On information and belief, the alleged discoveries and ideas and any purported inventions disclosed in the ’811 Provisional and/or the ’547 Application were made, conceived, or reduced to practice as a result of the studies described in the MTAs—*i.e.*, the studies for which GSI provided significant quantities of its proprietary drugs to CDC free of charge. *See, e.g.*, Compl. ¶ 121 (“The earliest MTA ***related to the research leading to the Patents-in-Suit*** was signed in December 2004 by Dr. Heneine, and later by Dr. Mick Hitchcock, Gilead’s then Vice President of Medical Affairs, in response to Dr. Heneine’s email request for a transfer of FTC to CDC.” (emphasis added)); *id.* ¶ 120 (“Under several MTAs with CDC, signed during the period from 2004 to 2008, Gilead provided the FTC, TDF, and tenofovir used in CDC’s research.”); *id.* ¶ 122 (“Ultimately, several additional MTAs were signed relating to transfers of drugs used in CDC’s patented research.”).

36. Furthermore, GSI and the Government, acting through CDC, also entered into a Clinical Trial Agreement (“CTA”) with an effective date of November 18, 2004. Ex. S. This agreement set forth the terms under which GSI would provide antiviral products free of charge for a clinical trial about HIV prevention in Botswana. The Government agreed, among other things, “to put the results of the Trial, patentable or otherwise, in the public domain for all to use without obligation or compensation to CDC.” “For clarity,” the CTA provided, “CDC agrees not to seek patent protection in connection with any inventions that derive from the use of the Study Drug in the Trial.” In compliance with its obligations under the CTA, GSI provided to CDC compounds and placebos at no cost. On information and belief, CDC utilized the compounds that GSI provided in the Botswana trial contemplated by the CTA. On information and belief, CDC relied on information derived from the Botswana clinical trial to make decisions concerning the prosecution of the ’547 Application.

37. ~~48.~~ In spite of the express terms of the MTAs requiring CDC failed to “promptly notify ~~GSI of~~” Gilead of any claimed “Inventions” arising out of the research conducted under the MTAs and the clear term of the CTA expressly providing that “CDC agrees not to seek patent protection in connection with any inventions that derive from the use of the Study Drug in the Trial,” CDC not only filed patent applications seeking patent protection for purported “Inventions” derived from the use of the compounds Gilead supplied under the MTAs and CTA, but also failed to disclose to Gilead the purported invention(s) ~~described~~ claimed in the ’811 Provisional, the ’547 Application, and in the later applications that resulted in the HHS Patents. Instead, CDC and the Government waited several years—until October 2014 at the earliest—to provide the contractually required notice to GSI, and another two years, until March 11, 2016, to

assert that Gilead required a license under the HHS Patents in order to continue marketing Truvada® for PrEP.

38. ~~49.~~ In the interim, in 2012, and with the encouragement and support of ~~CDC~~the Government (including the FDA), GSI obtained approval from the FDA to market Truvada®, which contains TDF and FTC—the medications that GSI provided to CDC under the MTAs—for HIV-1 PrEP. ~~Had CDC fulfilled its contractual obligations to promptly notify~~ By the time that the Government first communicated with GSI of ~~concerning~~ the purported invention(s) described in the '811 Provisional ~~and in the applications that resulted in the HHS Patents in or around 2006, GSI would have identified invalidating prior art and/or have indicated the role of GSI scientists in the work that led to the alleged inventions.~~ or the '547 Application in October 2014, GSI had already invested substantial amounts in educating at-risk patient populations about the potential benefits of Truvada® for PrEP, and some of those at-risk patient populations had already come to rely on Truvada® for prophylaxis to attempt to minimize their potential for contracting HIV-1.

39. ~~Had CDC fulfilled its contractual obligations to promptly notify GSI of the purported invention(s) described in the '811 Provisional and in the applications that resulted in the HHS Patents, GSI would have had the opportunity to consider its options, including providing CDC and/or the PTO with information showing why any such patent would be invalid.~~

40. ~~50.~~ Even after 2006, because of the Government's continuing failure to promptly notify GSI of the purported invention(s) described in the '811 Provisional, the '547 Application, and in the later applications that resulted in the HHS Patents, GSI was further denied the opportunity to ~~make the Government aware of pertinent prior art that was not presented during the examination of one or more of the HHS Patents and to indicate~~ consider its options, including:

providing CDC and/or the PTO with information showing why any such patent would be invalid;
changing its application for FDA approval to market Truvada® for PrEP; or indicating the role of GSI scientists in the work that led to the alleged inventions before developing and marketing Truvada® for PrEP and Descovy® for PrEP.

41. ~~51.~~ Because the Government failed to fulfill its contractual obligations to GSI under the MTAs and the CTA, the Government brings its infringement claims against GSI with unclean hands; ~~as a result, Counterclaim Plaintiff GSI is entitled to a declaration that,~~ and the HHS ~~Patents~~ patents are therefore unenforceable against ~~it~~ Defendants.

~~**H. The Government's Failure to Disclose Material Information During Prosecution of the HHS Patents**~~

FIFTH AFFIRMATIVE DEFENSE
(INEQUITABLE CONDUCT)

42. The claims of the Patents-in-Suit are unenforceable because of the doctrine of inequitable conduct.

43. ~~52. During~~ Specifically, during prosecution of the HHS Patents, the Government ~~also~~ failed to provide material information to the Patent Office relating to the inventiveness of the claimed inventions. On information and belief, these omissions were knowing and willful, made with an intent to deceive the Patent Office.

44. ~~53.~~ On August 21, 2019, GSI filed a Petition for *Inter Partes* Review of claims 1-18 of the '509 Patent before the Patent Trial and Appeal Board, *see* Ex. H, Petition, Case No. IPR2019-01453 (P.T.A.B. Aug. 21, 2019), and a Petition for *Inter Partes* Review of claims 1-17 of the '333 Patent before the Patent Trial and Appeal Board, *see* Ex. I, Petition, Case No. IPR2019-01454 (P.T.A.B. Aug. 21, 2019) (the "IPR Petitions"). These Petitions are incorporated by reference into these ~~Counterclaims~~ affirmative defenses as if fully set forth herein.

45. ~~54.~~ Among the prior art asserted in the IPR Petitions were the CDC’s own Post-Exposure Prophylaxis guidelines (“CDC-PEP,” Ex. J), which were published and made available to the public on January 21, 2005, in Volume 54, No. RR-2 of the CDC periodical *Morbidity and Mortality Weekly Report Recommendations and Reports* (MMWR-RR). The CDC-PEP publication identified five authors affiliated with the CDC (including the first named author, Dr. Dawn K. Smith), as well as three authors affiliated with the National Institutes of Health, one author affiliated with the FDA, and two authors affiliated with the Health Resources and Services Administration. Ex. J (CDC-PEP) at 1. Furthermore, two of the named inventors of the four HHS Patents, Robert Janssen and Ronald Otten, were identified as “federal consultants” for the CDC-PEP guidelines. *Id.* at 20.

46. ~~55.~~ CDC-PEP describes a regimen of daily administrations of combinations of antiretroviral agents for an extended period following an HIV exposure to prevent an HIV infection. CDC-PEP identifies TDF+FTC as one of two “preferred” backbone combinations to use in post-exposure prophylaxis (“PEP”), and notes that Truvada[®] is an oral formulation containing 300 mg of TDF and 200 mg of FTC. Ex. J (CDC-PEP) at 8, 9 tbl.2, 10.

47. ~~56.~~ The January 21, 2005 publication date of CDC-PEP preceded the critical date of February 3, 2005—one year before the earliest priority date claimed by the ’509 Patent or ’333 Patent. Therefore, CDC-PEP constitutes prior art to both the ’509 Patent and ’333 Patent under 35 U.S.C. § 102(b).

48. ~~57.~~ By virtue of the CDC’s publication of CDC-PEP, that document was in the CDC’s possession prior to the CDC’s filing of the ’811 Provisional on February 3, 2006, or the filing of the ’547 Application on January 31, 2007—the applications that together led to the issuance of each of the HHS Patents, including the ’509 Patent and ’333 Patent.

49. ~~58.~~ On information and belief, the Government was aware of the CDC-PEP reference during the prosecution of the '509 Patent and '333 Patent, including by virtue of its possession and publication of that reference on or before January 21, 2005. As evidence thereof, and as noted above, two of the named inventors of the four HHS Patents, Robert Janssen and Ronald Otten, were identified as “federal consultants” for the CDC-PEP guidelines and were therefore aware of that document and the findings therein.

50. ~~59.~~ However, during prosecution of the '509 Patent and '333 Patent, the Government did not disclose the CDC-PEP reference to the Patent Office, notwithstanding the duty to disclose material prior art, and notwithstanding the named inventors' oaths concerning inventorship. Nor did the examiner consider that reference during her evaluation of the applications leading to issuance of those patents.

51. ~~60.~~ As set forth in the IPR Petitions, which are incorporated herein by reference, claims 12-18 of the '509 Patent and claims 12-17 of the '333 Patent are anticipated by the CDC-PEP reference under 35 U.S.C. § 102(b). Similarly, and as set forth in the aforementioned IPR Petitions, the prior art—including CDC-PEP—also renders all challenged claims of the '509 Patent and '333 Patent obvious under 35 U.S.C. § 103.

52. ~~61.~~ Unlike claim 1 of the '509 Patent, which specifies administration “prior to an exposure” to an immunodeficiency retrovirus, claim 12 and dependent claims 14-18 of the '509 Patent did not specify administration prior to an actual or potential exposure.

53. ~~62.~~ Unlike claim 1 of the '333 Patent, which specifies administration “prior to the exposure” to an immunodeficiency retrovirus, claim 12 and dependent claims 14-17 of the '333 Patent did not specify administration prior to an actual or potential exposure.

54. ~~63.~~ On December 2, 2019—after GSI filed its Petition in Case No. IPR2019-01453—the Government disclaimed claims 12 and 14-18 of the ’509 Patent. Ex. K (Disclaimer in Patent Under 37 C.F.R. § 1.321(a), U.S. Patent No. 9,044,509).

55. ~~64.~~ Likewise, on December 2, 2019, after GSI filed its Petition in Case No. IPR2019-01454, the Government disclaimed claims 12 and 14-17 of the ’333 Patent. Ex. L (Disclaimer in Patent Under 37 C.F.R. § 1.321(a), U.S. Patent No. 9,579,333).

56. ~~65.~~ On information and belief, the Government’s disclaimer of claims 12 and 14-18 of the ’509 Patent and claims 12 and 14-17 of the ’333 Patent was prompted by its recognition that CDC-PEP anticipated each of these claims.

57. ~~66.~~ The Government also did not disclose the CDC-PEP reference in its original filings on January 13, 2017 for Application No. 15,406,344, which later issued as the ’191 Patent. Application No. 15,406,344, as originally filed, include at least one independent claim directed to the use of FTC and TFV or a TFV prodrug for PEP (original claim 12), but the Government failed to disclose CDC-PEP with its January 2017 filing. *See* Ex. M (Application No. 15406344, filed Jan. 13, 2017) at 23 (claim 12); *id.* at 32-36 (initial Information Disclosure Statement). The Government eventually disclosed CDC-PEP to the examiner during that prosecution on March 7, 2017, but did not alert the examiner to its materiality. *See* Ex. N (subsequent Information Disclosure Statement, filed March 7, 2017). The examiner subsequently relied upon CDC-PEP in issuing a non-final rejection of claims 1-19 for obviousness under 35 U.S.C. § 103(a). Ex. O (Aug. 8, 2017 Non-Final Rejection) at 4-5, ¶¶ 5-10 (relying on “Smith et al.,” *i.e.*, CDC-PEP). Rather than overcome that rejection directly, the Government canceled several claims, added several claims, and simply amended the remaining claims “to correspond with the claims of U.S. Patent No. 9,044,509.” Ex. P (Amendment and

Response) at 7. The amended claims included independent claim 12 (issued as claim 13), to which the Government included the limitation that the claimed combination must be “administered prior to a potential exposure of the human to the human immunodeficiency retrovirus.” *Id.* at 3.

58. ~~67.~~ On information and belief, the Government’s failure to disclose the CDC-PEP reference materially affected the prosecution of the ’509 and ’333 Patents because at least some claims of those patents would not have been allowed if the CDC-PEP reference had been disclosed during prosecution. This materiality is evidenced by the fact that CDC-PEP anticipates and/or renders obvious all claims of the ’509 and ’333 Patents, including for the reasons set forth in GSI’s IPR Petitions relating to those patents, which are incorporated by reference into these ~~Counterclaims~~affirmative defenses as if set forth fully herein. *See* Ex. H, Petition, Case No. IPR2019-01453 (P.T.A.B. Aug. 21, 2019) (’509 Patent); Ex. I, Petition, Case No. IPR2019-01454 (P.T.A.B. Aug. 21, 2019) (’333 Patent). This materiality is also evidenced by the Government’s subsequent disclaimer of claims 12 and 14-18 of the ’509 Patent and claims 12 and 14-17 of the ’333 Patent after the CDC-PEP was asserted as prior art in GSI’s IPR Petitions.

59. ~~68.~~ Furthermore, the materiality of the CDC-PEP reference is also supported by the record in the subsequent prosecution of the ’191 Patent. After the Government’s belated disclosure of CDC-PEP during the prosecution of the ’191 Patent, the examiner rejected claims in reliance on that reference, noting that CDC-PEP disclosed the use of Truvada® for PEP purposes and that it would have been obvious to treat uninfected individuals “who are exposed to or at risk of exposure to HIV” with Truvada®. Ex. O (Aug. 8, 2017 Non-Final Rejection) at 5-6, ¶ 9. This rejection prompted an amendment to include an explicit limitation confining claim 12 (allowed as claim 13) to pre-exposure administration. Ex. P (Amendment and Response) at 3.

60. ~~69.~~ Furthermore, individuals with a duty to disclose material information during prosecution—including the named inventors and prosecuting attorneys—failed to disclose the CDC-PEP reference to the examiner during prosecution of the '509 and '333 Patents. On information and belief, at least some of these individuals failed to disclose this reference despite knowing of that reference and its materiality. On information and belief, the withholding of the CDC-PEP reference by those individuals was done with the intent to deceive the Patent Office. This intent is supported by the but-for materiality of the CDC-PEP reference to the prosecution of the '509 and '333 Patents; the individuals' possession and knowledge of that reference, including based on the involvement of at least two of the named inventors, Robert Janssen and Ronald Otten; and the individuals' knowledge of that reference's materiality to the inventiveness of the pending claims. The individuals' knowledge and intent is further supported by the Government's subsequent, belated disclosure of this reference during its prosecution of the '191 Patent.

61. ~~70.~~ The Government's failure to disclose the CDC-PEP reference during the prosecution of the '509 and '333 Patents constitutes inequitable conduct, rendering all claims of the '509 Patent and '333 Patent unenforceable.

62. ~~71.~~ The Government's inequitable conduct during the prosecution of the '509 and '333 Patents also constitutes inequitable conduct with respect to the '191 and '423 Patents, which are continuations of the '509 and '333 Patents. As confirmed by the examiner's findings during prosecution, as well as the Government's terminal disclaimers, the allowed claims of the '191 and '423 Patents are not patentably distinct from those of the '509 and '333 Patents. Furthermore, in allowing the claims of the '191 and '429 Patents, the examiner relied substantially on the previous allowance of the claims of the '509 and '333 Patents.

63. ~~72.~~ During the prosecution of the '191 and '423 Patents, the Government did not cure its earlier inequitable conduct. The Government did not disclose the CDC-PEP reference with the initial application for the '191 Patent and disclosed it only later during prosecution. *Compare* Ex. M at 32-36 (initial Information Disclosure Statement for '191 application), *with* Ex. N (subsequent Information Disclosure Statement, filed March 7, 2017). During the prosecution of the '191 and '423 Patents, the Government provided only a bare disclosure of CDC-PEP and did not alert the examiner to the materiality of the CDC-PEP reference. When the examiner relied on her prior allowance of the claims of the '509 Patent to support the patentability of the '191 and '423 Patents, *see, e.g.*, Ex. Q ('191 Notice of Allowance) at 2, ¶ 5, and found the claims of the '191 Patent to be “not patentably distinct” from those in the '509 or '333 Patents, Ex. O (Aug. 8, 2017 Non-Final Rejection) at 3, ¶¶ 2-3, the Government did not alert the examiner to the fact that the Government had not disclosed the material CDC-PEP reference during the prosecution of the '509 and '333 Patents. On the contrary, in amending the claims for the '191 Patent, the Government noted that its amendments were made “to correspond to with the claims of U.S. Patent No. 9,044,509.” Ex. P (Amendment and Response) at 7. Similarly, after the examiner noted that the claims of the '423 Patent were “not patentably distinct” from those in the parent applications and were “allowable over prior art for reasons as set forth in [the] parent applications,” Ex. R (Jan. 23, 2019 Non-Final Rejection) at 3-4, ¶¶ 3-5, the Government did not alert the examiner to the fact that the CDC-PEP reference was not disclosed during the prosecution of the '509 or '333 Patents.

64. ~~73.~~ The Government's subsequent disclaimer of claims 12 and 14-18 of the '509 Patent and claims 12 and 14-17 of the '333 Patent cannot cure its inequitable conduct during prosecution. The Government's subsequent disclosure of the CDC-PEP reference during

prosecution of the '191 and '423 Patents also cannot cure its inequitable conduct with respect to any of the HHS Patents.

SIXTH AFFIRMATIVE DEFENSE
(DERIVATION)

65. The Patents-in-Suit are invalid because the alleged invention(s) were derived and/or misappropriated from the true inventor(s).

SEVENTH AFFIRMATIVE DEFENSE
(SAFE HARBOR)

66. Defendants are exempt from liability under the safe harbor of 35 U.S.C. § 271(e)(1), at least to the extent the Government claims that uses related to the clinical trials to obtain FDA approval of Descovy[®] for PrEP are acts of infringement.

EIGHTH AFFIRMATIVE DEFENSE
(ACQUIESCENCE AND/OR ESTOPPEL)

67. The Government's Complaint, and each of its purported causes of action, is barred in whole or in part by the doctrines of acquiescence and/or estoppel.

68. As set forth above, the Government has encouraged both the public use and the prescription of Truvada[®] for PrEP purposes—including in CDC guidelines published even before the PrEP indication had been approved by the FDA in 2012. For example, the CDC's January 28, 2011 guidelines—issued more than one year before the FDA's approval of the PrEP indication for Truvada[®]—identified “[p]rescrib[ing] 1 tablet of Truvada[®] (TDF [300 mg] plus FTC [200 mg]) daily” as part of “[b]eginning [a] PrEP medication regimen.” Ex. A (January 28, 2011 Interim Guidance) at 68. Furthermore, the Government requested that GSI provide TDF/FTC for use in preclinical and clinical studies concerning PrEP, and the Government (including the FDA) actively encouraged GSI to seek FDA approval for the PrEP indication for Truvada[®]. The Government's promotion of the use of Truvada[®] for the indication that it now alleges infringes the Patents-in-

Suit indicates that its Complaint, and each of its purported causes of action, is barred in whole or in part by the of acquiescence and/or estoppel.

NINTH AFFIRMATIVE DEFENSE **(IMPLIED WAIVER)**

69. The Government's Complaint, and each of its purported causes of action, is barred in whole or in part by the equitable doctrine of implied waiver.

70. For example, the Government has demonstrated implied waiver by seeking patent protection for the use of Truvada® for PrEP purposes, failing to disclose to Defendants that the Government was seeking such patent protection, and encouraging GSI to market Truvada® for PrEP purposes.

71. The Government filed the '811 Provisional (Ex. F) on February 3, 2006, followed by the '547 Application (Ex. G) on January 31, 2007, which claimed priority to the '811 Provisional. The '509 Patent issued from the '547 Application on June 2, 2015, and the remaining HHS Patents have since issued and claim priority to the same provisional and nonprovisional applications. The Government alleges that the administration of Truvada® for PrEP purposes infringes the issued claims of the HHS Patents and that Defendants induce infringement of the HHS Patents through sales of Truvada® for PrEP purposes. E.g., Compl. ¶¶ 282-283, 285, 291-293, 299-301, 307-308, 310.

72. However, the Government failed to provide adequate or timely notice to Defendants that the Government had sought patent protection for the subject matter claimed in the HHS Patents. The CDC and the Government waited several years—until October 2014 at the earliest—to provide notice to either Defendant concerning the existence of the HHS Patents. See Aff. Defenses ¶ 38. The Government's failure to provide such notice violated the terms of several MTAs between GSI and the CDC. See id. ¶¶ 6-42 (incorporated herein by reference).

73. Despite this lack of notice to Defendants, the Government extensively encouraged both the public use and the prescription of Truvada® for PrEP purposes—including in CDC guidelines published even before the Truvada® PrEP indication had been approved by the FDA in 2012. For example, the CDC’s January 28, 2011 guidelines—issued more than one year before the FDA’s approval of the PrEP indication for Truvada®—identified “[p]rescrib[ing] 1 tablet of Truvada® (TDF [300 mg] plus FTC [200 mg]) daily” as part of “[b]eginning [a] PrEP medication regimen.” Ex. A (January 28, 2011 Interim Guidance) at 68. Furthermore, the Government requested that GSI provide TDF/FTC for use in preclinical and clinical studies concerning PrEP. Furthermore, the Government (including the FDA) actively encouraged GSI to seek FDA approval for the PrEP indication for Truvada®, which was approved in August 2012.

74. The Government’s conduct—including its failure to provide timely notice to Defendants of the applications that resulted in the HHS Patents, its promotion of the use of Truvada® for the indication that it now alleges infringes the Patents-in-Suit, and its encouragement of GSI to seek FDA approval for the for the PrEP indication for Truvada®—is “so inconsistent with an intent to enforce its rights as to induce a reasonable belief that such right has been relinquished.” *Core Wireless Licensing S.A.R.L. v. Apple Inc.*, 899 F.3d 1356, 1365 (Fed. Cir. 2018) (quoting *Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1348 (Fed. Cir. 2011)) (internal quotation mark omitted). For this reason, the Government is barred under the doctrine of implied waiver from enforcing the HHS Patents against Gilead.

TENTH AFFIRMATIVE DEFENSE
(NO WILLFULNESS)

75. Defendants have not willfully infringed any claim of the Patents-in-Suit.

ELEVENTH AFFIRMATIVE DEFENSE
(NO EXCEPTIONAL CASE)

76. Defendants' actions in defending this case do not give rise to an exceptional case under 35 U.S.C. § 285.

TWELFTH AFFIRMATIVE DEFENSE
(NO RECOVERY OF COSTS)

77. The Government is barred by 35 U.S.C. § 288 from recovering any costs associated with this action.

THIRTEENTH AFFIRMATIVE DEFENSE
(FAILURE TO MITIGATE)

78. The Government has failed to mitigate the harm it claims to have sustained, if any.

FOURTEENTH AFFIRMATIVE DEFENSE
(NO STANDING)

79. The Government lacks standing to assert one or more of the Patents-in-Suit.

FIFTEENTH AFFIRMATIVE DEFENSE
(NO CONSTITUTIONAL AUTHORITY)

80. The Government lacks authority under the United States Constitution, including the Intellectual Property Clause thereof (art. I, § 8, cl. 8), to own or assert the four Patents-in-Suit.

RESERVATION OF DEFENSES

As Defendants' investigation is ongoing and discovery has not yet been completed, Defendants are without complete information regarding the existence or non-existence of other facts or acts that would constitute a defense to the purported causes of action in the Government's Complaint. Accordingly, Defendants reserve the right to assert any other defenses that discovery may reveal.

GSI'S FIRST AMENDED COUNTERCLAIMS

Without admitting any of the Government's allegations other than those expressly admitted herein, and without prejudice of the rights of Defendant/Counterclaim-Plaintiff Gilead Sciences, Inc. ("GSI") to plead additional Counterclaims as the facts of the matter warrant, Defendant/Counterclaim-Plaintiff GSI hereby asserts the following Counterclaims against the Government. Defendants contend that Defendant Gilead Sciences Ireland UC is not a proper party to this action; however, if Gilead Sciences Ireland UC is deemed to be a proper party or otherwise remains in this action, Gilead Sciences Ireland UC reserves the right to bring or seek to bring counterclaims on its own behalf at a later stage in the case.

For its Counterclaims against the Government, Defendant/Counterclaim-Plaintiff GSI states as follows:

THE PARTIES

1. Counterclaim-Plaintiff Gilead Sciences, Inc. ("GSI") is a corporation organized under the laws of the State of Delaware, having its principal place of business at 333 Lakeside Drive, Foster City, California 94404.

2. Counterclaim-Defendant alleges in its Complaint that it is acting on behalf of the Department of Health and Human Services (HHS) and is headquartered at 200 Independence Avenue, S.W., Washington, D.C. 20201.

JURISDICTION & VENUE

3. Defendant/Counterclaim-Plaintiff GSI brings these [Counterclaims](#) under the Patent Laws of the United States, 35 U.S.C. §§ 1 *et seq.*, for a declaratory judgment pursuant to 28 U.S.C. §§ 2201-2202 that U.S. Patent Nos. 9,044,509 (the "'509 Patent"), 9,579,333 (the "'333 Patent"), 9,937,191 (the "'191 Patent"), and 10,335,423 (the "'423 Patent") (collectively, the "HHS

Patents”) have not been infringed and are not being infringed by Defendant/Counterclaim-Plaintiff GSI, that the HHS Patents are invalid, and that the HHS Patents are unenforceable.

4. This Court has subject matter jurisdiction over Defendant’s Counterclaims under 28 U.S.C. §§ 1331 and 1338. The Government’s sovereign immunity does not bar GSI’s counterclaims. See, e.g., *U.S. Dep’t of Health & Human Servs. v. Mylan Pharms., Inc.*, No. 10-cv-5956-WHW, 2011 WL 13238650 (D.N.J. July 13, 2011) (holding that because “Defendants’ counterclaims [for declaratory judgment of noninfringement and invalidity] are ... of the same kind or nature as the Government’s claims, as the declaratory judgment sought by defendants is a mirror-image of the judgment sought by the Government,” *id.* at *3, the federal government “is subject to adjudication of defendants’ compulsory counterclaims properly sounding in recoupment,” *id.* at *4); *Delano Farms Co. v. California Table Grape Comm’n*, 655 F.3d 1337, 1343-1344, 1349 & n.6 (Fed. Cir. 2011) (holding that 5 U.S.C. § 702 “waives sovereign immunity for non-monetary claims against federal agencies,” *id.* at 1344, including “declaratory judgment claims under the Patent Act,” *id.* at 1349).

5. This Court has personal jurisdiction over Plaintiff/Counterclaim-Defendant. Plaintiff/Counterclaim-Defendant has subjected itself to personal jurisdiction by maintaining its lawsuit against Defendant/Counterclaim-Plaintiff GSI in this District.

6. Venue in this case is proper in this District by virtue of the Government’s filing of the Complaint in this District, which gave rise to these Counterclaims. The Government contends in its Complaint that venue is proper in this District.

THE HHS PATENTS

7. The ’509 Patent, titled “Inhibition of HIV Infection through Chemoprophylaxis,” issued on June 2, 2015. The Government alleges that it owns the ’509 Patent. The earliest possible

priority date for the '509 Patent is February 3, 2006. The Government alleges that the '509 Patent expires on May 12, 2031.

8. The '333 Patent, titled “Inhibition of HIV Infection through Chemoprophylaxis,” issued on February 28, 2017. The Government alleges that it owns the '333 Patent. The earliest possible priority date for the '333 Patent is February 3, 2006. The Government alleges that the '333 Patent expires on January 31, 2027.

9. The '191 Patent, titled “Inhibition of HIV Infection through Chemoprophylaxis,” issued on April 10, 2018. The Government alleges that it owns the '191 Patent. The earliest possible priority date for the '191 Patent is February 3, 2006. The Government alleges that the '191 Patent expires on January 31, 2027.

10. The '423 Patent, titled “Inhibition of HIV Infection through Chemoprophylaxis,” issued on July 2, 2019. The Government alleges that it owns the '423 Patent. The earliest possible priority date for the '423 Patent is February 3, 2006. The Government alleges that the '423 Patent expires on January 31, 2027.

FACTUAL BACKGROUND

11. GSI is the holder of New Drug Application (“NDA”) No. 21-752, which relates to tablets containing emtricitabine (“FTC”) and tenofovir disoproxil fumarate (“TDF”). On August 2, 2004, the United States Food and Drug Administration (“FDA”) approved the use of the tablets described in NDA No. 21-752 for the treatment of HIV-1 infection in adults. These tablets are prescribed and sold in the United States under the trademark Truvada®. Truvada® was originally available in one dosage form: 200 mg FTC and 300 mg TDF.

12. On July 16, 2012, FDA approved Truvada® for use in combination with safer sex practices for pre-exposure prophylaxis (“PrEP”) to reduce the risk of sexually acquired human

immunodeficiency virus 1 (“HIV-1”) in adults at high risk. GSI promotes this indication under the trademark Truvada for PrEP®. Only the original dosage form of Truvada®, 200 mg FTC and 300 mg TDF, is indicated for use in Truvada for PrEP®.

13. GSI is also the holder of NDA No. 208215, which relates to tablets containing FTC and TAF. On April 4, 2016, FDA approved the use of the tablets described in NDA No. 208215 for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age or older. These tablets are prescribed and sold in the United States under the trademark Descovy®. Descovy® is available in one dosage form: 200 mg FTC and 25 mg TAF.

14. On October 3, 2019, FDA approved Descovy® for use in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex, and provided that individuals must have a negative HIV-1 test immediately prior to initiating Descovy® for HIV-1 PrEP. GSI promotes this indication under the trademark Descovy for PrEP®.

15. In its Complaint, the Government asserts that Defendants have induced infringement of certain claims of the HHS Patents by, among other things, selling Truvada® and instructing doctors and patients on how to administer Truvada® for PrEP. The Government further asserts that Defendants have induced infringement of certain claims of the '509 Patent and the '423 Patent by, among other things, selling Descovy® and instructing doctors and patients on how to administer Descovy® for PrEP.

16. The HHS Patents are invalid and/or have not been and will not be infringed by Defendants, either directly or indirectly, literally or under the doctrine of equivalents.

COUNT I:
DECLARATORY JUDGMENT OF NON-INFRINGEMENT
OF U.S. PATENT NO. 9,044,509

17. ~~74.~~ Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-~~73~~16 above as if fully set forth herein.

18. ~~75.~~ The Government has alleged that it is the owner of all right, title, and interest in the '509 Patent.

19. ~~76.~~ A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '509 Patent.

20. ~~77.~~ Counterclaim-Plaintiff GSI has not infringed, and does not infringe, directly or indirectly, any valid or enforceable claim of the '509 Patent.

21. ~~78.~~ The controversy between the parties is amenable to specific relief through a decree of conclusive character.

22. ~~79.~~ Counterclaim-Plaintiff GSI is entitled to a judicial declaration that Counterclaim-Plaintiff GSI has not and will not infringe, directly or indirectly, any valid and enforceable claim of the '509 Patent. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT II:
DECLARATORY JUDGMENT OF INVALIDITY
OF U.S. PATENT NO. 9,044,509

23. ~~80.~~ Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-~~73~~16 above as if fully set forth herein.

24. ~~81.~~ The Government has alleged that it is the owner of all right, title, and interest in the '509 Patent.

25. ~~82.~~ A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '509 Patent.

26. ~~83.~~ One or more claims of the '509 Patent are invalid for failure to satisfy one or more requirements of patentability under 35 U.S.C. § 101 *et seq.*, including without limitation §§ 101, 102, 103, 112, and/or any judicially created doctrine of invalidity, including obviousness-type double patenting.

27. ~~84.~~ The controversy between the parties is amenable to specific relief through a decree of conclusive character.

28. ~~85.~~ Counterclaim-Plaintiff GSI is entitled to a judicial declaration that one or more claims of the '509 Patent are invalid. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT III:
~~DECLARATORY JUDGMENT OF UNENFORCEABILITY~~
~~OF U.S. PATENT NO. 9,044,509~~

~~86. Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-73 above as if fully set forth herein.~~

~~87. The Government has alleged that it is the owner of all right, title, and interest in the '509 Patent.~~

~~88. A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '509 Patent.~~

~~89. The '509 Patent is unenforceable against Counterclaim-Plaintiff GSI because of the Government's unclean hands following from the Government's breach of the MTAs and the Government's inequitable conduct during the prosecution of the HHS Patents.~~

~~90. The controversy between the parties is amenable to specific relief through a decree of conclusive character.~~

~~91. Counterclaim-Plaintiff GSI is entitled to a judicial declaration that the '509 Patent is unenforceable against GSI. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.~~

COUNT IV:
DECLARATORY JUDGMENT OF NON-INFRINGEMENT
OF U.S. PATENT NO. 9,579,333

29. ~~92.~~ Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-~~73~~16 above as if fully set forth herein.

30. ~~93.~~ The Government has alleged that it is the owner of all right, title, and interest in the '333 Patent.

31. ~~94.~~ A case or controversy exists because the Government has alleged that Defendants have infringed and will infringe one or more claims of the '333 Patent.

32. ~~95.~~ Counterclaim-Plaintiff GSI has not infringed, and does not infringe, directly or indirectly, any valid or enforceable claim of the '333 Patent.

33. ~~96.~~ The controversy between the parties is amenable to specific relief through a decree of conclusive character.

34. ~~97.~~ Counterclaim-Plaintiff GSI is entitled to a judicial declaration that Counterclaim-Plaintiff GSI has not and will not infringe, directly or indirectly, any valid and enforceable claim of the '333 Patent. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT ~~V~~IV:
DECLARATORY JUDGMENT OF INVALIDITY
OF U.S. PATENT NO. 9,579,333

35. ~~98.~~ Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-~~73~~16 above as if fully set forth herein.

36. ~~99.~~ The Government has alleged that it is the owner of all right, title, and interest in the '333 Patent.

37. ~~100.~~ A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '333 Patent.

38. ~~101.~~ One or more claims of the '333 Patent are invalid for failure to satisfy one or more requirements of patentability under 35 U.S.C. § 101 *et seq.*, including without limitation §§ 101, 102, 103, 112, and/or any judicially created doctrine of invalidity, including obviousness-type double patenting.

39. ~~102.~~ The controversy between the parties is amenable to specific relief through a decree of conclusive character.

40. ~~103.~~ Counterclaim-Plaintiff GSI is entitled to a judicial declaration that one or more claims of the '333 Patent are invalid. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT ~~V~~IV:
~~DECLARATORY JUDGMENT OF UNENFORCEABILITY~~
~~OF U.S. PATENT NO. 9,579,333~~

~~104. Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-73 above as if fully set forth herein.~~

~~105. The Government has alleged that it is the owner of all right, title, and interest in the '333 Patent.~~

~~106. A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '333 Patent.~~

~~107. The '333 Patent is unenforceable against Counterclaim-Plaintiff GSI because of the Government's unclean hands following from the Government's breach of the MTAs and the Government's inequitable conduct during the prosecution of the HHS Patents.~~

~~108. The controversy between the parties is amenable to specific relief through a decree of conclusive character.~~

~~109. Counterclaim-Plaintiff GSI is entitled to a judicial declaration that the '333 Patent is unenforceable against GSI. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.~~

COUNT VII:
DECLARATORY JUDGMENT OF NON-INFRINGEMENT
OF U.S. PATENT NO. 9,937,191

41. ~~110.~~ Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-~~73~~16 above as if fully set forth herein.

42. ~~111.~~ The Government has alleged that it is the owner of all right, title, and interest in the '191 Patent.

43. ~~112.~~ A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '191 Patent.

44. ~~113.~~ Counterclaim-Plaintiff GSI has not infringed, and does not infringe, directly or indirectly, any valid or enforceable claim of the '191 Patent.

45. ~~114.~~ The controversy between the parties is amenable to specific relief through a decree of conclusive character.

46. ~~115.~~—Counterclaim-Plaintiff GSI is entitled to a judicial declaration that Counterclaim-Plaintiff GSI has not and will not infringe, directly or indirectly, any valid and enforceable claim of the '191 Patent. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT ~~VIII~~VI:
DECLARATORY JUDGMENT OF INVALIDITY
OF U.S. PATENT NO. 9,937,191

47. ~~116.~~—Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-~~73~~16 above as if fully set forth herein.

48. ~~117.~~—The Government has alleged that it is the owner of all right, title, and interest in the '191 Patent.

49. ~~118.~~—A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '191 Patent.

50. ~~119.~~—One or more claims of the '191 Patent are invalid for failure to satisfy one or more requirements of patentability under 35 U.S.C. § 101 *et seq.*, including without limitation §§ 101, 102, 103, 112, and/or any judicially created doctrine of invalidity, including obviousness-type double patenting.

51. ~~120.~~—The controversy between the parties is amenable to specific relief through a decree of conclusive character.

52. ~~121.~~—Counterclaim-Plaintiff GSI is entitled to a judicial declaration that one or more claims of the '191 Patent are invalid. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT ~~IX~~VII:
~~DECLARATORY JUDGMENT OF UNENFORCEABILITY~~
~~OF U.S. PATENT NO. 9,937,191~~

~~122. Counterclaim Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-73 above as if fully set forth herein.~~

~~123. The Government has alleged that it is the owner of all right, title, and interest in the '191 Patent.~~

~~124. A case or controversy exists because the Government has alleged that Counterclaim Plaintiff GSI has infringed and will infringe one or more claims of the '191 Patent.~~

~~125. The '191 Patent is unenforceable against Counterclaim Plaintiff GSI because of the Government's unclean hands following from the Government's breach of the MTAs and the Government's inequitable conduct during the prosecution of the HHS Patents.~~

~~126. The controversy between the parties is amenable to specific relief through a decree of conclusive character.~~

~~127. Counterclaim Plaintiff GSI is entitled to a judicial declaration that the '191 Patent is unenforceable against GSI. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.~~

COUNT X:
~~DECLARATORY JUDGMENT OF NON-INFRINGEMENT~~
~~OF U.S. PATENT NO. 10,335,423~~

53. ~~128.~~ Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-~~73~~16 above as if fully set forth herein.

54. ~~129.~~ The Government has alleged that it is the owner of all right, title, and interest in the '423 Patent.

55. ~~130.~~ A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '423 Patent.

56. ~~131.~~ Counterclaim-Plaintiff GSI has not infringed, and does not infringe, directly or indirectly, any valid or enforceable claim of the '423 Patent.

57. ~~132.~~ The controversy between the parties is amenable to specific relief through a decree of conclusive character.

58. ~~133.~~ Counterclaim-Plaintiff GSI is entitled to a judicial declaration that Counterclaim-Plaintiff GSI has not and will not infringe, directly or indirectly, any valid and enforceable claim of the '423 Patent. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT ~~XIV~~III:
DECLARATORY JUDGMENT OF INVALIDITY
OF U.S. PATENT NO. 10,335,423

59. ~~134.~~ Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-~~73~~16 above as if fully set forth herein.

60. ~~135.~~ The Government has alleged that it is the owner of all right, title, and interest in the '423 Patent.

61. ~~136.~~ A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '423 Patent.

62. ~~137.~~ One or more claims of the '423 Patent are invalid for failure to satisfy one or more requirements of patentability under 35 U.S.C. § 101 *et seq.*, including without limitation §§ 101, 102, 103, 112, and/or any judicially created doctrine of invalidity, including obviousness-type double patenting.

63. ~~138.~~ The controversy between the parties is amenable to specific relief through a decree of conclusive character.

64. ~~139.~~ Counterclaim-Plaintiff GSI is entitled to a judicial declaration that one or more claims of the '423 Patent are invalid. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT XII:
DECLARATORY JUDGMENT OF UNENFORCEABILITY
OF U.S. PATENT NO. 10,335,423

~~140. Counterclaim-Plaintiff GSI restates and incorporates by reference the allegations in paragraphs 1-73 above as if fully set forth herein.~~

~~141. The Government has alleged that it is the owner of all right, title, and interest in the '423 Patent.~~

~~142. A case or controversy exists because the Government has alleged that Counterclaim-Plaintiff GSI has infringed and will infringe one or more claims of the '423 Patent.~~

~~143. The '423 Patent is unenforceable against Counterclaim Plaintiff GSI because of the Government's unclean hands following from the Government's breach of the MTAs and the Government's inequitable conduct during the prosecution of the HHS Patents.~~

~~144. The controversy between the parties is amenable to specific relief through a decree of conclusive character.~~

~~145. Counterclaim Plaintiff GSI is entitled to a judicial declaration that the '423 Patent is unenforceable against GSI. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.~~

PRAYER FOR RELIEF

WHEREFORE, Counterclaim-Plaintiff GSI respectfully requests that this Court enter judgment in its favor against the Government and grant the following relief:

- (a) Adjudge and decree that the Government be denied all forms of relief requested in its Complaint;
- (b) Dismiss the Complaint in its entirety with prejudice;
- (c) Declare that Counterclaim-Plaintiff GSI has not, does not, and will not infringe any valid and enforceable claim of U.S. Patent Nos. 9,044,509, 9,579,333, 9,937,191, or 10,335,423;
- (d) Declare that one or more claims of U.S. Patent Nos. 9,044,509, 9,579,333, 9,937,191, and 10,335,423 are invalid;
- ~~(e) Declare that U.S. Patent Nos. 9,044,509, 9,579,333, 9,937,191, and 10,335,423 are unenforceable against Counterclaim-Plaintiff GSI;~~
- (e) ~~(f)~~ Declare that this is an exceptional case in favor of Counterclaim-Plaintiff GSI and award Counterclaim-Plaintiff its reasonable attorneys' fees pursuant to 35 U.S.C. § 285;
- (f) ~~(g)~~ Award Counterclaim-Plaintiff GSI costs and expenses; and
- (g) Award any and all such other relief as the Court determines to be just and proper.

(h)

Dated: ~~January 23~~ March 27, 2020

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EXHIBIT A

Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men

An estimated 56,000 human immunodeficiency virus (HIV) infections occur each year in the United States (1). Men who have sex with men (MSM) account for 53% of the estimated incident infections, and surveillance data suggest that the annual number of new HIV infections among MSM has been rising since the mid-1990s (1). Strategies for reducing acquisition of HIV infection by MSM have included 1) expanded HIV testing so that infected persons can be treated and their risk for transmitting infection minimized; 2) individual, small-group, and community-level behavioral interventions to reduce risk behaviors (2); 3) promotion of condom use; 4) detection and treatment of sexually transmitted infections (3); and 5) mental health and substance abuse counseling when needed. On November 23, 2010, investigators for the Pre-Exposure Prophylaxis Initiative (iPrEX) study announced results from a multinational, randomized, double-blind, placebo-controlled, phase III clinical trial of daily oral antiretrovirals (tenofovir disoproxil fumarate [TDF] and emtricitabine [FTC]) to prevent acquisition of HIV infection among uninfected but exposed MSM (4). This report provides interim guidance to health-care providers based on the reported results of that trial, which indicated that TDF plus FTC taken orally once a day as preexposure prophylaxis (PrEP) is safe and partially effective in reducing HIV acquisition among MSM when provided with regular monitoring of HIV status and ongoing risk-reduction and PrEP medication adherence counseling.

The iPrEX study was conducted in Peru, Ecuador, Brazil, Thailand, South Africa, and the United States. Eligible participants were consenting HIV-uninfected men and male-to-female transgender adults (aged ≥ 18 years) who reported sex with a man and reported engaging in high-risk sexual behaviors during the preceding 6 months, and had no clinical contraindication to taking a combined formulation of 300 mg TDF and 200 mg FTC (TDF/FTC).*

Enrolled participants were randomized to receive either daily doses of TDF/FTC or a placebo pill. Participants were seen every 4 weeks for an interview, HIV testing, risk-reduction and PrEP medication adherence counseling, pill count, and dispensing of pills and condoms. Every 3 months, participants received physical examinations with collection of blood and urine samples for evaluation of renal and liver function, and were tested for sexually transmitted infections and treated as needed. Positive HIV rapid tests were confirmed by Western blot. The cohort was followed for an average 1.2 years with a maximum of 2.8 years. Participants were tested for hepatitis B infection at enrollment, and those found to be susceptible to hepatitis B infection were offered vaccination; 94% accepted.

Based on analysis of data from visits through May 1, 2010, for 2,499 enrolled participants (including 29 male-to-female transgender persons) in the modified “intent to treat” analysis (excluding 10 participants found to be HIV-infected at enrollment and 48 who did not have an HIV test after enrollment), 36 of 1,224 participants in the PrEP arm and 64 of 1,217 participants in the placebo arm who were followed for acquisition of HIV infection. Enrollment in the PrEP arm was associated with a 44% reduction in HIV acquisition (95% confidence interval [CI] = 15%–63%). The reduction was greater in the “as treated” analysis; participants at visits with $\geq 50\%$ adherence by

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* Marketed under the brand name Truvada (Gilead Sciences, Inc., Foster City, California).



self-report and pill count/dispensing had a 50% reduction in HIV acquisition (CI = 18%–70%). Reduction in risk for HIV acquisition was 21% among participants at visits with <90% adherence (CI = -31%–52%) and 73% at visits with ≥90% adherence (CI = 41%–88%). Among those randomly assigned to the TDF/FTC arm, drug level testing was performed for all HIV seroconverters and a matched subset of participants who remained uninfected; a 92% reduction in risk for HIV acquisition (CI = 40%–99%) was found in participants with detectable levels of TDF/FTC versus those with no drug detected. TDF/FTC generally was well tolerated, although nausea in the first month was more common among those taking medication than among those on placebo (9% versus 5%). No differences in severe (grade 3) or life-threatening (grade 4) laboratory abnormalities were observed between the active and placebo arms, and no drug-resistant virus was found in the 100 participants infected after enrollment. Among 10 participants who were seronegative at enrollment but later found to have been infected before enrollment, two cases of FTC resistance occurred in the active arm, and one occurred in the placebo arm. Participants in both arms reported lower total numbers of sex partners with whom the participants had receptive anal intercourse and higher percentages of partners who used condoms than reported at baseline.

What is already known on this topic?

HIV infections are increasing among men who have sex with men (MSM) in the United States despite awareness of HIV/AIDS and the protective effect of consistent condom use. A recent international study indicated that HIV infection among MSM can be reduced by daily preexposure prophylaxis (PrEP) with a well-tolerated combination of specific antiviral medications.

What is added by this report?

This report provides interim guidance for health-care providers in the United States based on results of the only large clinical trial testing the efficacy and safety of PrEP for reducing HIV acquisition by MSM.

What are the implications for public health practice?

For MSM whose behaviors place them at high risk for HIV infection and who do not use other effective prevention methods consistently, PrEP might reduce their risk for HIV infection. Until comprehensive U.S. Public Health Service guidelines are available, CDC is providing interim guidance to help guide clinical practice.

Reported by

DK Smith, MD, RM Grant, MD, PJ Weidle, PharmD, A Lansky, PhD, J Mermin, MD, KA Fenton, MD, PhD, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC.

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Editorial Note

This clinical trial demonstrated the safety and efficacy of daily TDF/FTC, in conjunction with behavioral interventions, in reducing sexual HIV acquisition in a multinational population of MSM exposed to HIV through high-risk sex (4). A recent safety study of PrEP with TDF among 400 MSM in the United States also revealed few safety concerns (5). As a component of a comprehensive HIV prevention intervention, PrEP showed a significant added benefit, although effectiveness was highly dependent on medication adherence.

The findings in this report are subject to at least five limitations. First, the trial was not large enough to evaluate efficacy in each of the sites, and the majority of the participants were in South America; only 10% were in the United States, making it impossible to determine effects on incidence in the United States trial sites specifically. Second, the assessment of adherence by drug-level testing was not performed for all trial participants and was performed for seroconverters at the first clinical visit in which infection was diagnosed; therefore, the findings might not reflect drug levels at the time of infection. Third, the study does not provide information about long-term health effects of TDF/FTC in HIV-uninfected men or men who became HIV-infected while on PrEP medications. Fourth, results of drug-level testing showed that adherence measures in the trial might overstate levels of actual adherence; many of those with high levels of adherence to the daily regimen by self-report, pill count, and bottles dispensed had low levels or no drug measured in their blood (4). Finally, sexual risk behavior and adherence to PrEP medications among MSM taking TDF/FTC for PrEP outside of a trial setting, and with awareness of trial results, might be different from what was observed for men in the iPrEx trial.

Based on the results of this study, CDC and other U.S. Public Health Service (PHS) agencies have begun to develop PHS guidelines on the use of PrEP for MSM at high risk for HIV acquisition in the United States as part of a comprehensive set of HIV prevention services. Completing the guidelines and obtaining expert input and public comment will take several months before they can be published. Concerns exist that without early guidance, various unsafe and potentially less effective PrEP-related practices could develop among health-care providers and MSM beginning to use PrEP in the coming weeks and months. These concerns include 1) use of other antiretrovirals than those so far proven safe for uninfected persons (e.g., more than two drugs or protease inhibitors); 2) use of dosing schedules of unproven efficacy (e.g., “intermittent” dosing just before and/or after sex); 3) not screening for acute infection before beginning PrEP or long intervals without retesting for HIV infection; and 4) providing prescriptions

without other HIV prevention support (e.g., condom access and risk-reduction counseling). Until the more detailed PHS guidelines are available, CDC is providing interim recommendations to help guide clinical practice (3,6–9) (Box).

Until the safety and efficacy of PrEP is determined in trials now under way with populations at high risk for HIV acquisition by other routes of transmission (10), PrEP should be considered only for MSM. The iPrEx trial results provide strong evidence that support for adherence to the prescribed medication regimen must be a routine component of any PrEP program. To minimize the risk for drug resistance, PrEP should not be started in persons with signs or symptoms of acute viral infection unless HIV-uninfected status is confirmed by HIV RNA testing or a repeat antibody test performed after the viral syndrome resolves (6). When evaluating MSM for the prescription of PrEP medications, it is important to establish whether other effective risk-reduction measures (e.g., condom use) are not being used consistently and to ascertain that the risk for HIV acquisition is high (e.g., frequent partner change or concurrent partners in a geographic setting with high HIV prevalence) because these patients might benefit most from the addition of PrEP to their HIV prevention regimen. Health-care providers and patients should be aware that HIV prevention is not a labeled indication for the use of Truvada[†] and that its long-term safety in HIV-uninfected persons is not yet known. Health-care providers should report any serious adverse events resulting from prescribed TDF/FTC for PrEP to the Food and Drug Administration’s MedWatch.[§] In addition, because the medication is costly, ensuring that patients understand the financial implications of starting PrEP is critical.

PrEP has the potential to contribute to effective and safe HIV prevention for MSM if 1) it is targeted to MSM at high risk for HIV acquisition; 2) it is delivered as part of a comprehensive set of prevention services, including risk-reduction and PrEP medication adherence counseling, ready access to condoms, and diagnosis and treatment of sexually transmitted infections; and 3) it is accompanied by monitoring of HIV status, side effects, adherence, and risk behaviors at regular intervals.

[†] These recommendations do not reflect current Food and Drug Administration–approved labeling for TDF/FTC.

[§] Available at <http://www.fda.gov/safety/medwatch>.

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1. Hall HI, Song RG, Rhodes P, et al. Estimation of HIV incidence in the United States. *JAMA* 2008;300:520–9.
2. CDC. Diffusion of Effective Behavioral Interventions. Atlanta, GA: US Department of Health and Human Services, CDC; 2010. Available at <http://www.effectiveinterventions.org/en/home.aspx>. Accessed January 20, 2011.

BOX. CDC interim guidance for health-care providers electing to provide preexposure prophylaxis (PrEP) for the prevention of HIV infection in adult men who have sex with men and who are at high risk for sexual acquisition of HIV

Before initiating PrEP

Determine eligibility

- Document negative HIV antibody test(s) immediately before starting PrEP medication.
- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection.
- Confirm that patient is at substantial, ongoing, high risk for acquiring HIV infection.
- Confirm that calculated creatinine clearance is ≥ 60 mL per minute (via Cockcroft-Gault formula).

Other recommended actions

- Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision about prescribing PrEP.
- Screen and treat as needed for STIs.

Beginning PrEP medication regimen

- Prescribe 1 tablet of Truvada* (TDF [300 mg] plus FTC [200 mg]) daily.
- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected.
- If active hepatitis B infection is diagnosed, consider using TDF/FTC for both treatment of active hepatitis B infection and HIV prevention.
- Provide risk-reduction and PrEP medication adherence counseling and condoms.

Follow-up while PrEP medication is being taken

- Every 2–3 months, perform an HIV antibody test; document negative result.
- Evaluate and support PrEP medication adherence at each follow-up visit, more often if inconsistent adherence is identified.
- Every 2–3 months, assess risk behaviors and provide risk-reduction counseling and condoms. Assess STI symptoms and, if present, test and treat for STI as needed.
- Every 6 months, test for STI even if patient is asymptomatic, and treat as needed.
- 3 months after initiation, then yearly while on PrEP medication, check blood urea nitrogen and serum creatinine.

On discontinuing PrEP (at patient request, for safety concerns, or if HIV infection is acquired)

- Perform HIV test(s) to confirm whether HIV infection has occurred.
- If HIV positive, order and document results of resistance testing and establish linkage to HIV care.
- If HIV negative, establish linkage to risk-reduction support services as indicated.
- If active hepatitis B is diagnosed at initiation of PrEP, consider appropriate medication for continued treatment of hepatitis B.

Abbreviations: HIV = human immunodeficiency virus; STI = sexually transmitted infection; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine.

Sources: CDC. Sexually transmitted diseases treatment guidelines, 2010. MMWR 2010;59(No. RR-12).

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Lead Poisoning of a Child Associated with Use of a Cambodian Amulet — New York City, 2009

Lead poisoning in children is a preventable public health problem that can adversely affect the developing nervous system and result in learning and behavior problems. The most common source of exposure for lead-poisoned children aged <6 years in the United States is lead-based paint. However, nonpaint sources have been identified increasingly as the cause of lead poisoning, particularly in immigrant communities. This report describes a case of lead poisoning in a child aged 1 year that was investigated by the New York City Department of Health and Mental Hygiene's (NYC DOHMH) Lead Poisoning Prevention Program in 2009. The likely source of exposure was an amulet made in Cambodia with leaded beads that was worn by the child. Health-care providers and public health workers should consider traditional customs when seeking sources of lead exposure in Southeast Asian populations. Health-care providers should ask parents about their use of amulets, especially those in Southeast Asian families and those with children found to have elevated blood lead levels (BLLs). Educational efforts are needed to inform Southeast Asian immigrants that amulets can be a source of lead poisoning.

Restrictions in the use of lead in paint and gasoline have reduced the amount of environmental lead, resulting in a 98% decline in the number of children with BLLs ≥ 10 $\mu\text{g}/\text{dL}$ from 1976 to 2004. The geometric mean BLL of children aged 1–5 years declined from 14.9 $\mu\text{g}/\text{dL}$ in the late 1970s to 1.9 $\mu\text{g}/\text{dL}$ in 2004 (1,2). Despite this improvement, some children remain at greater risk for lead poisoning: black children, children aged 1–5 years (especially children aged 1–2 years because of hand-to-mouth activity typical for this age group), children living in older deteriorated housing, and children living in poverty (2). In New York City, Asian children also have been noted to be at risk for lead poisoning (3).

The most common source of lead poisoning for young children is lead-based paint; however, nonpaint sources of lead are being identified increasingly in lead poisoning cases (4). Children with immigrant backgrounds might be at increased risk through exposure to lead-containing products from their family's country of origin. In New York City in 2007, among children with BLLs ≥ 15 $\mu\text{g}/\text{dL}$, 38% of foreign-born children did not have a lead paint hazard in the home compared with 21% of U.S.-born children ($p < 0.05$) (3). Nonpaint lead risk factors include recent travel to a foreign country and use of imported products such as spices, food, candy, cosmetics, health remedies, ceramics or pottery, and jewelry.

Case Report

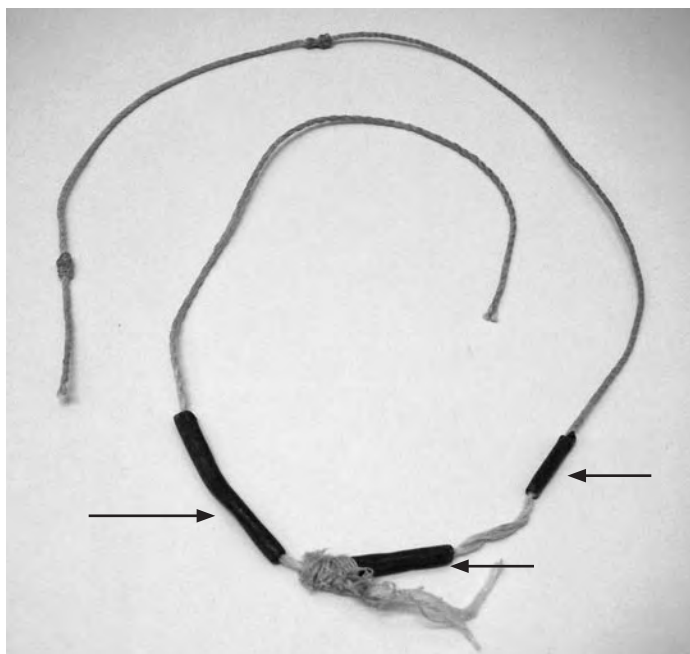
In March 2009, routine lead testing of a healthy, nonanemic boy aged 1 year who was born in the United States to Cambodian-born parents showed an elevated BLL of 10 $\mu\text{g}/\text{dL}$. Because the toddler shared a household with a cousin who had lead poisoning, he also had been tested at age 6 months, and was found to have a BLL of 1 $\mu\text{g}/\text{dL}$ at that time. During the first home interview and inspection after the elevated BLL, the child's home and routine activities were evaluated by a risk assessor certified by the Environmental Protection Agency. The boy's father denied use of imported products, and no paint or nonpaint lead sources were identified. Out of 29 X-ray fluorescence (XRF) readings of painted areas obtained during the inspection, none were above U.S. Housing and Urban Development guidelines of 1 mg/cm^2 of lead (5).

Three months later, the child's BLL increased to 20 $\mu\text{g}/\text{dL}$. In a telephone interview before a second home inspection, the boy's father again denied that the child wore jewelry or charms, but when questioned more closely, he said that the toddler wore an amulet or "something to protect him." The amulet, acquired by the boy's mother in a rural Cambodian market, was a knotted string onto which gray metallic beads had been molded (Figure). The father reported that the boy had worn the amulet around his neck since age 3 months and had been observed mouthing it.

The second home inspection revealed one positive XRF reading of 2.2 mg/cm^2 on an interior window sill and several potential nonpaint lead sources: two imported spices, imported rice, and the amulet. All four nonpaint samples were sent to a laboratory for acid-digestion testing. The lead contents of the food items were below the limits of detection used, which were 0.94 mg/kg and 0.95 mg/kg for the spices and 0.49 mg/kg for the rice. The amulet's metal beads had a total lead content of 450,000 mg/kg (45%).

Within 8 days of the amulet being removed from the home, the child's BLL had decreased from 20 $\mu\text{g}/\text{dL}$ to 14 $\mu\text{g}/\text{dL}$. Six weeks after the amulet was removed, and 2 days after the lead paint violation was reported as abated, the child's BLL was 10 $\mu\text{g}/\text{dL}$. Five months after the amulet was removed, the boy's BLL was down to 5 $\mu\text{g}/\text{dL}$. Although other factors might have contributed to the child's overall lead burden, the most likely source identified was the amulet, based on its high lead content, statements that the child had been observed mouthing it, and the rapid decrease in the child's BLL after its removal.

FIGURE. Amulet with leaded beads (indicated by arrows) made in Cambodia similar to the one worn by a lead-poisoned child — New York City, 2009.



Photo/New York City Department of Health and Mental Hygiene

The toddler's cousin, aged 6 years, who was living in the same home, had lead poisoning diagnosed in September 2008. His BLL had been 17 $\mu\text{g}/\text{dL}$. Fifty-eight violations for lead had been repaired in the home, and during the next 8 months the boy had BLLs of 11–15 $\mu\text{g}/\text{dL}$. He also had worn a Cambodian amulet, and 3 months after he stopped wearing his amulet, his BLL was 7 $\mu\text{g}/\text{dL}$. The toddler's sister, aged 10 years, was tested and had a BLL of 4 $\mu\text{g}/\text{dL}$. Although she also wore an amulet, she presumably was old enough not to mouth it.

Reported by

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Editorial Note

Wearing amulets is common among Cambodians and other ethnic groups in Southeast Asia, including Vietnamese, Hmong, and Lao populations. Typically, infants and toddlers wear these “protection strings” around their necks, wrists, or waists (6). The amulets usually are made of black or white string with several knots, metal beads, or both. The knots and beads

What is already known on this topic?

Although the most common source of lead poisoning for young children is lead-based paint, nonpaint sources of lead are being identified increasingly in lead poisoning cases, particularly in immigrant communities.

What is added by this report?

This report describes a case of pediatric lead poisoning that likely resulted from wearing an amulet made in Cambodia with leaded beads, a newly identified lead risk factor for the Southeast Asian community.

What are the implications for public health practice?

Educational efforts are needed to inform Southeast Asian immigrants that amulets can be a potential source of lead poisoning. Health-care providers should ask parents about use of amulets, especially Southeast Asian families and those with children found to have elevated blood lead levels.

are believed by some to be infused with protective powers. In this case, the mother of the toddler reported that on her most recent trip to Cambodia, she had three amulets custom-made (“cooked in a pot”) for the children in her family. Anecdotal information suggests that lead bullets sometimes are melted to make the beads for such amulets.

This case identified a lead risk factor not previously recognized for the Southeast Asian community. In addition, this case highlights the importance of blood lead testing in children of immigrants because of the increased risk for exposure to lead-containing foreign products. CDC recommends blood lead testing for internationally adopted and refugee children.* NYC DOHMH recommends testing all children with recent travel to foreign countries.

This case also adds to the medical literature of nonpaint lead sources as causes of lead poisoning. Some incidents of lead poisoning in children from atypical sources have been documented previously (4,7), and two cases of jewelry-associated lead poisonings in children have been reported recently. In 2004, a boy aged 4 years from Oregon had a BLL of 123 $\mu\text{g}/\text{dL}$ after ingesting a necklace with a 38.8% lead content that had come from a vending machine (8). In 2006, another boy aged 4 years from Minnesota died from acute lead poisoning after ingesting a heart-shaped metallic charm containing 99.1% lead (9). These two cases led to the recall of 150 million pieces of imported metallic toy jewelry sold in vending machines and a voluntary recall of 300,000 heart-shaped charm bracelets, respectively. These cases also call attention to ingestion of jewelry as a mechanism for lead poisoning.

Educational efforts are needed to inform Southeast Asian immigrants that amulets can be sources of lead poisoning for

* Guidelines available at <http://www.cdc.gov/nceh/lead/tips/populations.htm>.

children. Health-care providers and public health workers should ask about this custom when seeking a source of exposure in Southeast Asians with elevated BLLs. Targeted educational efforts in Southeast Asian communities also should be considered. This case also underscores the importance of being aware of different cultural practices, such as wearing amulets, and highlights the need to assess and reassess the same risk factors and rephrasing questions using different words when communicating with immigrant families.

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Updated Recommendations for Use of Meningococcal Conjugate Vaccines — Advisory Committee on Immunization Practices (ACIP), 2010

On October 27, 2010, the Advisory Committee on Immunization Practices (ACIP) approved updated recommendations for the use of quadrivalent (serogroups A, C, Y, and W-135) meningococcal conjugate vaccines (Menveo, Novartis; and Menactra, Sanofi Pasteur) in adolescents and persons at high risk for meningococcal disease. These recommendations supplement the previous ACIP recommendations for meningococcal vaccination (1,2). The Meningococcal Vaccines Work Group of ACIP reviewed available data on immunogenicity in high-risk groups, bactericidal antibody persistence after immunization, current epidemiology, vaccine effectiveness (VE), and cost-effectiveness of different strategies for vaccination of adolescents. The Work Group then presented policy options for consideration by the full ACIP. This report summarizes two new recommendations approved by ACIP: 1) routine vaccination of adolescents, preferably at age 11 or 12 years, with a booster dose at age 16 years and 2) a 2-dose primary series administered 2 months apart for persons aged 2 through 54 years with persistent complement component deficiency (e.g., C5–C9, properdin, factor H, or factor D) and functional or anatomic asplenia, and for adolescents with human immunodeficiency virus (HIV) infection. CDC guidance for vaccine providers regarding these updated recommendations also is included.

Rationale for Adding a Booster Dose to the Adolescent Schedule

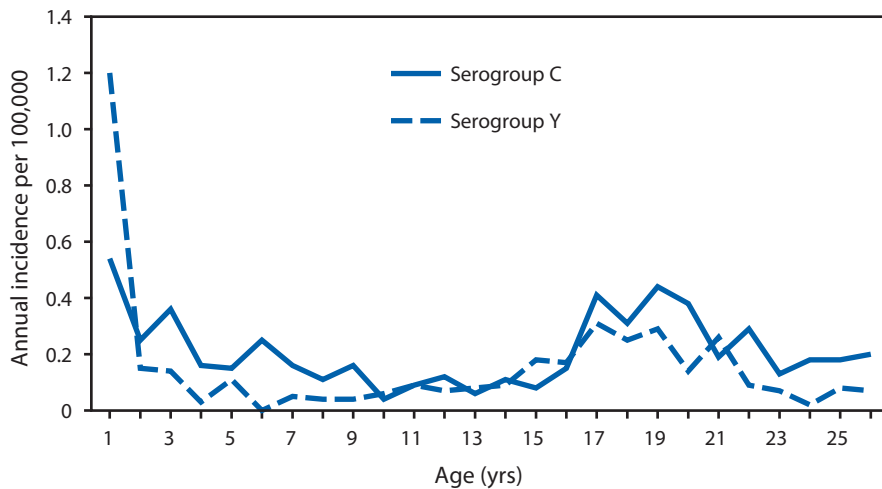
The goal of the 2005 ACIP meningococcal immunization recommendations was to protect persons aged 16 through 21 years, when meningococcal disease rates peak. At that time, vaccination was recommended at age 11 or 12 years rather than at age 14 or 15 years because 1) more persons have preventive-care visits at age 11 or 12 years, 2) adding this vaccine at the 11 or 12 year-old visit would strengthen the pre-adolescent vaccination platform, and 3) the vaccine was expected to protect adolescents through the entire period of increased risk. Meningococcal conjugate vaccines were licensed in 2005 based on immunogenicity (because a surrogate of protection had been defined) and safety data. After licensure, additional data on bactericidal antibody persistence, trends in meningococcal disease epidemiology in the United States, and VE have indicated many adolescents might not be protected for more than 5 years. Therefore, persons immunized at age 11 or 12 years might have decreased protective immunity by ages 16 through 21 years, when their risk for disease is greatest.

Meningococcal disease incidence has decreased since 2000, and incidence for serogroups C and Y, which represent the majority of cases of vaccine-preventable meningococcal disease, are at historic lows. However, the peak in disease among persons aged 18 years (Figure) has persisted, even after routine vaccination was recommended in 2005. In the 2009 National Immunization Survey-Teen, 53.6% of adolescents aged 13 through 17 years had received a dose of meningococcal vaccine (3). From 2000–2004 to 2005–2009, the estimated annual number of cases of serogroups C and Y meningococcal disease decreased 74% among persons aged 11 through 14 years but only 27% among persons aged 15 through 18 years. Cases of meningococcal disease caused by serogroups C and Y among persons who were vaccinated with meningococcal conjugate vaccine have been reported. An early VE analysis that modeled expected cases of disease in vaccinated persons estimated a VE of 80%–85% up to 3 years after vaccination (4). In 2010, CDC received 12 reports of serogroup C or Y meningococcal disease among persons who had received a meningococcal conjugate vaccine. The mean age of these persons was 18.2 years (range: 16 through 22 years). The mean time since vaccination was 3.25 years (range: 1.5–4.6 years). Five of these 12 persons had an underlying condition that might have increased their risk for meningococcal disease (CDC, unpublished data, 2010).

A case-control study evaluating the VE of meningococcal conjugate vaccine was begun in January 2006 (ACIP meeting, October 2010). Because Menactra was the only licensed vaccine until February 2010, the preliminary results are estimates for Menactra only; no data are available regarding the effectiveness of Menveo. As of October 1, 2010, 108 case-patients and 158 controls were enrolled in the effectiveness study. The overall VE estimate in persons vaccinated 0–5 years earlier was 78.0% (95% confidence interval [CI] = 29%–93%). VE for persons vaccinated less than 1 year earlier was 95% (CI = 10%–100%), VE for persons vaccinated 1 year earlier was 91% (CI = 10%–101%), and VE for persons vaccinated 2 through 5 years earlier was 58% (CI = -72%–89%). Although the CIs around the point estimates are wide, the ACIP Work Group concluded that VE wanes.

The ACIP Work Group also concluded that serologic data are consistent with waning immunity. Three characteristics of conjugate vaccines are believed to be important for establishing long-term protection against a bacterial pathogen: memory response, herd immunity, and circulating antibody (5). Recent data from the United Kingdom indicate that

FIGURE. Annual incidence of meningococcal disease (serogroup C and serogroup Y), by age — Active Bacterial Core surveillance (ABCs), United States, 1999–2008



although vaccination primes the immune system, the memory response after exposure might not be rapid enough to protect against meningococcal disease. After initial priming with a serogroup C meningococcal conjugate vaccine (MenC), a memory response after a booster dose was not measurable until 5–7 days later (6). The incubation period for meningococcal disease usually is less than 3 days. Although herd immunity has been an important component associated with long-term protection with MenC vaccine in the United Kingdom and other countries, immunization coverage has increased slowly in the United States, and to date no evidence of herd immunity has been observed (ACIP meeting, October 2010). Therefore, the Work Group concluded that circulating bactericidal antibody is critical for protection against meningococcal disease. The Work Group took into consideration the proportion of subjects with bactericidal antibody levels above thresholds considered protective, depending on the assay used, evaluating antibody persistence in five studies (Table 1). Although each study tested a small number of vaccine recipients, the Work Group concluded that the studies found sufficient evidence to indicate that approximately 50% of persons vaccinated 5 years earlier had bactericidal antibody levels protective against meningococcal disease. Therefore, more than 50% of persons immunized at age 11 or 12 years might not be protected when they are at higher risk at ages 16 through 21 years.

Two studies evaluated the response after a booster dose of Menactra at 3 and 5 years after the primary vaccination (7; ACIP meeting, June 2009). At both 3 and 5 years after the first dose, the booster dose elicited substantially higher geometric mean antibody titers (GMT), compared with the titers elicited by a primary dose. Using a complement serum bactericidal activity (SBA) assay and baby rabbit complement (brSBA) as

a measure of immune response, a booster dose administered 5 years after the first dose elicited a GMT for serogroup C of 23,613, compared with 9,045 among subjects administered a primary dose (ACIP meeting, October 2010). As expected with conjugate vaccines, the first dose primes the immune system to have a strong response to the booster dose. Local and systemic reactions to the booster were comparable to those in persons receiving a first dose. The duration of protective antibody after the booster dose is not known but is expected to last through age 21 years for booster doses administered at ages 16 through 18 years.

Optimizing meningococcal vaccination.

Despite the current low burden of meningococcal disease, the ACIP Work Group agreed that because of mounting evidence of waning immunity by 5 years postvaccination, vaccinating adolescents with a single dose at age 11 or 12 years is not the best strategy for protection through age 21 years. The Work Group considered two other options for optimizing protection: moving the dose from age 11 or 12 years to age 14 or 15 years or vaccinating at age 11 or 12 years and providing a booster dose at age 16 years. Although a single dose at age 14 or 15 years likely would protect most adolescents through the higher risk period at ages 16 through 21 years, the opportunities to administer vaccine at age 14 or 15 years might be more limited. Data indicate that as adolescents grow older, they are less likely to visit a health-care provider for preventive care (8). Adding a booster dose to the recommended schedule would provide more opportunities to increase vaccination coverage, while persons aged 11 through 13 years would continue to be protected. An economic analysis comparing the three adolescent vaccination strategies concluded that administering a booster dose has a cost per quality-adjusted life year similar to that of a single dose at age 11 years or age 15 years but is estimated to prevent twice the number of cases and deaths (CDC, unpublished data, 2010).

Rationale for 2-Dose Primary Series for Persons with a Reduced Response to a Single Dose

Evidence supporting the need for a 2-dose primary meningococcal vaccine series for the small number of persons at increased risk for meningococcal disease was reviewed. Data indicated that SBA could be increased with 2 doses, 2 months apart. For persons who are asplenic or have HIV infection, a 2-dose primary series improves the initial immune response to vaccination. A 2-dose primary series in patients with persistent complement component deficiency will help achieve the high

TABLE 1. Summary of serogroup C bactericidal antibody persistence as determined by serum bactericidal activity (SBA) 2–5 years after vaccination with Menveo and/or Menactra

Age group (yrs) at vaccination	Years postvaccination	Serogroup C SBA	Vaccine	No. of vaccine recipients in study	% of recipients with protective antibody levels
11 through 18*	2	% hSBA $\geq$ 1:8	Menveo	273	62
			Menactra	185	58
11 through 18 [†]	3	% hSBA $\geq$ 1:4	Menactra	52	35
			MPSV4	48	35
11 through 18 [§]	3	% brSBA $\geq$ 1:128	Menactra	71	75
			MPSV4	72	60
2 through 10 [§]	5	% brSBA $\geq$ 1:128	Menactra	108	55
			MPSV4	207	42
11 through 18 [§]	5	% brSBA $\geq$ 1:128	Menactra	16	56
			MPSV4	10	60

Abbreviations: hSBA = SBA using human complement; brSBA = SBA using baby rabbit complement; MPSV4 = quadrivalent meningococcal polysaccharide vaccine.

* **Source:** Gill C, Baxter R, Anemona A, Ciavarrò G, Dull P. Persistence of immune responses after a single dose of Novartis meningococcal serogroup A, C, W-135 and Y CRM-197 conjugate vaccine (Menveo) or Menactra among healthy adolescents. *Human Vaccines* 2010;6:881–7.

[†] **Source:** Vu DM, Welsch JA, Zuno-Mitchell P, Dela Cruz JV, Granoff DM. Antibody persistence 3 years after immunization of adolescents with quadrivalent meningococcal conjugate vaccine. *J Infect Dis* 2006;193:821–8.

[§] **Source:** Proceedings of the Advisory Committee on Immunization Practices (ACIP) meeting, June 2009.

levels of SBA activity needed to confer protection in the absence of effective opsonization.

The complement pathway is important to preventing meningococcal disease, and *Neisseria meningitidis* is the primary bacterial pathogen affecting persons with late component complement (LCCD) or properdin deficiency. Although persons with LCCD are able to mount an overall antibody response equal to or greater than complement-sufficient persons after vaccination with quadrivalent meningococcal polysaccharide vaccine (MPSV4), antibody titers wane more rapidly in persons with complement component deficiency, and higher antibody levels are needed for other clearance mechanisms such as opsonophagocytosis to function (9,10). Asplenic persons are at increased risk for invasive infection caused by many encapsulated bacteria, including *N. meningitidis*. Moreover, the mortality rate is 40%–70% among these persons when they become infected with *N. meningitidis*. Asplenic persons achieve significantly lower geometric mean SBA titers than healthy persons after vaccination with meningococcal C conjugate vaccine, with 20% not achieving brSBA titers $\geq$ 1:8. This proportion was reduced to 7% when a second dose of vaccine was administered to nonresponders 2 months later, suggesting a booster might be effective in achieving higher circulating antibody levels and improving immunologic memory (11).

Patients with HIV infection likely are at increased risk for meningococcal disease, although not to the extent that they are at risk for invasive *Streptococcus pneumoniae* infection. The

risk to persons with HIV infection also is not as great as to persons with complement component deficiency or asplenia. One study has investigated the response rates to a single dose of meningococcal conjugate vaccine among HIV-infected adolescents. Response to vaccination measured by brSBA titers $\geq$ 1:128 was 86%, 55%, 73%, and 72% for serogroups A, C, Y, and W-135, respectively. Response rates were significantly lower among patients with a CD4+ T-lymphocyte percentage of <15% or viral loads >10,000 copies/mL (12).

The immunogenicity and safety of a 2-dose primary series has not been studied in older children and adults. However, Menactra and Menveo have been studied following administration as a 2-dose primary series in infants and young children. Infants vaccinated with a 2-dose primary series of Menactra at ages 9 months and 12 through 15 months achieved high antibody titers after the second dose. Administration of 2 doses of Menveo 2 months apart to children aged 2 through 5 years was associated with a similar rate of adverse events as a single dose (13).

Recommendation for Routine Vaccination of Persons Aged 11 Through 18 Years

ACIP recommends routine vaccination of persons with quadrivalent meningococcal conjugate vaccine at age 11 or 12 years, with a booster dose at age 16 years. After a booster dose of meningococcal conjugate vaccine, antibody titers are higher than after the first dose and are expected to protect adolescents through the period of increased risk through age 21 years. For adolescents who receive the first dose at age 13 through 15 years, a one-time booster dose should be administered, preferably at age 16 through 18 years, before the peak in increased risk. Persons who receive their first dose of meningococcal conjugate vaccine at or after age 16 years do not need a booster dose. Routine vaccination of healthy persons who are not at increased risk for exposure to *N. meningitidis* is not recommended after age 21 years.

Recommendation for Persons Aged 2 Through 54 Years with Reduced Immune Response

Data indicate that the immune response to a single dose of meningococcal conjugate vaccine is not sufficient in persons with certain medical conditions. Persons with persistent

complement component deficiencies (e.g., C5–C9, properdin, factor H, or factor D) or asplenia should receive a 2-dose primary series administered 2 months apart and then receive a booster dose every 5 years. Adolescents aged 11 through 18 years with HIV infection should be routinely vaccinated with a 2-dose primary series. Other persons with HIV who are vaccinated should receive a 2-dose primary series administered 2 months apart. All other persons at increased risk for meningococcal disease (e.g., microbiologists or travelers to an epidemic or highly endemic country) should receive a single dose.

CDC Guidance for Transition to an Adolescent Booster Dose

Some schools, colleges, and universities have policies requiring vaccination against meningococcal disease as a condition of enrollment. For ease of program implementation, persons aged 21 years or younger should have documentation of receipt of a dose of meningococcal conjugate vaccine not more than 5 years before enrollment. If the primary dose was administered before the 16th birthday, a booster dose should be administered before enrollment in college. The booster dose can be administered anytime after the 16th birthday to ensure that the booster is provided. The minimum interval between doses of meningococcal conjugate vaccine is 8 weeks.

No data are available on the interchangeability of vaccine products. Whenever feasible, the same brand of vaccine should be used for all doses of the vaccination series. If vaccination providers do not know or have available the type of vaccine product previously administered, any product should be used

to continue or complete the series. Persons with complement component deficiency, asplenia, or HIV infection who have previously received a single dose of meningococcal conjugate vaccine should receive their booster dose at the earliest opportunity.

These updated meningococcal conjugate vaccine recommendations from ACIP have been summarized (Table 2). Additionally, a meningococcal conjugate vaccine information statement is available at <http://www.cdc.gov/vaccines/pubs/vis/default.htm>, and details regarding the routine meningococcal conjugate vaccination schedule are available at <http://www.cdc.gov/vaccines/recs/schedules/default.htm#child>. Adverse events after receipt of any vaccine should be reported to the Vaccine Adverse Event Reporting System at <http://vaers.hhs.gov>.

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TABLE 2. Summary of meningococcal conjugate vaccine recommendations, by risk group — Advisory Committee on Immunization Practices (ACIP), 2010

Risk group	Primary series	Booster dose
Persons aged 11 through 18 years	1 dose, preferably at age 11 or 12 years	At age 16 years if primary dose at age 11 or 12 years At age 16 through 18 years if primary dose at age 13 through 15 years No booster needed if primary dose on or after age 16 years
HIV-infected persons in this age group	2 doses, 2 months apart	At age 16 years if primary dose at age 11 or 12 years At age 16 through 18 years if primary dose at age 13 through 15 years No booster needed if primary dose on or after age 16 years
Persons aged 2 through 55 years with persistent complement component deficiency* or functional or anatomical asplenia	2 doses, 2 months apart	Every 5 years At the earliest opportunity if a 1-dose primary series administered, then every 5 years
Persons aged 2 through 55 years with prolonged increased risk for exposure [†]	1 dose	Persons aged 2 through 6 years: after 3 years Persons aged 7 years or older: after 5 years [§]

Abbreviation: HIV = human immunodeficiency virus.

* Such as C5–C9, properdin, or factor D.

[†] Microbiologists routinely working with *Neisseria meningitidis* and travelers to or residents of countries where meningococcal disease is hyperendemic or epidemic.

[§] If the person remains at increased risk.

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Notes from the Field

Respiratory Diphtheria-Like Illness Caused by Toxigenic *Corynebacterium ulcerans* — Idaho, 2010

On September 12, 2010, the Idaho Department of Health and Welfare was notified of a case of respiratory diphtheria-like illness in an Idaho man aged 80 years whose pharyngeal specimens yielded *Corynebacterium ulcerans*. Although *C. ulcerans* is zoonotic, the patient reported no animal contact or consumption of an unpasteurized dairy product. His vaccination history was unknown. Respiratory diphtheria-like illness from *C. ulcerans* is uncommon but has been reported in industrialized countries where respiratory diphtheria is rare. The last case of diphtheria-like illness caused by *C. ulcerans* in the United States was reported in 2005 (1).

On September 5, the patient had sought medical attention for nasal congestion and voice changes; treatment for allergic rhinitis did not improve his condition. On September 9, the patient was hospitalized for a surgical procedure to alleviate bilateral obstruction of the nasal passages, during which a pseudomembrane was observed. On September 11, he experienced stridor, required intubation, and became febrile with signs of sepsis. Throughout the next day, severe neck swelling developed, and a computed tomography scan revealed pronounced hypopharyngeal mucosal thickening. On suspicion of respiratory diphtheria, the patient was treated with azithromycin. On September 12, *C. ulcerans* was isolated from pharyngeal tissue surgically removed on September 9, and a 100,000 international-unit dose of diphtheria antitoxin (DAT) was requested and received from CDC. After DAT administration on September 12, the patient had a complicated recovery and was discharged on October 6. On September 20, CDC reported that the *C. ulcerans* isolates were toxigenic by the Elek agar virulence test.

Respiratory diphtheria-like illness caused by toxigenic *C. ulcerans* infections can be clinically indistinguishable from toxigenic *Corynebacterium diphtheriae* infections. Both organisms can produce diphtheria toxin and lead to life-threatening disease that requires urgent treatment with DAT and antibiotics. Although the hallmark of respiratory diphtheria is the presence of a pseudomembrane in the pharynx (1), the pseudomembrane in this patient was only visible during a

surgical procedure. Clinicians should consider respiratory diphtheria among patients who have low-grade fever and pseudomembranous pharyngitis. If diphtheria is suspected, patients should receive urgent treatment with DAT without waiting for laboratory confirmation. Health-care providers can obtain DAT by contacting CDC's Emergency Operations Center at 770-488-7100.

Antibiotic treatment of diphtheria-like illness caused by *C. ulcerans* should follow clinical guidelines for patients infected with *C. diphtheriae* (2). Unlike *C. diphtheriae* infections, human-to-human transmission of *C. ulcerans* infections has not been documented (3); therefore, postexposure antibiotic prophylaxis was not administered to close contacts of the Idaho patient. However, because studies on the transmission of *C. ulcerans* are limited, vaccination status of contacts should be assessed and brought up-to-date, if necessary, with an age-appropriate diphtheria-toxoid-containing vaccine, which prevents disease from toxigenic strains of *C. diphtheriae* and *C. ulcerans*. CDC recommends that adults receive a diphtheria-toxoid-containing vaccine every 10 years after completing a primary childhood vaccination series (4).

Reported by

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Notifiable Diseases and Mortality Tables

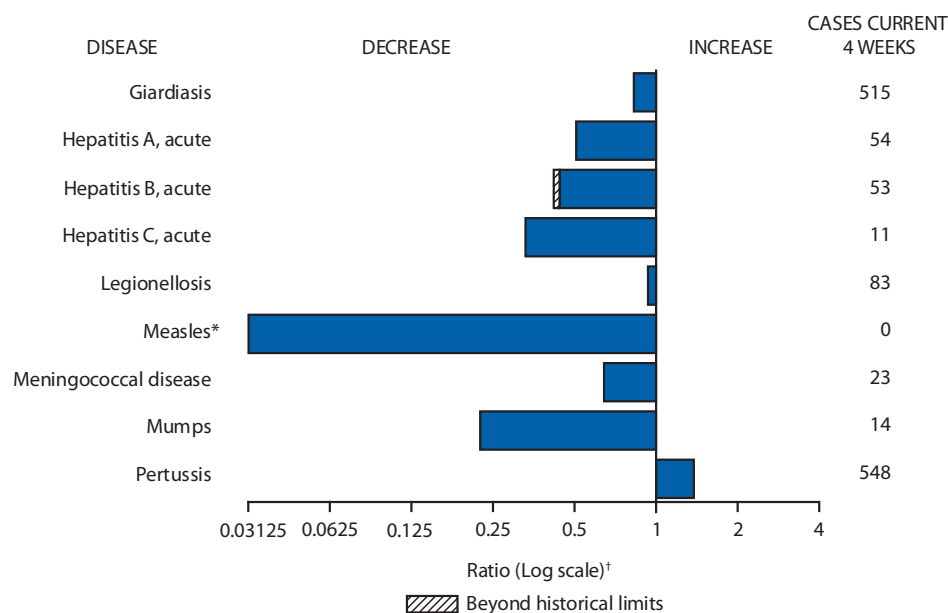
TABLE I. Provisional cases of infrequently reported notifiable diseases (<1,000 cases reported during the preceding year) — United States, week ending January 22, 2011 (3rd week)*

Disease	Current week	Cum 2011	5-year weekly average†	Total cases reported for previous years					States reporting cases during current week (No.)
				2010	2009	2008	2007	2006	
Anthrax	—	—	—	—	1	—	1	1	
Arboviral diseases §, ¶:									
California serogroup virus disease	—	—	—	72	55	62	55	67	
Eastern equine encephalitis virus disease	—	—	—	10	4	4	4	8	
Powassan virus disease	—	—	0	5	6	2	7	1	
St. Louis encephalitis virus disease	—	—	0	8	12	13	9	10	
Western equine encephalitis virus disease	—	—	—	—	—	—	—	—	
Babesiosis	—	—	—	NN	NN	NN	NN	NN	
Botulism, total	—	1	1	108	118	145	144	165	
foodborne	—	—	0	7	10	17	32	20	
infant	—	1	1	76	83	109	85	97	
other (wound and unspecified)	—	—	0	25	25	19	27	48	
Brucellosis	—	3	1	125	115	80	131	121	
Chancroid	—	2	1	37	28	25	23	33	
Cholera	—	1	0	11	10	5	7	9	
Cyclosporiasis §	1	2	4	171	141	139	93	137	FL (1)
Diphtheria	—	—	—	—	—	—	—	—	
<i>Haemophilus influenzae</i> , ** invasive disease (age <5 yrs):									
serotype b	—	—	1	17	35	30	22	29	
nonserotype b	—	—	5	153	236	244	199	175	
unknown serotype	4	15	4	264	178	163	180	179	PA (1), FL (1), OK (1), CA (1)
Hansen disease §	1	2	2	58	103	80	101	66	CA (1)
Hantavirus pulmonary syndrome §	—	1	0	17	20	18	32	40	
Hemolytic uremic syndrome, postdiarrheal §	—	3	1	219	242	330	292	288	
Influenza-associated pediatric mortality §, ††	3	9	2	61	358	90	77	43	WV (1), CO (1), UT (1)
Listeriosis	6	14	13	764	851	759	808	884	NY (2), FL (2), CO (1), OR (1)
Measles §§	—	—	0	57	71	140	43	55	
Meningococcal disease, invasive ¶¶:									
A, C, Y, and W-135	—	4	5	243	301	330	325	318	
serogroup B	—	—	3	109	174	188	167	193	
other serogroup	—	—	1	9	23	38	35	32	
unknown serogroup	6	20	11	414	482	616	550	651	MO (1), NE (1), KS (1), CA (3)
Novel influenza A virus infections***	—	—	—	4	43,774	2	4	NN	
Plague	—	—	0	2	8	3	7	17	
Poliomyelitis, paralytic	—	—	—	—	1	—	—	—	
Polio virus Infection, nonparalytic §	—	—	—	—	—	—	—	NN	
Psittacosis §	—	—	0	4	9	8	12	21	
Q fever, total §	1	3	1	120	113	120	171	169	
acute	1	3	1	91	93	106	—	—	CA (1)
chronic	—	—	0	29	20	14	—	—	
Rabies, human	—	—	—	1	4	2	1	3	
Rubella †††	—	—	0	6	3	16	12	11	
Rubella, congenital syndrome	—	—	0	—	2	—	—	1	
SARS-CoV §	—	—	—	—	—	—	—	—	
Smallpox §	—	—	—	—	—	—	—	—	
Streptococcal toxic-shock syndrome §	2	7	2	159	161	157	132	125	VT (1), PA (1)
Syphilis, congenital (age <1 yr) §§§	—	—	8	233	423	431	430	349	
Tetanus	—	—	0	8	18	19	28	41	
Toxic-shock syndrome (staphylococcal) §	—	2	1	75	74	71	92	101	
Trichinellosis	—	2	0	4	13	39	5	15	
Tularemia	—	—	0	110	93	123	137	95	
Typhoid fever	—	2	8	415	397	449	434	353	
Vancomycin-intermediate <i>Staphylococcus aureus</i> §	—	2	1	90	78	63	37	6	
Vancomycin-resistant <i>Staphylococcus aureus</i> §	—	—	—	1	1	—	2	1	
Vibriosis (noncholera <i>Vibrio</i> species infections) §	1	4	5	767	789	588	549	NN	FL (1)
Viral hemorrhagic fever ¶¶¶	—	—	0	1	NN	NN	NN	NN	
Yellow fever	—	—	—	—	—	—	—	—	

See Table 1 footnotes on next page.

TABLE I. (Continued) Provisional cases of infrequently reported notifiable diseases (<1,000 cases reported during the preceding year) — United States, week ending January 22, 2011 (3rd week)*

—: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts.
 * Case counts for reporting years 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see <http://www.cdc.gov/ncphi/diss/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf>.
 † Calculated by summing the incidence counts for the current week, the 2 weeks preceding the current week, and the 2 weeks following the current week, for a total of 5 preceding years. Additional information is available at <http://www.cdc.gov/ncphi/diss/nndss/phs/files/5yearweeklyaverage.pdf>.
 ‡ Not reportable in all states. Data from states where the condition is not reportable are excluded from this table except starting in 2007 for the arboviral diseases, STD data, TB data, and influenza-associated pediatric mortality, and in 2003 for SARS-CoV. Reporting exceptions are available at <http://www.cdc.gov/ncphi/diss/nndss/phs/infdis.htm>.
 ¶ Includes both neuroinvasive and nonneuroinvasive. Updated weekly from reports to the Division of Vector-Borne Infectious Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases (ArboNET Surveillance). Data for West Nile virus are available in Table II.
 ** Data for H. influenzae (all ages, all serotypes) are available in Table II.
 †† Updated weekly from reports to the Influenza Division, National Center for Immunization and Respiratory Diseases. Since October 3, 2010, 13 influenza-associated pediatric deaths occurred during the 2010-11 influenza season. Since August 30, 2009, a total of 282 influenza-associated pediatric deaths occurring during the 2009-10 influenza season have been reported.
 ‡‡ No measles cases were reported for the current week.
 ¶¶ Data for meningococcal disease (all serogroups) are available in Table II.
 *** CDC discontinued reporting of individual confirmed and probable cases of 2009 pandemic influenza A (H1N1) virus infections on July 24, 2009. During 2009, four cases of human infection with novel influenza A viruses, different from the 2009 pandemic influenza A (H1N1) strain, were reported to CDC. The four cases of novel influenza A virus infection reported to CDC during 2010 were identified as swine influenza A (H3N2) virus and are unrelated to the 2009 pandemic influenza A (H1N1) virus. Total case counts for 2009 were provided by the Influenza Division, National Center for Immunization and Respiratory Diseases (NCIRD).
 ††† No rubella cases were reported for the current week.
 §§§ Updated weekly from reports to the Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention.
 ¶¶¶ There was one case of viral hemorrhagic fever reported during week 12 of 2010. The one case report was confirmed as lassa fever. See Table II for dengue hemorrhagic fever.

FIGURE I. Selected notifiable disease reports, United States, comparison of provisional 4-week totals January 22, 2011, with historical data

* No measles cases were reported for the current 4-week period yielding a ratio for week three of zero (0).

† Ratio of current 4-week total to mean of 15 4-week totals (from previous, comparable, and subsequent 4-week periods for the past 5 years). The point where the hatched area begins is based on the mean and two standard deviations of these 4-week totals.

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Morbidity and Mortality Weekly Report

TABLE II. Provisional cases of selected notifiable diseases, United States, weeks ending January 22, 2011, and January 23, 2010 (3rd week)*

Reporting area	Chlamydia trachomatis infection					Coccidioidomycosis					Cryptosporidiosis				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	10,001	23,909	26,327	42,487	66,493	156	0	370	737	NN	36	119	348	145	364
New England	494	781	1,213	1,600	1,623	—	0	0	—	NN	—	7	19	2	97
Connecticut	—	177	402	—	112	N	0	0	N	NN	—	0	2	2	71
Maine†	—	50	100	—	149	N	0	0	N	NN	—	1	7	—	7
Massachusetts	389	402	693	1,279	997	N	0	0	N	NN	—	3	9	—	9
New Hampshire	32	50	113	121	134	—	0	0	—	NN	—	1	5	—	4
Rhode Island†	43	66	121	115	169	—	0	0	—	NN	—	0	2	—	1
Vermont†	30	23	51	85	62	N	0	0	N	NN	—	1	5	—	5
Mid. Atlantic	1,472	3,354	5,066	4,838	8,931	—	0	0	—	NN	6	15	38	18	32
New Jersey	352	509	680	1,120	1,402	N	0	0	N	NN	—	0	4	—	1
New York (Upstate)	582	696	1,496	1,372	1,144	N	0	0	N	NN	3	4	13	4	3
New York City	—	1,220	2,768	—	3,814	N	0	0	N	NN	—	2	6	—	3
Pennsylvania	538	946	1,092	2,346	2,571	N	0	0	N	NN	3	8	26	14	25
E.N. Central	911	3,511	3,994	5,630	10,694	—	0	0	—	NN	8	29	126	41	89
Illinois	18	781	1,036	590	2,902	N	0	0	N	NN	—	4	21	1	17
Indiana	—	367	798	344	554	N	0	0	N	NN	—	3	10	1	10
Michigan	599	946	1,419	2,607	2,891	—	0	0	—	NN	—	5	18	6	20
Ohio	152	988	1,109	1,287	3,065	—	0	0	—	NN	7	8	24	30	17
Wisconsin	142	427	516	802	1,282	N	0	0	N	NN	1	10	61	3	25
W.N. Central	167	1,379	1,556	1,635	4,148	—	0	0	—	NN	7	21	83	20	24
Iowa	13	200	237	320	659	N	0	0	N	NN	—	4	24	2	8
Kansas	7	189	235	313	607	N	0	0	N	NN	1	2	9	1	6
Minnesota	—	280	349	117	950	—	0	0	—	NN	—	0	16	—	—
Missouri	109	505	620	571	1,335	—	0	0	—	NN	1	4	30	5	5
Nebraska†	19	95	179	160	339	N	0	0	N	NN	5	3	26	10	3
North Dakota	—	28	79	—	61	N	0	0	N	NN	—	0	9	—	—
South Dakota	19	61	78	154	197	N	0	0	N	NN	—	1	6	2	2
S. Atlantic	2,592	4,719	5,652	10,414	12,872	—	0	0	—	NN	5	19	51	37	37
Delaware	64	84	220	197	244	—	0	0	—	NN	—	0	1	1	1
District of Columbia	—	91	177	76	207	—	0	0	—	NN	—	0	1	—	1
Florida	631	1,460	1,708	3,025	3,908	N	0	0	N	NN	5	7	19	24	15
Georgia	—	610	1,217	—	910	N	0	0	N	NN	—	5	31	7	13
Maryland†	—	469	804	735	725	—	0	0	—	NN	—	1	3	2	1
North Carolina	519	756	1,436	2,577	3,332	N	0	0	N	NN	—	0	12	—	2
South Carolina†	492	530	847	1,150	1,459	N	0	0	N	NN	—	1	8	1	1
Virginia†	819	599	882	2,381	1,926	N	0	0	N	NN	—	2	8	2	2
West Virginia	67	74	122	273	161	N	0	0	N	NN	—	0	3	—	1
E.S. Central	617	1,751	2,415	2,877	4,332	—	0	0	—	NN	1	4	19	3	10
Alabama†	285	533	796	1,209	1,287	N	0	0	N	NN	—	2	13	—	—
Kentucky	99	264	614	153	565	N	0	0	N	NN	1	1	6	2	3
Mississippi	233	377	780	815	953	N	0	0	N	NN	—	0	2	—	3
Tennessee†	—	572	796	700	1,527	N	0	0	N	NN	—	1	5	1	4
W.S. Central	2,098	3,002	4,310	7,395	10,100	—	0	0	—	NN	1	7	29	1	3
Arkansas†	226	273	391	796	790	N	0	0	N	NN	—	0	3	—	—
Louisiana	417	310	824	1,449	1,761	—	0	0	—	NN	—	1	6	—	—
Oklahoma	253	254	1,374	550	1,764	N	0	0	N	NN	1	1	8	1	—
Texas†	1,202	2,294	3,183	4,600	5,785	N	0	0	N	NN	—	4	22	—	3
Mountain	399	1,438	1,913	1,847	3,695	75	0	315	571	NN	5	10	30	11	37
Arizona	234	509	706	622	1,089	75	0	314	570	NN	—	0	3	1	2
Colorado	—	336	560	185	1,102	N	0	0	N	NN	5	2	8	6	10
Idaho†	—	68	200	—	139	N	0	0	N	NN	—	2	7	3	6
Montana†	22	62	82	148	156	N	0	0	N	NN	—	1	4	—	3
Nevada†	143	176	329	527	482	—	0	0	—	NN	—	0	7	—	1
New Mexico†	—	162	274	293	141	—	0	0	—	NN	—	2	12	1	8
Utah	—	118	151	72	440	—	0	1	1	NN	—	1	5	—	5
Wyoming†	—	42	90	—	146	—	0	0	—	NN	—	0	2	—	2
Pacific	1,251	3,695	4,558	6,251	10,098	81	0	55	166	NN	3	12	28	12	35
Alaska	—	112	148	213	374	N	0	0	N	NN	—	0	1	—	2
California	878	2,771	3,569	4,648	7,650	81	0	55	166	NN	1	6	18	5	21
Hawaii	—	112	158	—	353	N	0	0	N	NN	—	0	1	—	1
Oregon	83	212	496	481	515	N	0	0	N	NN	2	3	13	7	8
Washington	290	404	661	909	1,206	N	0	0	N	NN	—	1	6	—	3
Territories															
American Samoa	—	0	0	—	—	N	0	0	N	NN	N	0	0	N	NN
C.N.M.I.	—	—	—	—	—	—	—	—	—	NN	—	—	—	—	—
Guam	—	8	31	—	—	—	0	0	—	NN	—	0	0	—	—
Puerto Rico	—	93	265	286	260	N	0	0	N	NN	N	0	0	N	NN
U.S. Virgin Islands	—	12	29	—	27	—	0	0	—	NN	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see <http://www.cdc.gov/ncphi/diss/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf>. Data for TB are displayed in Table IV, which appears quarterly.

† Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending January 22, 2011, and January 23, 2010 (3rd week)*

Reporting area	Dengue Virus Infection									
	Dengue Fever [†]					Dengue Hemorrhagic Fever [‡]				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max		
United States	—	6	37	—	23	—	0	2	—	—
New England	—	0	3	—	1	—	0	0	—	—
Connecticut	—	0	0	—	—	—	0	0	—	—
Maine [¶]	—	0	2	—	1	—	0	0	—	—
Massachusetts	—	0	0	—	—	—	0	0	—	—
New Hampshire	—	0	0	—	—	—	0	0	—	—
Rhode Island [¶]	—	0	0	—	—	—	0	0	—	—
Vermont [¶]	—	0	1	—	—	—	0	0	—	—
Mid. Atlantic	—	1	12	—	11	—	0	1	—	—
New Jersey	—	0	0	—	—	—	0	0	—	—
New York (Upstate)	—	0	0	—	—	—	0	0	—	—
New York City	—	1	12	—	8	—	0	1	—	—
Pennsylvania	—	0	3	—	3	—	0	0	—	—
E.N. Central	—	1	7	—	3	—	0	1	—	—
Illinois	—	0	2	—	1	—	0	0	—	—
Indiana	—	0	2	—	—	—	0	0	—	—
Michigan	—	0	2	—	—	—	0	0	—	—
Ohio	—	0	2	—	2	—	0	0	—	—
Wisconsin	—	0	2	—	—	—	0	1	—	—
W.N. Central	—	0	6	—	—	—	0	1	—	—
Iowa	—	0	1	—	—	—	0	0	—	—
Kansas	—	0	1	—	—	—	0	0	—	—
Minnesota	—	0	2	—	—	—	0	0	—	—
Missouri	—	0	0	—	—	—	0	0	—	—
Nebraska [¶]	—	0	6	—	—	—	0	0	—	—
North Dakota	—	0	1	—	—	—	0	0	—	—
South Dakota	—	0	0	—	—	—	0	1	—	—
S. Atlantic	—	2	17	—	4	—	0	1	—	—
Delaware	—	0	0	—	—	—	0	0	—	—
District of Columbia	—	0	0	—	—	—	0	0	—	—
Florida	—	2	14	—	3	—	0	1	—	—
Georgia	—	0	2	—	1	—	0	0	—	—
Maryland [¶]	—	0	0	—	—	—	0	0	—	—
North Carolina	—	0	1	—	—	—	0	0	—	—
South Carolina [¶]	—	0	3	—	—	—	0	0	—	—
Virginia [¶]	—	0	3	—	—	—	0	0	—	—
West Virginia	—	0	1	—	—	—	0	0	—	—
E.S. Central	—	0	2	—	—	—	0	0	—	—
Alabama [¶]	—	0	2	—	—	—	0	0	—	—
Kentucky	—	0	1	—	—	—	0	0	—	—
Mississippi	—	0	0	—	—	—	0	0	—	—
Tennessee [¶]	—	0	1	—	—	—	0	0	—	—
W.S. Central	—	0	1	—	—	—	0	1	—	—
Arkansas [¶]	—	0	0	—	—	—	0	1	—	—
Louisiana	—	0	0	—	—	—	0	0	—	—
Oklahoma	—	0	1	—	—	—	0	0	—	—
Texas [¶]	—	0	0	—	—	—	0	0	—	—
Mountain	—	0	2	—	1	—	0	0	—	—
Arizona	—	0	1	—	—	—	0	0	—	—
Colorado	—	0	0	—	—	—	0	0	—	—
Idaho [¶]	—	0	1	—	—	—	0	0	—	—
Montana [¶]	—	0	1	—	—	—	0	0	—	—
Nevada [¶]	—	0	1	—	1	—	0	0	—	—
New Mexico [¶]	—	0	1	—	—	—	0	0	—	—
Utah	—	0	0	—	—	—	0	0	—	—
Wyoming [¶]	—	0	0	—	—	—	0	0	—	—
Pacific	—	0	5	—	3	—	0	0	—	—
Alaska	—	0	1	—	—	—	0	0	—	—
California	—	0	5	—	1	—	0	0	—	—
Hawaii	—	0	0	—	—	—	0	0	—	—
Oregon	—	0	0	—	—	—	0	0	—	—
Washington	—	0	2	—	2	—	0	0	—	—
Territories										
American Samoa	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	109	525	—	239	—	1	14	—	6
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see <http://www.cdc.gov/ncphi/diss/nndss/phs/files/ProvisionalNationa%20NotifiableDiseasesSurveillanceData20100927.pdf>. Data for TB are displayed in Table IV, which appears quarterly.[†] Dengue Fever includes cases that meet criteria for Dengue Fever with hemorrhage, other clinical and unknown case classifications.[‡] DHF includes cases that meet criteria for dengue shock syndrome (DSS), a more severe form of DHF.[¶] Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending January 22, 2011, and January 23, 2010 (3rd week)*

Reporting area	Ehrlichiosis/Anaplasmosis†														
	<i>Ehrlichia chaffeensis</i>				<i>Anaplasma phagocytophilum</i>				Undetermined						
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	1	8	47	2	3	—	11	56	1	3	—	1	10	1	—
New England	—	0	1	—	—	—	1	8	—	1	—	0	2	—	—
Connecticut	—	0	0	—	—	—	0	5	—	—	—	0	2	—	—
Maine§	—	0	1	—	—	—	0	2	—	1	—	0	0	—	—
Massachusetts	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
New Hampshire	—	0	1	—	—	—	0	3	—	—	—	0	1	—	—
Rhode Island§	—	0	0	—	—	—	0	5	—	—	—	0	0	—	—
Vermont§	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Mid. Atlantic	—	1	5	—	—	—	4	12	1	—	—	0	1	—	—
New Jersey	—	0	0	—	—	—	0	1	—	—	—	0	0	—	—
New York (Upstate)	—	0	5	—	—	—	4	12	1	—	—	0	1	—	—
New York City	—	0	3	—	—	—	0	1	—	—	—	0	0	—	—
Pennsylvania	—	0	1	—	—	—	0	0	—	—	—	0	0	—	—
E.N. Central	—	0	4	—	—	—	4	39	—	—	—	1	7	1	—
Illinois	—	0	2	—	—	—	0	2	—	—	—	0	2	—	—
Indiana	—	0	0	—	—	—	0	0	—	—	—	0	3	1	—
Michigan	—	0	1	—	—	—	0	0	—	—	—	0	1	—	—
Ohio	—	0	3	—	—	—	0	1	—	—	—	0	0	—	—
Wisconsin	—	0	1	—	—	—	4	39	—	—	—	0	4	—	—
W.N. Central	—	1	13	—	—	—	0	3	—	—	—	0	3	—	—
Iowa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Kansas	—	0	1	—	—	—	0	0	—	—	—	0	0	—	—
Minnesota	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Missouri	—	1	13	—	—	—	0	3	—	—	—	0	3	—	—
Nebraska§	—	0	1	—	—	—	0	0	—	—	—	0	0	—	—
North Dakota	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
South Dakota	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
S. Atlantic	1	4	19	2	3	—	1	7	—	2	—	0	2	—	—
Delaware	—	0	3	—	—	—	0	1	—	—	—	0	0	—	—
District of Columbia	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Florida	1	0	2	1	1	—	0	1	—	—	—	0	0	—	—
Georgia	—	0	4	1	1	—	0	1	—	1	—	0	1	—	—
Maryland§	—	0	3	—	1	—	0	2	—	1	—	0	2	—	—
North Carolina	—	1	13	—	—	—	0	4	—	—	—	0	0	—	—
South Carolina§	—	0	2	—	—	—	0	1	—	—	—	0	0	—	—
Virginia§	—	1	8	—	—	—	0	2	—	—	—	0	1	—	—
West Virginia	—	0	1	—	—	—	0	0	—	—	—	0	0	—	—
E.S. Central	—	0	10	—	—	—	0	2	—	—	—	0	1	—	—
Alabama§	—	0	3	—	—	—	0	2	—	—	—	0	0	—	—
Kentucky	—	0	2	—	—	—	0	0	—	—	—	0	0	—	—
Mississippi	—	0	1	—	—	—	0	1	—	—	—	0	0	—	—
Tennessee§	—	0	6	—	—	—	0	2	—	—	—	0	1	—	—
W.S. Central	—	0	5	—	—	—	0	2	—	—	—	0	1	—	—
Arkansas§	—	0	5	—	—	—	0	2	—	—	—	0	0	—	—
Louisiana	—	0	1	—	—	—	0	0	—	—	—	0	0	—	—
Oklahoma	—	0	5	—	—	—	0	1	—	—	—	0	0	—	—
Texas§	—	0	1	—	—	—	0	1	—	—	—	0	1	—	—
Mountain	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Arizona	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Colorado	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Idaho§	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Montana§	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Nevada§	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
New Mexico§	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Utah	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Wyoming§	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Pacific	—	0	1	—	—	—	0	0	—	—	—	0	1	—	—
Alaska	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
California	—	0	1	—	—	—	0	0	—	—	—	0	1	—	—
Hawaii	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Oregon	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Washington	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Territories															
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see <http://www.cdc.gov/ncphi/diss/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf>. Data for TB are displayed in Table IV, which appears quarterly.† Cumulative total *E. ewingii* cases reported for year 2010 = 10 and 0 case reports for 2011.

§ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending January 22, 2011, and January 23, 2010 (3rd week)*

Reporting area	Giardiasis					Gonorrhea					Haemophilus influenzae, invasive† All ages, all serotypes				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	99	330	481	444	862	2,494	5,595	6,399	10,679	16,411	36	58	77	141	218
New England	—	32	54	5	87	55	100	196	145	197	—	3	9	3	14
Connecticut	—	5	13	—	20	—	39	169	—	48	—	0	6	—	—
Maine [§]	—	4	12	3	9	—	3	11	—	15	—	0	1	1	—
Massachusetts	—	13	25	—	42	54	47	80	138	100	—	2	5	—	11
New Hampshire	—	3	8	2	8	1	3	7	5	13	—	0	2	1	2
Rhode Island [§]	—	1	7	—	1	—	4	15	—	17	—	0	2	—	1
Vermont [§]	—	3	10	—	7	—	0	17	2	4	—	0	3	1	—
Mid. Atlantic	20	61	106	95	161	386	690	1,166	1,178	1,954	4	11	21	31	45
New Jersey	—	6	18	—	28	136	109	174	360	343	—	2	5	4	5
New York (Upstate)	9	22	54	25	36	82	108	203	208	198	1	3	12	3	9
New York City	4	17	33	37	45	—	235	531	—	752	—	2	6	3	7
Pennsylvania	7	14	27	33	52	168	256	366	610	661	3	4	11	21	24
E.N. Central	15	54	86	71	156	246	954	1,197	1,638	3,095	6	10	20	22	35
Illinois	—	11	28	—	32	4	191	244	164	754	—	3	7	2	11
Indiana	—	5	13	—	24	—	99	222	92	205	—	1	6	—	3
Michigan	4	13	25	21	35	170	254	471	824	895	—	0	3	3	—
Ohio	10	17	29	44	42	44	313	381	371	971	6	2	6	15	11
Wisconsin	1	9	33	6	23	28	93	156	187	270	—	2	5	2	10
W.N. Central	8	24	101	37	69	44	287	350	409	828	3	3	14	4	9
Iowa	1	5	11	8	21	2	33	57	60	111	—	0	1	—	—
Kansas	2	3	10	4	15	1	40	62	60	112	—	0	2	—	1
Minnesota	—	0	75	—	—	—	37	62	20	126	—	0	9	—	—
Missouri	3	8	26	14	15	33	141	181	199	373	1	2	4	2	7
Nebraska [§]	2	4	9	10	12	8	22	49	55	78	2	0	3	2	1
North Dakota	—	0	5	—	—	—	1	8	—	4	—	0	2	—	—
South Dakota	—	1	7	1	6	—	7	20	15	24	—	0	0	—	—
S. Atlantic	23	71	101	108	156	699	1,335	1,790	2,819	4,093	12	14	26	40	50
Delaware	—	0	5	—	2	13	19	48	48	37	—	0	1	—	—
District of Columbia	—	1	5	—	—	—	34	66	30	90	—	0	1	—	—
Florida	22	41	75	88	94	176	382	489	861	1,205	6	4	9	20	10
Georgia	1	7	51	6	16	—	205	392	—	291	3	3	7	11	19
Maryland [§]	—	5	11	4	17	—	133	217	221	225	—	1	5	2	2
North Carolina	N	0	0	N	N	212	242	596	867	1,274	—	2	9	—	6
South Carolina [§]	—	2	9	1	6	159	152	262	348	457	—	2	5	—	10
Virginia [§]	—	9	19	9	18	122	148	223	389	488	3	2	4	7	3
West Virginia	—	0	6	—	3	17	11	26	55	26	—	0	3	—	—
E.S. Central	—	5	12	1	9	189	473	697	864	1,301	1	3	10	14	18
Alabama [§]	—	4	11	1	4	92	158	247	405	406	—	1	4	6	1
Kentucky	N	0	0	N	N	23	73	160	39	160	—	1	3	3	4
Mississippi	N	0	0	N	N	74	111	216	253	296	—	0	2	—	—
Tennessee [§]	—	0	6	—	5	—	135	195	167	439	1	2	5	5	13
W.S. Central	—	7	14	2	21	556	833	1,298	1,992	2,832	3	2	10	5	5
Arkansas [§]	—	2	7	1	3	71	80	133	255	251	—	0	3	—	—
Louisiana	—	3	8	1	12	110	90	273	400	592	—	0	4	1	4
Oklahoma	—	0	5	—	6	107	75	332	196	482	3	1	7	4	1
Texas [§]	N	0	0	N	N	268	602	959	1,141	1,507	—	0	1	—	—
Mountain	10	31	51	34	78	62	178	235	345	408	5	5	15	11	36
Arizona	1	3	8	4	11	38	59	100	106	163	—	2	7	—	17
Colorado	7	13	27	22	23	—	54	95	47	130	5	1	5	6	3
Idaho [§]	2	4	9	8	11	—	2	14	—	8	—	0	2	2	1
Montana [§]	—	2	7	—	2	1	2	6	5	4	—	0	1	—	—
Nevada [§]	—	1	11	—	3	23	30	94	121	77	—	0	2	—	2
New Mexico [§]	—	2	5	—	2	—	21	35	65	14	—	1	3	3	7
Utah	—	4	11	—	16	—	5	15	1	12	—	0	4	—	4
Wyoming [§]	—	1	3	—	10	—	0	4	—	—	—	0	2	—	2
Pacific	23	53	92	91	125	257	605	815	1,289	1,703	2	2	21	11	6
Alaska	—	1	6	1	6	—	23	37	29	76	—	0	2	1	3
California	19	33	57	68	87	200	501	691	1,111	1,392	1	0	18	4	—
Hawaii	—	0	4	—	1	—	14	26	—	45	—	0	2	—	—
Oregon	4	9	20	19	25	13	19	34	37	51	1	1	5	6	3
Washington	—	8	46	3	6	44	53	83	112	139	—	0	2	—	—
Territories	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	1	—	—	—	0	5	—	—	—	0	0	—	—
Puerto Rico	1	1	8	1	—	—	6	14	16	6	—	0	1	—	—
U.S. Virgin Islands	—	0	0	—	—	—	3	7	—	4	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

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† Data for H. influenzae (age <5 yrs for serotype b, nonserotype b, and unknown serotype) are available in Table I.

§ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending January 22, 2011, and January 23, 2010 (3rd week)*

Reporting area	Hepatitis (viral, acute), by type														
	A					B					C				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	13	30	44	46	76	7	61	91	39	138	3	13	25	10	35
New England	—	2	5	1	7	—	1	5	1	4	—	1	4	—	5
Connecticut	—	0	3	—	2	—	0	2	—	2	—	0	4	—	1
Maine†	—	0	1	—	—	—	0	2	—	—	—	0	0	—	—
Massachusetts	—	1	5	—	5	—	0	2	—	2	—	0	1	—	4
New Hampshire	—	0	1	—	—	—	0	2	1	—	N	0	0	N	N
Rhode Island†	—	0	4	—	—	U	0	0	U	U	U	0	0	U	U
Vermont†	—	0	1	1	—	—	0	1	—	—	—	0	1	—	—
Mid. Atlantic	2	4	10	5	13	2	5	10	4	9	2	2	6	2	3
New Jersey	—	0	2	—	2	—	1	5	—	1	—	0	2	—	—
New York (Upstate)	1	1	4	1	—	2	1	6	2	1	2	1	4	2	3
New York City	1	1	7	2	5	—	1	4	—	3	—	0	1	—	—
Pennsylvania	—	1	4	2	6	—	1	5	2	4	—	0	3	—	—
E.N. Central	1	4	9	4	16	—	9	17	1	27	—	2	7	1	4
Illinois	—	1	3	—	2	—	2	5	—	5	—	0	1	—	—
Indiana	—	0	2	—	—	—	1	5	—	4	—	0	2	1	—
Michigan	—	1	5	1	5	—	2	6	—	8	—	1	6	—	4
Ohio	1	1	5	3	2	—	2	6	1	6	—	0	1	—	—
Wisconsin	—	0	3	—	7	—	2	8	—	4	—	0	2	—	—
W.N. Central	—	1	13	1	5	2	2	7	4	7	—	0	8	—	—
Iowa	—	0	3	1	3	—	0	2	—	2	—	0	0	—	—
Kansas	—	0	2	—	—	—	0	2	—	—	—	0	1	—	—
Minnesota	—	0	12	—	—	—	0	4	—	—	—	0	6	—	—
Missouri	—	0	2	—	1	2	1	3	2	4	—	0	2	—	—
Nebraska†	—	0	4	—	1	—	0	2	2	1	—	0	1	—	—
North Dakota	—	0	3	—	—	—	0	0	—	—	—	0	0	—	—
South Dakota	—	0	1	—	—	—	0	1	—	—	—	0	0	—	—
S. Atlantic	3	6	14	10	13	2	16	32	17	43	—	2	6	2	5
Delaware	—	0	1	1	—	—	0	2	—	1	U	0	0	U	U
District of Columbia	—	0	1	—	—	—	0	1	—	—	—	0	1	—	1
Florida	1	3	7	3	3	2	5	11	12	20	—	0	0	—	—
Georgia	—	1	3	2	3	—	3	7	—	16	—	0	2	—	—
Maryland†	—	0	3	2	1	—	1	6	2	—	—	0	3	2	2
North Carolina	—	0	5	—	—	—	1	16	—	3	—	1	3	—	2
South Carolina†	—	0	3	—	5	—	1	4	—	—	—	0	1	—	—
Virginia†	2	1	6	2	1	—	1	6	3	3	—	0	2	—	—
West Virginia	—	0	5	—	—	—	0	12	—	—	—	0	5	—	—
E.S. Central	—	1	5	1	2	—	7	13	9	28	—	3	8	2	7
Alabama†	—	0	2	—	1	—	1	4	—	7	—	0	1	—	—
Kentucky	—	0	5	1	—	—	2	8	5	11	—	2	6	1	7
Mississippi	—	0	1	—	—	—	0	3	—	—	U	0	0	U	U
Tennessee†	—	0	2	—	1	—	3	8	4	10	—	1	4	1	—
W.S. Central	—	2	7	1	1	—	9	29	1	8	1	1	5	1	2
Arkansas†	—	0	1	—	—	—	0	4	—	—	—	0	0	—	—
Louisiana	—	0	2	—	—	—	1	3	—	3	—	0	1	—	—
Oklahoma	—	0	1	—	—	—	2	6	—	1	1	0	3	1	—
Texas†	—	2	7	1	1	—	5	25	1	4	—	0	3	—	2
Mountain	1	3	8	4	11	—	2	8	—	8	—	1	5	1	1
Arizona	—	1	4	2	5	—	0	2	—	2	U	0	0	U	U
Colorado	1	1	3	2	4	—	0	5	—	1	—	0	2	1	1
Idaho†	—	0	2	—	—	—	0	1	—	—	—	0	2	—	—
Montana†	—	0	1	—	1	—	0	0	—	—	—	0	1	—	—
Nevada†	—	0	2	—	—	—	0	3	—	4	—	0	1	—	—
New Mexico†	—	0	1	—	—	—	0	1	—	—	—	0	2	—	—
Utah	—	0	1	—	1	—	0	1	—	1	—	0	2	—	—
Wyoming†	—	0	3	—	—	—	0	1	—	—	—	0	0	—	—
Pacific	6	5	17	19	8	1	6	17	2	4	—	1	3	1	8
Alaska	—	0	1	—	—	—	0	1	—	1	U	0	0	U	U
California	5	4	16	18	7	—	4	16	—	2	—	0	2	—	5
Hawaii	—	0	1	—	—	—	0	1	—	—	U	0	0	U	U
Oregon	1	0	2	1	1	1	1	3	2	1	—	0	3	—	3
Washington	—	0	2	—	—	—	1	3	—	—	—	0	3	1	—
Territories															
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	6	—	—	—	1	6	—	—	—	0	7	—	—
Puerto Rico	—	0	2	—	—	—	0	2	—	1	—	0	0	—	—
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

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† Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending January 22, 2011, and January 23, 2010 (3rd week)*

Reporting area	Legionellosis					Lyme disease					Malaria				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	14	53	116	73	139	25	397	1,670	150	767	8	26	80	35	69
New England	—	4	15	1	8	—	126	503	3	252	1	1	5	1	5
Connecticut	—	1	6	—	2	—	46	212	—	122	—	0	1	—	—
Maine†	—	0	4	—	—	—	11	65	—	1	—	0	1	—	—
Massachusetts	—	2	10	—	3	—	41	223	—	81	—	1	4	—	5
New Hampshire	—	0	5	—	1	—	24	68	1	40	—	0	2	—	—
Rhode Island†	—	0	4	—	1	—	1	40	—	—	—	0	1	—	—
Vermont†	—	0	2	1	1	—	4	27	2	8	1	0	1	1	—
Mid. Atlantic	3	14	47	16	28	16	171	735	101	358	—	7	17	6	21
New Jersey	—	1	11	—	5	—	49	220	—	103	—	0	1	—	—
New York (Upstate)	2	5	19	5	7	6	38	200	8	13	—	1	6	1	4
New York City	—	2	17	3	7	—	2	7	—	11	—	4	14	4	12
Pennsylvania	1	6	18	8	9	10	86	385	93	231	—	1	3	1	5
E.N. Central	4	12	44	16	27	—	26	324	—	29	1	2	9	4	7
Illinois	—	2	15	—	5	—	1	17	—	1	—	1	7	—	4
Indiana	—	2	6	3	3	—	1	7	—	2	—	0	2	—	—
Michigan	—	2	20	3	5	—	1	13	—	—	—	0	4	—	1
Ohio	4	4	15	10	13	—	0	9	—	2	1	1	5	4	2
Wisconsin	—	1	11	—	1	—	21	297	—	24	—	0	1	—	—
W.N. Central	—	2	9	1	1	—	1	11	—	1	—	1	4	—	5
Iowa	—	0	2	—	—	—	0	10	—	1	—	0	2	—	2
Kansas	—	0	2	—	—	—	0	1	—	—	—	0	2	—	1
Minnesota	—	0	8	—	—	—	0	0	—	—	—	0	3	—	—
Missouri	—	0	4	1	1	—	0	1	—	—	—	0	3	—	1
Nebraska†	—	0	2	—	—	—	0	2	—	—	—	0	2	—	1
North Dakota	—	0	1	—	—	—	0	5	—	—	—	0	1	—	—
South Dakota	—	0	2	—	—	—	0	1	—	—	—	0	2	—	—
S. Atlantic	6	10	28	12	29	9	56	174	42	116	5	7	44	19	24
Delaware	—	0	3	—	3	1	10	32	10	32	—	0	1	—	—
District of Columbia	—	0	4	—	—	—	0	4	—	—	—	0	2	—	—
Florida	4	3	9	7	8	—	2	10	1	4	2	2	7	6	9
Georgia	—	1	4	—	2	—	0	2	—	1	—	0	6	2	2
Maryland†	—	2	6	3	10	—	24	101	11	39	—	1	24	6	7
North Carolina	—	0	7	—	1	—	1	9	—	2	—	0	13	—	2
South Carolina†	—	0	2	—	—	—	0	3	—	1	—	0	1	—	—
Virginia†	2	1	10	2	4	8	18	77	20	36	3	1	5	5	4
West Virginia	—	0	3	—	1	—	0	29	—	1	—	0	1	—	—
E.S. Central	—	2	10	2	11	—	0	4	—	4	—	0	3	—	2
Alabama†	—	0	2	—	—	—	0	1	—	—	—	0	1	—	1
Kentucky	—	0	4	1	3	—	0	1	—	—	—	0	1	—	1
Mississippi	—	0	3	—	2	—	0	0	—	—	—	0	2	—	—
Tennessee†	—	1	6	1	6	—	0	4	—	4	—	0	2	—	—
W.S. Central	1	3	8	4	2	—	2	9	—	1	—	1	7	—	3
Arkansas†	—	0	2	—	—	—	0	0	—	—	—	0	1	—	—
Louisiana	—	0	2	—	1	—	0	1	—	—	—	0	1	—	1
Oklahoma	—	0	3	—	—	—	0	0	—	—	—	0	1	—	—
Texas†	1	2	7	4	1	—	2	9	—	1	—	1	7	—	2
Mountain	—	3	10	—	9	—	0	3	—	2	—	1	4	1	1
Arizona	—	1	7	—	2	—	0	1	—	—	—	0	3	1	—
Colorado	—	0	2	—	3	—	0	1	—	—	—	0	3	—	—
Idaho†	—	0	1	—	—	—	0	2	—	1	—	0	1	—	—
Montana†	—	0	1	—	—	—	0	1	—	—	—	0	1	—	—
Nevada†	—	0	2	—	3	—	0	1	—	—	—	0	1	—	—
New Mexico†	—	0	2	—	1	—	0	2	—	—	—	0	1	—	—
Utah	—	0	2	—	—	—	0	1	—	1	—	0	1	—	1
Wyoming†	—	0	2	—	—	—	0	0	—	—	—	0	0	—	—
Pacific	—	5	14	21	24	—	4	10	4	4	1	3	10	4	1
Alaska	—	0	2	—	—	—	0	1	—	—	—	0	1	—	—
California	—	4	13	20	24	—	3	7	4	2	1	2	9	3	1
Hawaii	—	0	1	—	—	N	0	0	N	N	—	0	1	—	—
Oregon	—	0	3	1	—	—	1	4	—	2	—	0	3	1	—
Washington	—	0	5	—	—	—	0	3	—	—	—	0	5	—	—
Territories															
American Samoa	—	0	0	—	—	N	0	0	N	N	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	1	—	—	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	0	0	—	—	N	0	0	N	N	1	0	2	1	1
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

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Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending January 22, 2011, and January 23, 2010 (3rd week)*

Reporting area	Meningococcal disease, invasive† All serogroups					Mumps					Pertussis				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	6	15	26	24	56	5	26	221	10	143	95	459	788	452	504
New England	—	0	3	1	1	—	0	4	—	3	—	9	23	—	12
Connecticut	—	0	1	1	—	—	0	2	—	—	—	1	8	—	2
Maine [§]	—	0	1	—	—	—	0	1	—	1	—	1	5	—	—
Massachusetts	—	0	2	—	1	—	0	2	—	2	—	5	13	—	8
New Hampshire	—	0	0	—	—	—	0	1	—	—	—	0	2	—	1
Rhode Island [§]	—	0	0	—	—	—	0	0	—	—	—	0	9	—	—
Vermont [§]	—	0	1	—	—	—	0	0	—	—	—	0	4	—	1
Mid. Atlantic	—	1	5	6	7	1	16	209	1	130	18	37	143	60	26
New Jersey	—	0	2	—	2	—	3	24	—	53	—	3	9	—	4
New York (Upstate)	—	0	2	—	1	—	2	99	—	77	11	11	80	24	2
New York City	—	0	3	4	2	—	1	201	—	—	—	0	9	—	—
Pennsylvania	—	0	2	2	2	1	0	16	1	—	7	14	69	36	20
E.N. Central	—	2	9	2	14	2	1	7	4	6	28	108	185	144	176
Illinois	—	0	3	—	3	—	0	2	—	2	—	20	50	9	26
Indiana	—	0	2	—	5	—	0	1	—	1	—	12	26	—	17
Michigan	—	0	4	—	2	—	0	2	—	2	4	28	57	38	45
Ohio	—	0	2	2	1	2	0	5	4	—	24	33	80	93	69
Wisconsin	—	0	3	—	3	—	0	2	—	1	—	9	21	4	19
W.N. Central	3	1	5	6	3	1	1	14	2	1	8	35	193	34	45
Iowa	—	0	3	1	1	—	0	7	—	1	—	12	34	1	8
Kansas	1	0	2	1	—	—	0	1	—	—	—	3	9	—	12
Minnesota	—	0	1	—	—	—	0	1	—	—	—	0	143	—	—
Missouri	1	0	4	2	2	1	0	2	1	—	8	8	44	24	16
Nebraska [§]	1	0	2	2	—	—	0	10	1	—	—	4	13	9	6
North Dakota	—	0	1	—	—	—	0	1	—	—	—	0	30	—	—
South Dakota	—	0	0	—	—	—	0	1	—	—	—	0	5	—	3
S. Atlantic	—	2	7	1	14	—	0	4	—	2	9	29	79	61	62
Delaware	—	0	1	—	1	—	0	0	—	—	—	0	4	2	—
District of Columbia	—	0	0	—	—	—	0	1	—	—	—	0	2	—	—
Florida	—	1	5	1	6	—	0	3	—	1	4	6	28	12	12
Georgia	—	0	2	—	2	—	0	1	—	—	—	4	18	9	8
Maryland [§]	—	0	1	—	—	—	0	1	—	1	—	3	8	5	10
North Carolina	—	0	2	—	1	—	0	0	—	—	—	0	32	—	26
South Carolina [§]	—	0	1	—	1	—	0	2	—	—	—	6	23	15	3
Virginia [§]	—	0	2	—	3	—	0	2	—	—	5	5	38	18	2
West Virginia	—	0	1	—	—	—	0	1	—	—	—	1	21	—	1
E.S. Central	—	1	3	—	2	—	0	2	—	—	1	16	34	22	46
Alabama [§]	—	0	1	—	1	—	0	2	—	—	—	4	8	3	11
Kentucky	—	0	2	—	1	—	0	1	—	—	1	6	16	14	20
Mississippi	—	0	1	—	—	—	0	0	—	—	—	1	8	—	2
Tennessee [§]	—	0	2	—	—	—	0	1	—	—	—	4	11	5	13
W.S. Central	—	1	9	—	6	1	1	11	1	—	6	57	113	10	44
Arkansas [§]	—	0	1	—	1	—	0	1	—	—	—	3	14	—	4
Louisiana	—	0	4	—	5	—	0	2	—	—	—	1	3	—	6
Oklahoma	—	0	7	—	—	—	0	0	—	—	—	0	23	—	—
Texas [§]	—	1	7	—	—	1	1	11	1	—	6	49	108	10	34
Mountain	—	1	6	3	2	—	0	4	1	—	15	30	92	73	67
Arizona	—	0	2	2	1	—	0	1	—	—	—	7	20	8	24
Colorado	—	0	4	—	—	—	0	1	—	—	15	6	76	59	8
Idaho [§]	—	0	1	1	—	—	0	1	—	—	—	2	15	6	15
Montana [§]	—	0	1	—	—	—	0	0	—	—	—	1	16	—	1
Nevada [§]	—	0	1	—	—	—	0	1	—	—	—	0	7	—	—
New Mexico [§]	—	0	1	—	1	—	0	2	1	—	—	2	11	—	11
Utah	—	0	1	—	—	—	0	1	—	—	—	4	13	—	8
Wyoming [§]	—	0	1	—	—	—	0	1	—	—	—	0	2	—	—
Pacific	3	3	9	5	7	—	0	18	1	1	10	84	220	48	26
Alaska	—	0	1	—	—	—	0	1	—	—	—	0	6	3	2
California	3	2	9	4	5	—	0	18	—	—	10	60	192	42	6
Hawaii	—	0	1	—	—	—	0	1	—	—	—	0	6	—	—
Oregon	—	1	2	1	2	—	0	1	1	1	—	6	15	3	18
Washington	—	0	4	—	—	—	0	2	—	—	—	6	48	—	—
Territories	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
American Samoa	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	1	15	—	—	—	0	0	—	—
Puerto Rico	—	0	0	—	—	—	0	1	—	—	—	0	1	1	—
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

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† Data for meningococcal disease, invasive caused by serogroups A, C, Y, and W-135; serogroup B; other serogroup; and unknown serogroup are available in Table I.

§ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending January 22, 2011, and January 23, 2010 (3rd week)*

Reporting area	Rabies, animal					Salmonellosis					Shiga toxin-producing <i>E. coli</i> (STEC) [†]				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	5	62	143	42	100	178	859	1,738	812	2,093	23	86	214	86	167
New England	1	4	13	4	10	—	31	68	18	537	—	2	13	—	64
Connecticut	—	0	9	—	2	—	0	8	8	480	—	0	0	—	57
Maine [§]	—	1	4	1	3	—	2	7	3	2	—	0	3	—	—
Massachusetts	—	0	0	—	—	—	23	52	—	40	—	1	9	—	6
New Hampshire	—	0	5	—	1	—	3	12	4	6	—	0	2	—	1
Rhode Island [§]	—	0	4	—	—	—	1	17	—	8	—	0	1	—	—
Vermont [§]	1	1	3	3	4	—	2	5	3	1	—	0	2	—	—
Mid. Atlantic	3	19	41	14	29	18	95	218	78	224	6	9	32	13	10
New Jersey	—	0	0	—	—	—	16	57	—	44	—	1	9	—	2
New York (Upstate)	3	9	19	14	16	9	25	63	20	32	4	4	13	8	1
New York City	—	1	12	—	—	1	24	56	21	69	—	1	7	—	2
Pennsylvania	—	8	24	—	13	8	31	81	37	79	2	3	13	5	5
E.N. Central	—	2	27	2	2	10	90	244	68	195	—	11	43	2	28
Illinois	—	1	11	1	—	—	32	114	6	65	—	2	9	—	9
Indiana	—	0	0	—	—	—	13	62	—	27	—	2	10	—	2
Michigan	—	1	5	1	1	—	15	49	13	35	—	2	16	—	4
Ohio	—	0	12	—	1	10	24	47	49	49	—	2	11	2	2
Wisconsin	—	0	0	—	—	—	9	45	—	19	—	3	17	—	11
W.N. Central	—	4	14	—	6	6	46	97	47	70	2	11	39	5	11
Iowa	—	0	3	—	—	1	9	34	8	7	—	2	16	—	—
Kansas	—	1	4	—	5	3	7	18	10	13	—	1	5	—	3
Minnesota	—	0	4	—	—	—	0	32	—	—	—	0	7	—	—
Missouri	—	1	6	—	1	1	13	44	23	34	1	4	27	1	5
Nebraska [§]	—	1	4	—	—	1	4	13	5	10	1	2	6	4	3
North Dakota	—	0	3	—	—	—	0	13	—	2	—	0	10	—	—
South Dakota	—	0	0	—	—	—	2	17	1	4	—	0	4	—	—
S. Atlantic	1	20	104	21	37	82	260	614	311	553	9	14	30	32	17
Delaware	—	0	0	—	—	2	3	11	6	4	—	0	2	—	—
District of Columbia	—	0	0	—	—	—	1	6	—	2	—	0	1	—	1
Florida	1	0	96	1	—	55	108	226	166	245	7	4	23	18	4
Georgia	—	0	0	—	—	8	43	133	47	104	—	2	15	3	2
Maryland [§]	—	6	14	—	14	—	17	55	20	33	—	2	9	5	6
North Carolina	—	0	0	—	—	—	31	240	3	98	—	1	10	—	1
South Carolina [§]	—	0	0	—	—	7	25	99	24	35	—	0	2	—	—
Virginia [§]	—	11	25	20	20	10	19	57	45	29	2	2	9	6	3
West Virginia	—	1	7	—	3	—	2	13	—	3	—	0	3	—	—
E.S. Central	—	3	7	—	4	12	55	177	64	105	—	5	22	7	5
Alabama [§]	—	1	4	—	—	1	18	52	18	39	—	1	4	1	4
Kentucky	—	0	4	—	—	1	11	32	12	22	—	1	6	1	—
Mississippi	—	0	1	—	—	—	18	67	8	15	—	0	12	—	1
Tennessee [§]	—	1	4	—	4	10	17	53	26	29	—	2	7	5	—
W.S. Central	—	0	30	—	—	6	122	264	22	83	1	5	18	2	7
Arkansas [§]	—	0	7	—	—	2	12	43	9	8	—	1	5	1	1
Louisiana	—	0	0	—	—	—	20	49	3	33	—	0	2	—	2
Oklahoma	—	0	30	—	—	4	12	39	9	6	1	0	8	1	—
Texas [§]	—	0	0	—	—	—	76	173	1	36	—	4	14	—	4
Mountain	—	1	7	—	3	12	48	108	53	142	3	11	34	5	16
Arizona	—	0	0	—	—	2	15	42	11	57	—	1	13	1	3
Colorado	—	0	0	—	—	9	11	24	33	26	1	3	21	1	6
Idaho [§]	—	0	2	—	—	1	3	9	6	10	2	2	7	3	2
Montana [§]	—	0	3	—	—	—	1	5	—	15	—	1	5	—	1
Nevada [§]	—	0	2	—	—	—	4	22	2	5	—	0	5	—	1
New Mexico [§]	—	0	2	—	—	—	6	19	1	12	—	1	6	—	2
Utah	—	0	2	—	—	—	5	17	—	12	—	1	7	—	1
Wyoming [§]	—	0	4	—	3	—	1	8	—	5	—	0	3	—	—
Pacific	—	2	12	1	9	32	114	252	151	184	2	12	35	20	9
Alaska	—	0	2	—	4	—	1	5	1	5	—	0	1	—	1
California	—	1	12	—	4	29	79	217	132	156	2	6	22	19	6
Hawaii	—	0	0	—	—	—	3	14	—	—	—	0	4	—	—
Oregon	—	0	2	1	1	3	8	48	18	23	—	2	14	1	2
Washington	—	0	0	—	—	—	14	51	—	—	—	3	17	—	—
Territories															
American Samoa	N	0	0	N	N	—	0	1	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	0	2	—	—	—	0	0	—	—
Puerto Rico	1	1	3	1	3	—	10	21	1	18	—	0	0	—	—
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see <http://www.cdc.gov/ncphi/diss/nndss/phps/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf>. Data for TB are displayed in Table IV, which appears quarterly.[†] Includes *E. coli* O157:H7; Shiga toxin-positive, serogroup non-O157; and Shiga toxin-positive, not serogrouped.[§] Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending January 22, 2011, and January 23, 2010 (3rd week)*

Reporting area	Spotted Fever Rickettsiosis (including RMSF) [†]														
	Shigellosis					Confirmed					Probable				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	91	275	452	312	719	1	2	11	5	5	1	24	91	5	20
New England	—	4	17	2	78	—	0	0	—	—	—	0	1	—	—
Connecticut	—	0	1	1	63	—	0	0	—	—	—	0	0	—	—
Maine [§]	—	0	1	—	1	—	0	0	—	—	—	0	1	—	—
Massachusetts	—	3	16	—	13	—	0	0	—	—	—	0	0	—	—
New Hampshire	—	0	2	—	1	—	0	0	—	—	—	0	1	—	—
Rhode Island [§]	—	0	2	—	—	—	0	0	—	—	—	0	0	—	—
Vermont [§]	—	0	1	1	—	—	0	0	—	—	—	0	0	—	—
Mid. Atlantic	5	30	64	23	133	—	0	1	—	—	—	1	4	—	—
New Jersey	—	6	16	1	18	—	0	0	—	—	—	0	0	—	—
New York (Upstate)	2	3	15	5	7	—	0	1	—	—	—	0	3	—	—
New York City	2	5	14	10	22	—	0	1	—	—	—	0	4	—	—
Pennsylvania	1	12	55	7	86	—	0	1	—	—	—	0	3	—	—
E.N. Central	7	25	238	23	87	—	0	1	—	—	1	1	10	1	1
Illinois	—	9	228	—	40	—	0	1	—	—	—	0	5	—	—
Indiana [§]	—	1	4	—	2	—	0	1	—	—	—	0	5	—	1
Michigan	1	5	10	5	4	—	0	0	—	—	—	0	1	—	—
Ohio	6	5	18	18	25	—	0	0	—	—	1	0	2	1	—
Wisconsin	—	4	21	—	16	—	0	0	—	—	—	0	1	—	—
W.N. Central	6	35	81	33	176	—	0	4	—	—	—	4	21	—	—
Iowa	—	1	4	1	6	—	0	0	—	—	—	0	1	—	—
Kansas [§]	3	5	13	7	10	—	0	1	—	—	—	0	0	—	—
Minnesota	—	0	3	—	—	—	0	0	—	—	—	0	0	—	—
Missouri	3	27	66	24	160	—	0	4	—	—	—	4	20	—	—
Nebraska [§]	—	1	10	1	—	—	0	1	—	—	—	0	1	—	—
North Dakota	—	0	0	—	—	—	0	0	—	—	—	0	1	—	—
South Dakota	—	0	2	—	—	—	0	0	—	—	—	0	0	—	—
S. Atlantic	30	51	134	113	95	1	1	9	2	4	—	8	60	—	18
Delaware [§]	—	0	4	—	8	—	0	1	—	—	—	0	3	—	—
District of Columbia	—	0	4	—	2	—	0	1	—	—	—	0	0	—	—
Florida [§]	28	23	53	93	24	1	0	1	1	—	—	0	2	—	—
Georgia	2	14	39	15	42	—	0	6	—	4	—	0	0	—	—
Maryland [§]	—	2	8	3	3	—	0	1	1	—	—	0	5	—	1
North Carolina	—	3	36	—	10	—	0	3	—	—	—	2	48	—	16
South Carolina [§]	—	1	5	—	5	—	0	1	—	—	—	0	2	—	1
Virginia [§]	—	3	8	2	1	—	0	2	—	—	—	2	12	—	—
West Virginia	—	0	66	—	—	—	0	0	—	—	—	0	0	—	—
E.S. Central	4	13	40	15	23	—	0	3	—	—	—	5	29	1	—
Alabama [§]	1	4	14	7	5	—	0	1	—	—	—	1	8	—	—
Kentucky	—	3	28	1	9	—	0	2	—	—	—	0	0	—	—
Mississippi	—	1	4	—	1	—	0	0	—	—	—	0	3	—	—
Tennessee [§]	3	5	14	7	8	—	0	2	—	—	—	4	20	1	—
W.S. Central	20	52	112	35	44	—	0	3	—	—	—	1	18	—	—
Arkansas [§]	—	1	6	1	4	—	0	2	—	—	—	0	17	—	—
Louisiana	—	5	13	—	5	—	0	0	—	—	—	0	1	—	—
Oklahoma	2	5	13	2	2	—	0	3	—	—	—	0	6	—	—
Texas [§]	18	43	91	32	33	—	0	1	—	—	—	0	3	—	—
Mountain	4	15	32	22	43	—	0	5	3	—	—	0	3	3	1
Arizona	3	8	18	9	23	—	0	5	3	—	—	0	3	3	—
Colorado [§]	—	2	8	10	10	—	0	1	—	—	—	0	1	—	—
Idaho [§]	1	0	3	2	—	—	0	0	—	—	—	0	1	—	—
Montana [§]	—	0	1	—	1	—	0	1	—	—	—	0	1	—	—
Nevada [§]	—	0	6	—	1	—	0	0	—	—	—	0	0	—	—
New Mexico [§]	—	3	10	1	6	—	0	0	—	—	—	0	1	—	1
Utah	—	1	4	—	2	—	0	0	—	—	—	0	1	—	—
Wyoming [§]	—	0	0	—	—	—	0	0	—	—	—	0	1	—	—
Pacific	15	21	65	46	40	—	0	2	—	1	—	0	0	—	—
Alaska	—	0	1	—	—	N	0	0	N	N	N	0	0	N	N
California	15	17	53	44	38	—	0	2	—	1	—	0	0	—	—
Hawaii	—	0	3	—	—	N	0	0	N	N	N	0	0	N	N
Oregon	—	1	4	2	2	—	0	1	—	—	—	0	0	—	—
Washington	—	1	17	—	—	—	0	0	—	—	—	0	0	—	—
Territories															
American Samoa	—	1	1	1	—	N	0	0	N	N	N	0	0	N	N
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	1	—	—	N	0	0	N	N	N	0	0	N	N
Puerto Rico	—	0	1	—	—	N	0	0	N	N	N	0	0	N	N
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

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TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending January 22, 2011, and January 23, 2010 (3rd week)*

Reporting area	<i>Streptococcus pneumoniae</i> , [†] invasive disease										Syphilis, primary and secondary				
	All ages					Age <5									
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	176	270	535	867	1,034	15	39	84	55	142	53	244	319	266	631
New England	1	9	99	5	29	—	1	14	—	4	1	9	20	11	19
Connecticut	—	0	91	—	—	—	0	12	—	—	—	1	8	—	—
Maine [§]	—	2	6	3	5	—	0	1	—	1	—	0	3	—	1
Massachusetts	—	1	5	—	3	—	1	4	—	1	—	5	15	6	15
New Hampshire	—	0	7	—	12	—	0	1	—	2	1	0	2	1	1
Rhode Island [§]	—	0	36	—	—	—	0	3	—	—	—	1	4	4	2
Vermont [§]	1	1	6	2	9	—	0	1	—	—	—	0	2	—	—
Mid. Atlantic	18	29	56	116	83	2	7	19	5	23	6	32	45	25	85
New Jersey	—	1	8	2	10	—	1	5	2	6	3	4	12	8	12
New York (Upstate)	4	3	9	5	12	2	2	8	2	6	—	2	10	5	1
New York City	6	12	32	63	25	—	2	14	—	3	—	18	31	—	52
Pennsylvania	8	10	22	46	36	—	1	5	1	8	3	7	16	12	20
E.N. Central	29	59	99	167	242	2	6	18	8	30	—	27	48	6	94
Illinois	—	2	7	—	5	—	2	5	—	5	—	7	26	—	51
Indiana	—	10	24	7	40	—	1	6	—	7	—	3	14	1	—
Michigan	1	12	27	26	51	—	1	6	—	7	—	4	12	3	20
Ohio	25	25	45	111	115	2	2	6	5	5	—	9	19	1	20
Wisconsin	3	7	22	23	31	—	0	4	3	6	—	1	3	1	3
W.N. Central	6	10	61	22	29	3	1	12	4	5	—	6	18	8	12
Iowa	—	0	0	—	—	—	0	0	—	—	—	0	3	—	1
Kansas	1	2	7	5	3	—	0	2	—	—	—	0	3	—	—
Minnesota	—	0	46	—	—	—	0	8	—	—	—	2	9	5	1
Missouri	4	2	10	8	11	3	0	4	3	2	—	3	9	3	10
Nebraska [§]	1	2	9	9	12	—	0	2	1	2	—	0	2	—	—
North Dakota	—	0	11	—	—	—	0	1	—	—	—	0	0	—	—
South Dakota	—	0	3	—	3	—	0	2	—	1	—	0	1	—	—
S. Atlantic	59	62	144	294	281	2	9	27	23	37	12	56	103	75	117
Delaware	1	1	4	7	2	—	0	1	—	—	1	0	4	2	—
District of Columbia	—	0	3	—	2	—	0	2	—	2	—	2	20	2	7
Florida	52	25	89	170	99	2	3	18	10	6	1	21	44	26	42
Georgia	5	10	26	34	60	—	2	9	5	12	—	9	29	—	6
Maryland [§]	—	9	31	49	49	—	1	6	4	3	—	6	15	11	4
North Carolina	—	0	0	—	—	—	0	0	—	—	1	6	22	16	36
South Carolina [§]	1	8	23	30	58	—	1	4	—	8	2	3	7	7	10
Virginia [§]	—	1	4	4	5	—	1	4	4	5	7	5	22	11	11
West Virginia	—	2	9	—	6	—	0	4	—	1	—	0	2	—	1
E.S. Central	11	24	48	64	115	2	2	7	7	10	8	16	39	15	30
Alabama [§]	—	0	0	—	—	—	0	0	—	—	3	5	11	7	14
Kentucky	2	3	16	15	8	—	0	2	2	2	4	2	12	4	3
Mississippi	—	1	8	1	7	—	0	2	—	1	1	4	16	1	1
Tennessee [§]	9	20	43	48	100	2	2	6	5	7	—	5	17	3	12
W.S. Central	28	35	192	77	64	3	5	21	4	9	18	37	64	68	103
Arkansas [§]	3	3	19	12	6	—	0	3	1	1	4	3	10	8	17
Louisiana	—	2	6	8	14	—	0	3	—	4	1	7	29	1	26
Oklahoma	3	1	5	3	2	3	1	5	3	2	1	2	7	1	3
Texas [§]	22	27	171	54	42	—	3	17	—	2	12	24	33	58	57
Mountain	19	34	69	104	170	—	4	12	3	19	—	10	25	7	25
Arizona	7	13	38	53	98	—	2	7	2	12	—	3	8	2	6
Colorado	12	11	22	38	38	—	1	4	1	2	—	2	8	—	10
Idaho [§]	—	0	2	1	—	—	0	2	—	—	—	0	2	—	1
Montana [§]	—	0	2	—	1	—	0	1	—	—	—	0	2	—	—
Nevada [§]	—	1	4	1	8	—	0	1	—	2	—	2	9	4	3
New Mexico [§]	—	3	10	9	10	—	0	4	—	—	—	1	4	1	3
Utah	—	3	9	—	15	—	0	3	—	3	—	1	4	—	2
Wyoming [§]	—	0	15	2	—	—	0	1	—	—	—	0	0	—	—
Pacific	5	5	18	18	21	1	0	7	1	5	8	44	63	51	146
Alaska	—	2	9	5	12	—	0	5	—	3	—	0	1	—	—
California	5	3	17	13	9	1	0	5	1	2	5	38	52	43	123
Hawaii	—	0	2	—	—	—	0	0	—	—	—	0	5	—	2
Oregon	—	0	0	—	—	—	0	0	—	—	1	1	7	1	4
Washington	—	0	0	—	—	—	0	0	—	—	2	4	11	7	17
Territories															
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	0	0	—	—	—	0	0	—	—	—	3	15	2	8
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

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U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see <http://www.cdc.gov/ncphi/diss/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf>. Data for TB are displayed in Table IV, which appears quarterly.[†] Includes drug resistant and susceptible cases of invasive *Streptococcus pneumoniae* disease among children <5 years and among all ages. Case definition: Isolation of *S. pneumoniae* from a normally sterile body site (e.g., blood or cerebrospinal fluid).[§] Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending January 22, 2011, and January 23, 2010 (3rd week)*

Reporting area	Varicella (chickenpox)					West Nile virus disease†									
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Neuroinvasive					Nonneuroinvasive§				
		Med	Max			Current week	Previous 52 weeks	Cum 2011	Cum 2010		Current week	Previous 52 weeks	Cum 2011	Cum 2010	
							Med	Max				Med	Max		
United States	101	281	562	430	767	—	0	71	—	1	—	1	53	—	—
New England	—	18	43	15	63	—	0	3	—	—	—	0	2	—	—
Connecticut	—	6	20	—	10	—	0	2	—	—	—	0	2	—	—
Maine¶	—	4	15	—	22	—	0	0	—	—	—	0	0	—	—
Massachusetts	—	5	12	—	15	—	0	2	—	—	—	0	1	—	—
New Hampshire	—	2	8	—	9	—	0	1	—	—	—	0	0	—	—
Rhode Island¶	—	0	3	1	1	—	0	0	—	—	—	0	0	—	—
Vermont¶	—	1	10	14	6	—	0	0	—	—	—	0	0	—	—
Mid. Atlantic	6	32	62	36	97	—	0	19	—	—	—	0	13	—	—
New Jersey	—	8	30	2	34	—	0	3	—	—	—	0	6	—	—
New York (Upstate)	N	0	0	N	N	—	0	9	—	—	—	0	7	—	—
New York City	—	0	1	—	—	—	0	7	—	—	—	0	4	—	—
Pennsylvania	6	22	40	34	63	—	0	3	—	—	—	0	3	—	—
E.N. Central	42	95	176	196	292	—	0	15	—	—	—	0	8	—	—
Illinois	6	21	45	21	78	—	0	10	—	—	—	0	5	—	—
Indiana¶	5	5	35	11	10	—	0	2	—	—	—	0	2	—	—
Michigan	6	30	62	55	104	—	0	6	—	—	—	0	1	—	—
Ohio	25	28	58	109	89	—	0	1	—	—	—	0	1	—	—
Wisconsin	—	7	22	—	11	—	0	0	—	—	—	0	1	—	—
W.N. Central	—	15	32	18	47	—	0	7	—	—	—	0	11	—	—
Iowa	N	0	0	N	N	—	0	1	—	—	—	0	2	—	—
Kansas¶	—	4	22	7	24	—	0	1	—	—	—	0	3	—	—
Minnesota	—	0	0	—	—	—	0	1	—	—	—	0	3	—	—
Missouri	—	8	23	10	21	—	0	1	—	—	—	0	0	—	—
Nebraska¶	N	0	0	N	N	—	0	3	—	—	—	0	7	—	—
North Dakota	—	0	10	—	1	—	0	2	—	—	—	0	2	—	—
South Dakota	—	1	7	1	1	—	0	2	—	—	—	0	3	—	—
S. Atlantic	24	35	100	53	80	—	0	4	—	—	—	0	4	—	—
Delaware¶	—	0	3	—	—	—	0	0	—	—	—	0	0	—	—
District of Columbia	—	0	4	1	—	—	0	1	—	—	—	0	1	—	—
Florida¶	21	16	57	42	42	—	0	3	—	—	—	0	1	—	—
Georgia	N	0	0	N	N	—	0	1	—	—	—	0	3	—	—
Maryland¶	N	0	0	N	N	—	0	3	—	—	—	0	2	—	—
North Carolina	N	0	0	N	N	—	0	0	—	—	—	0	0	—	—
South Carolina¶	—	0	35	—	2	—	0	1	—	—	—	0	0	—	—
Virginia¶	3	10	29	10	12	—	0	1	—	—	—	0	1	—	—
West Virginia	—	7	26	—	24	—	0	0	—	—	—	0	0	—	—
E.S. Central	1	5	22	13	15	—	0	1	—	1	—	0	3	—	—
Alabama¶	1	5	22	13	15	—	0	1	—	—	—	0	1	—	—
Kentucky	N	0	0	N	N	—	0	1	—	—	—	0	1	—	—
Mississippi	—	0	2	—	—	—	0	1	—	1	—	0	2	—	—
Tennessee¶	N	0	0	N	N	—	0	1	—	—	—	0	2	—	—
W.S. Central	27	42	177	61	81	—	0	15	—	—	—	0	3	—	—
Arkansas¶	—	1	32	—	8	—	0	3	—	—	—	0	1	—	—
Louisiana	—	2	4	2	7	—	0	3	—	—	—	0	1	—	—
Oklahoma	N	0	0	N	N	—	0	1	—	—	—	0	0	—	—
Texas¶	27	39	171	59	66	—	0	15	—	—	—	0	2	—	—
Mountain	1	20	37	34	89	—	0	18	—	—	—	0	15	—	—
Arizona	—	0	0	—	—	—	0	13	—	—	—	0	9	—	—
Colorado¶	—	8	17	—	40	—	0	5	—	—	—	0	11	—	—
Idaho¶	N	0	0	N	N	—	0	0	—	—	—	0	1	—	—
Montana¶	—	3	28	30	14	—	0	0	—	—	—	0	0	—	—
Nevada¶	N	0	0	N	N	—	0	0	—	—	—	0	1	—	—
New Mexico¶	1	1	8	4	8	—	0	5	—	—	—	0	2	—	—
Utah	—	4	17	—	27	—	0	1	—	—	—	0	1	—	—
Wyoming¶	—	0	3	—	—	—	0	1	—	—	—	0	1	—	—
Pacific	—	1	6	4	3	—	0	7	—	—	—	0	6	—	—
Alaska	—	1	5	4	3	—	0	0	—	—	—	0	0	—	—
California	—	0	0	—	—	—	0	7	—	—	—	0	6	—	—
Hawaii	—	0	6	—	—	—	0	0	—	—	—	0	0	—	—
Oregon	N	0	0	N	N	—	0	0	—	—	—	0	0	—	—
Washington	N	0	0	N	N	—	0	1	—	—	—	0	1	—	—
Territories															
American Samoa	N	0	0	N	N	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	2	—	—	—	0	0	—	—	—	0	0	—	—
Puerto Rico	2	9	30	10	10	—	0	0	—	—	—	0	0	—	—
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2010 and 2011 are provisional and subject to change. For further information on interpretation of these data, see <http://www.cdc.gov/ncphi/diss/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf>. Data for TB are displayed in Table IV, which appears quarterly.

† Updated weekly from reports to the Division of Vector-Borne Infectious Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases (ArboNET Surveillance). Data for California serogroup, eastern equine, Powassan, St. Louis, and western equine diseases are available in Table I.

§ Not reportable in all states. Data from states where the condition is not reportable are excluded from this table, except starting in 2007 for the domestic arboviral diseases and influenza-associated pediatric mortality, and in 2003 for SARS-CoV. Reporting exceptions are available at <http://www.cdc.gov/ncphi/diss/nndss/phs/infdis.htm>.

¶ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

TABLE III. Deaths in 122 U.S. cities,* week ending January 22, 2011 (3rd week)

Reporting area	All causes, by age (years)						P&I†	Total	Reporting area (Continued)	All causes, by age (years)						P&I†	Total
	All Ages	≥65	45–64	25–44	1–24	<1				All Ages	≥65	45–64	25–44	1–24	<1		
New England	631	436	140	32	10	13	74		S. Atlantic	1,332	890	292	89	36	25	92	
Boston, MA	159	100	35	11	5	8	22		Atlanta, GA	176	111	38	18	7	2	9	
Bridgeport, CT	39	28	6	5	—	—	7		Baltimore, MD	123	71	33	14	1	4	5	
Cambridge, MA	13	9	3	1	—	—	1		Charlotte, NC	103	67	27	3	4	2	11	
Fall River, MA	30	26	3	1	—	—	6		Jacksonville, FL	199	140	41	9	5	4	24	
Hartford, CT	63	38	19	3	1	2	7		Miami, FL	159	104	36	9	5	5	10	
Lowell, MA	26	22	2	2	—	—	6		Norfolk, VA	81	51	15	7	7	1	2	
Lynn, MA	11	4	6	1	—	—	—		Richmond, VA	66	43	15	5	3	—	2	
New Bedford, MA	33	25	8	—	—	—	2		Savannah, GA	64	43	14	6	—	1	6	
New Haven, CT	56	32	17	3	2	2	4		St. Petersburg, FL	61	46	11	2	1	1	3	
Providence, RI	64	50	12	2	—	—	4		Tampa, FL	197	148	39	7	—	3	13	
Somerville, MA	3	2	1	—	—	—	—		Washington, D.C.	87	54	20	8	3	2	6	
Springfield, MA	37	28	6	1	1	1	1		Wilmington, DE	16	12	3	1	—	—	1	
Waterbury, CT	31	23	6	2	—	—	6		E.S. Central	990	656	247	59	12	16	76	
Worcester, MA	66	49	16	—	1	—	8		Birmingham, AL	169	112	43	5	5	4	14	
Mid. Atlantic	2,457	1,766	499	126	23	43	155		Chattanooga, TN	105	77	23	5	—	—	7	
Albany, NY	52	32	13	1	—	6	6		Knoxville, TN	114	77	27	9	1	—	13	
Allentown, PA	38	29	7	2	—	—	2		Lexington, KY	78	57	13	7	1	—	6	
Buffalo, NY	91	61	22	4	—	4	2		Memphis, TN	190	113	57	14	2	4	16	
Camden, NJ	19	14	2	1	—	2	—		Mobile, AL	125	86	27	7	1	4	8	
Elizabeth, NJ	21	15	5	—	—	1	1		Montgomery, AL	48	28	18	—	2	—	4	
Erie, PA	52	37	11	3	—	1	3		Nashville, TN	161	106	39	12	—	4	8	
Jersey City, NJ	19	13	5	1	—	—	3		W.S. Central	1,184	791	283	63	22	24	82	
New York City, NY	1,613	1,165	329	89	11	19	103		Austin, TX	69	43	20	3	1	2	6	
Newark, NJ	20	10	8	—	2	—	—		Baton Rouge, LA	71	60	7	3	1	—	—	
Paterson, NJ	21	10	5	4	1	1	1		Corpus Christi, TX	74	51	18	2	1	2	9	
Philadelphia, PA	142	96	32	5	3	6	6		Dallas, TX	182	108	58	13	3	—	16	
Pittsburgh, PA [§]	27	20	4	2	1	—	—		El Paso, TX	127	97	19	5	4	2	10	
Reading, PA	40	36	3	—	1	—	2		Fort Worth, TX	U	U	U	U	U	U	U	
Rochester, NY	81	51	21	5	1	3	6		Houston, TX	95	64	21	2	—	8	4	
Schenectady, NY	30	24	5	1	—	—	3		Little Rock, AR	77	51	17	5	4	—	—	
Scranton, PA	26	24	—	1	1	—	2		New Orleans, LA	U	U	U	U	U	U	U	
Syracuse, NY	90	68	15	5	2	—	12		San Antonio, TX	282	181	71	19	5	5	20	
Trenton, NJ	36	26	9	1	—	—	—		Shreveport, LA	102	58	34	4	1	5	4	
Utica, NY	8	7	1	—	—	—	1		Tulsa, OK	105	78	18	7	2	—	13	
Yonkers, NY	31	28	2	1	—	—	2		Mountain	1,159	780	270	64	28	16	82	
E.N. Central	2,105	1,415	513	126	27	24	142		Albuquerque, NM	116	85	23	7	1	—	5	
Akron, OH	47	33	12	—	—	2	8		Boise, ID	53	37	12	2	1	1	7	
Canton, OH	42	30	8	2	2	—	4		Colorado Springs, CO	52	37	11	1	3	—	3	
Chicago, IL	226	154	49	21	2	—	17		Denver, CO	112	78	26	5	1	2	8	
Cincinnati, OH	108	71	25	4	4	4	9		Las Vegas, NV	269	167	74	18	5	5	13	
Cleveland, OH	266	188	61	13	1	3	13		Ogden, UT	39	33	5	—	1	—	3	
Columbus, OH	323	204	88	22	4	5	30		Phoenix, AZ	195	124	46	13	5	6	15	
Dayton, OH	136	96	33	7	—	—	5		Pueblo, CO	27	14	11	1	1	—	4	
Detroit, MI	136	70	47	12	5	2	4		Salt Lake City, UT	135	90	28	9	7	1	12	
Evansville, IN	39	29	7	1	2	—	1		Tucson, AZ	161	115	34	8	3	1	12	
Fort Wayne, IN	65	44	15	5	—	1	1		Pacific	1,739	1,228	369	93	29	20	165	
Gary, IN	6	4	1	—	—	1	—		Berkeley, CA	12	5	6	1	—	—	1	
Grand Rapids, MI	54	45	6	2	1	—	2		Fresno, CA	119	92	18	7	1	1	9	
Indianapolis, IN	131	87	28	8	5	3	15		Glendale, CA	39	28	7	4	—	—	6	
Lansing, MI	62	50	10	1	1	—	8		Honolulu, HI	63	44	13	6	—	—	9	
Milwaukee, WI	124	75	40	7	—	2	5		Long Beach, CA	73	54	18	—	1	—	9	
Peoria, IL	60	40	12	8	—	—	2		Los Angeles, CA	265	169	66	14	10	6	27	
Rockford, IL	60	39	17	4	—	—	4		Pasadena, CA	24	20	2	—	1	1	3	
South Bend, IN	69	42	20	7	—	—	6		Portland, OR	81	57	17	7	—	—	4	
Toledo, OH	86	61	23	1	—	1	4		Sacramento, CA	217	160	42	8	4	3	23	
Youngstown, OH	65	53	11	1	—	—	4		San Diego, CA	193	136	43	10	1	3	17	
W.N. Central	556	386	124	33	9	4	43		San Francisco, CA	131	84	35	9	3	—	17	
Des Moines, IA	—	—	—	—	—	—	—		San Jose, CA	209	157	33	10	6	3	21	
Duluth, MN	27	22	4	1	—	—	2		Santa Cruz, CA	32	23	8	1	—	—	3	
Kansas City, KS	27	19	5	3	—	—	5		Seattle, WA	106	77	19	8	—	2	4	
Kansas City, MO	85	62	18	5	—	—	4		Spokane, WA	63	49	12	2	—	—	5	
Lincoln, NE	40	35	5	—	—	—	1		Tacoma, WA	112	73	30	6	2	1	7	
Minneapolis, MN	61	41	15	2	2	1	6		Total¶	12,153	8,348	2,737	685	196	185	911	
Omaha, NE	75	48	17	5	3	2	9										
St. Louis, MO	81	37	31	10	2	1	1										
St. Paul, MN	67	54	10	3	—	—	8										
Wichita, KS	93	68	19	4	2	—	7										

U: Unavailable. —: No reported cases.

* Mortality data in this table are voluntarily reported from 122 cities in the United States, most of which have populations of >100,000. A death is reported by the place of its occurrence and by the week that the death certificate was filed. Fetal deaths are not included.

† Pneumonia and influenza.

§ Because of changes in reporting methods in this Pennsylvania city, these numbers are partial counts for the current week. Complete counts will be available in 4 to 6 weeks.

¶ Total includes unknown ages.

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EXHIBIT B



final execution version

CDC Ref. NCHSTP-V043072-00

PUBLIC HEALTH SERVICE MATERIAL TRANSFER AGREEMENT

This Material Transfer Agreement ("MTA") has been adopted for use by the National Institutes of Health, the Food and Drug Administration and the Centers for Disease Control and Prevention, collectively referred to herein as the Public Health Service ("PHS") in all transfers of research material (Research Material) whether PHS is identified below as its Provider or Recipient.

Recipient: Centers for Disease Control and Prevention

Provider: Gilead Sciences, Inc. ("Gilead")

1. Provider agrees to transfer to Recipient's Investigator named below the following Research Material: **Tenofovir disoproxil fumarate (powder form) 55 gm**
Tenofovir (powder form) 2 gm

2. THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS. The Research Material will only be used for research purposes by Recipient's investigator in his/her laboratory, for the research project described below, under suitable containment conditions. This Research Material will not be used by Recipient or its Investigator for commercial purposes such as screening, production or sale, for which a commercialization license may be required nor will Recipient or its Investigator replicate, modify, formulate, analyze or otherwise use the Research Material in any manner that is not expressly permitted by this Agreement without the advance written consent of Gilead. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and the handling of the Research Material.

2(a). Are the Research Materials of human origin?

☐ Yes

☒ No

2(b). If Yes in 2(a), were Research Materials collected according to 45 CFR Part 46, "Protection of Human Subjects"?

☐ Yes (Please provide Assurance Number:)

☒ No

3. This Research Material will be used by Recipient's investigator solely in connection with the following research project ("Research Project") described with specificity as follows (use an attachment page if necessary):

Project Descriptions:

Project 1. Evaluation of Tenofovir pre-exposure prophylaxis (PREP) for the prevention of simian human immunodeficiency virus (SHIV) infection in a low-dose rectal challenge model in *Macaca mulatta*.

Unprotected sexual exposure, especially among women at high risk for acquiring human immunodeficiency virus (HIV) has resulted in very high rates of infection in sub-Saharan Africa and southeast Asia. The lack of an efficacious vaccine for HIV emphasizes the urgency for developing a simple, safe and effective strategy to prevent sexual transmission.

As a model for human treatment, Tenofovir will be used to treat male *Macaca mulatta* (Rhesus macaques) in a low-dose (10TCID) SHIV (SHIV_{SF162P3}) rectal challenge regimen. The low-dose SHIV_{SF162P3} rectal challenge regimen more closely approximates virus exposures in humans and thus serves as an appropriate model to test the effectiveness of anti-HIV drugs, microbicides or vaccines.

Method: The study will be conducted using the format described below. The maximum length of virus exposures in all arms will be 20 weeks. After conclusion of pre-determined virus exposure periods, all uninfected animals will be monitored for 20 weeks.

Arm number	Description of Arm	Number of Animals	Treatment Regimen oral @ 10 mg/Kg	Virus challenge (rectal, SHIV _{SF162P3} , 10TCID ₅₀)	Follow-up
1	Control; no pre-exposure prophylaxis (NO-PREP)	4	None	Weekly	Detectable virus anticipated at week 5
2	Daily-dose pre-exposure prophylaxis (DD-PREP)	4	Daily treatment for 20 weeks	First challenge 7 days after drug treatment and then weekly for up to 20 exposures	20 weeks f/u
3	weekly-dose pre-exposure prophylaxis (WD-PREP)	4	Single dose treatment for 20 weeks	Single challenge given 2 hours after treatment dose, treatment/challenge will be done for 20 weeks	20 weeks f/u

Project 2. In-vitro evaluation of development of Tenofovir resistance in SHIV_{SF162P3} and pattern of amino acid changes in RT over time under drug pressure.

In the first study the macaques will be under very intensive systemic drug pressure for a prolonged period of time. If animals become infected while on drug prophylaxis, drug resistance to Tenofovir is expected to emerge. It will become important to monitor the changes in drug resistance and effect on overall viral level and disease progression. It is also necessary to conduct parallel in-vitro assessment of drug resistance development in SHIV_{SF162P3}. The resistant genotype of this virus strain to Tenofovir is unknown. The selection of resistant quasispecies and their genotypic characteristics of the reverse transcriptase gene could be more easily determined from *in vitro* assays. This information is crucial for the understanding of potential prophylaxis failures that may be observed in this animal model.

4. In all oral presentations or written publications concerning the Research Project, Recipient and Recipient's Investigator will acknowledge Provider's contribution of this Research Material unless requested otherwise. To the extent permitted by law, Recipient agrees to treat in confidence, for a period

of five (5) years from the date of its disclosure, any of Provider's written information about this Research Material that is stamped "CONFIDENTIAL," or "PROPRIETARY" or some similar designation marking such documentation as confidential to Gilead except for information that was previously known to Recipient or that is or becomes publicly available or which is disclosed to Recipient without a confidentiality obligation. Recipient may publish or otherwise publicly disclose the results of the Research Project, but if Provider has given CONFIDENTIAL information to Recipient such public disclosure may be made only after Provider has had thirty (30) days to review the proposed disclosure to determine if it includes any CONFIDENTIAL information, except when a shortened time period under court order or the Freedom of Information Act pertains.

5. This Research Material represents a significant investment on the part of Provider and is considered proprietary to Provider. Provider retains all right, title and interest in and to the Research Materials. This Agreement does not give Recipient any right or license to any Research Material or intellectual property rights of Provider. Recipient's investigator therefore agrees to retain control over this Research Material and further agrees not to transfer the Research Material to other people not under her or his direct supervision without advance written approval of Provider. Provider reserves the right to distribute the Research Material to others and to use it for its own purposes. Upon Providers reasonable requests for any reason or when the Research Project is completed or three (3) years have elapsed, whichever occurs first, the Recipient will cease use of and the Research Material will be disposed of as directed by Provider.

6. This Research Material is provided as a service to the research community. IT IS BEING SUPPLIED TO RECIPIENT WITH NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. Provider makes no representations that the use of the Research Material will not infringe any patent or proprietary rights of third parties.

7. When Provider is the PHS: Recipient shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. Recipient agrees not to claim, infer, or imply Governmental endorsement of the Research Project, the institution or personnel conducting the Research Project or any resulting product(s). Unless prohibited by law from doing so, recipient agrees to hold the United States Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of Recipient's use for any purpose of the Research Material.

8. When Recipient is the PHS: Recipient will promptly disclose to Provider all results, data, and other information or materials derived from Recipient's use of Research Material and Provider's Confidential Information ("Results"). Provider may freely use the Results solely for internal research purposes. Provider may use Results for other purposes only with Recipient's express prior written consent, which shall not be unreasonably withheld. The ownership of any inventions, discoveries and ideas that are made, conceived or reduced to practice under this Agreement ("Inventions") either solely by Recipient's Investigator or jointly by Provider and Recipient's Investigator, and whether patentable or not, shall be determined in accordance with U.S. patent law on inventorship. Recipient agrees to promptly notify Provider of any Inventions. **The PHS shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. The PHS is not authorized to promise rights in advance for inventions developed under this Agreement, however, PHS agrees to give serious and reasonable consideration to Provider's request for a non-exclusive or exclusive license on commercially reasonable terms under PHS's intellectual property rights in or to any Inventions. It is the intention of NIAID that Provider not be liable to NIAID for any claims or damages arising from NIAID's**

use of the Research Material; however, no indemnification for any loss, claim, damage, or liability is intended or provided by NIAID under this Agreement. NIAID shall be liable for any loss, claim, damage or liability it incurs as a result of its activities under this Agreement, except that NIAID, as an agency of the United States, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. §§ 2671 *et seq*

9. The undersigned Provider and Recipient expressly certify and affirm that the contents of any statements made herein are truthful and accurate.

10. This MTA shall be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

11. Any additional terms: None.

Signatures Begin on Next Page

AGREED AND ACCEPTED BY :

Recipient Investigator:

Signature: Shambavi Subbarao Date: 05/27/04

Name: Shambavi Subbarao, Ph.D.

Title: Microbiologist

Authorized Signatory Official for Recipient:

Date: 6/4/04 Janet Collins

Janet L. Collins, Ph.D.
Acting Director
National Center for HIV, STD, and TB Prevention

Recipient's Mailing Address Centers for Disease Control and Prevention
1600 Clifton Road, N.E.
Atlanta, Georgia 30333
Attn: Technology Transfer Liaison (Mail Stop E-51)

Authorized Signature for Provider and Title:

Date: 21 June 2004 Mick Hitchcock
Mick Hitchcock, Ph.D.
Vice President, Medical Affairs

Provider's Mailing Address Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

EXHIBIT C

PUBLIC HEALTH SERVICE MATERIAL TRANSFER AGREEMENT

This Material Transfer Agreement ("MTA") has been adopted for use by the National Institutes of Health, the Food and Drug Administration and the Centers for Disease Control and Prevention, collectively referred to herein as the Public Health Service ("PHS") in all transfers of research material (Research Material) whether PHS is identified below as its Provider or Recipient.

Recipient: Centers for Disease Control and Prevention

Provider: Gilead Sciences, Inc. ("Gilead")

1. Provider agrees to transfer to Recipient's Investigator named below the following Research Material: 50 grams tenofovir powder

2. THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS. The Research Material will only be used for research purposes by Recipient's investigator in his/her laboratory, for the research project described below, under suitable containment conditions. This Research Material will not be used by Recipient or its Investigator for commercial purposes such as screening, production or sale, for which a commercialization license may be required nor will Recipient or its Investigator replicate, modify, formulate, analyze or otherwise use the Research Material in any manner that is not expressly permitted by this Agreement without the advance written consent of Gilead. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and the handling of the Research Material.

2(a). Are the Research Materials of human origin?

☐ Yes

☒ No

2(b). If Yes in 2(a), were Research Materials collected according to 45 CFR Part 46, "Protection of Human Subjects"?

☐ Yes (Please provide Assurance Number: _____)

☒ No

3. This Research Material will be used by Recipient's investigator solely in connection with the following research project ("Research Project") described with specificity as follows (use an attachment page if necessary): Using cervical and colorectal explant models to evaluate antiretroviral drugs for the prevention of HIV-1 infection – protocol is attached to this document (pages 5-7)

4. In all oral presentations or written publications concerning the Research Project, Recipient and Recipient's Investigator will acknowledge Provider's contribution of this Research Material unless requested otherwise. To the extent permitted by law, Recipient agrees to treat in confidence, for a period of five (5) years from the date of its disclosure, any of Provider's written information about this Research

Material that is stamped "CONFIDENTIAL," or "PROPRIETARY" or some similar designation marking such documentation as confidential to Gilead except for information that was previously known to Recipient or that is or becomes publicly available or which is disclosed to Recipient without a confidentiality obligation. Recipient may publish or otherwise publicly disclose the results of the Research Project, but if Provider has given CONFIDENTIAL information to Recipient such public disclosure may be made only after Provider has had thirty (30) days to review the proposed disclosure to determine if it includes any CONFIDENTIAL information, except when a shortened time period under court order or the Freedom of Information Act pertains.

5. This Research Material represents a significant investment on the part of Provider and is considered proprietary to Provider. Provider retains all right, title and interest in and to the Research Materials. This Agreement does not give Recipient any right or license to any Research Material or intellectual property rights of Provider. Recipient's investigator therefore agrees to retain control over this Research Material and further agrees not to transfer the Research Material to other people not under her or his direct supervision without advance written approval of Provider. Provider reserves the right to distribute the Research Material to others and to use it for its own purposes. Upon Providers reasonable requests for any reason or when the Research Project is completed or three (3) years have elapsed, whichever occurs first, the Recipient will cease use of and the Research Material will be disposed of as directed by Provider.

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8. When Recipient is the PHS: Recipient will promptly disclose to Provider all results, data, and other information or materials derived from Recipient's use of Research Material and Provider's Confidential Information ("Results"). Provider may freely use the Results solely for internal research purposes. Provider may use Results for other purposes only with Recipient's express prior written consent, which shall not be unreasonably withheld. The ownership of any inventions, discoveries and ideas that are made, conceived or reduced to practice under this Agreement ("Inventions") either solely by Recipient's Investigator or jointly by Provider and Recipient's Investigator, and whether patentable or not, shall be determined in accordance with U.S. patent law on inventorship. Recipient agrees to promptly notify Provider of any Inventions. The PHS shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. The PHS is not authorized to promise rights in advance for inventions developed under this Agreement, however, PHS agrees to give serious and reasonable consideration to Provider's request for a non-exclusive or exclusive license on commercially reasonable terms under PHS's intellectual property rights in or to any Inventions. It is the intention of PHS that Provider not be liable to PHS for any claims or damages arising from PHS use of

the Research Material; however, no indemnification for any loss, claim, damage, or liability is intended or provided by PHS under this Agreement. PHS shall be liable for any loss, claim, damage or liability it incurs as a result of its activities under this Agreement, except that PHS, as an agency of the United States, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. §§ 2671 *et seq*

9. The undersigned Provider and Recipient expressly certify and affirm that the contents of any statements made herein are truthful and accurate.

10. This MTA shall be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

11. Any additional terms: None.

Signatures Begin on Next Page

ACKNOWLEDGED AND UNDERSTOOD BY:

Recipient Investigator:

Signature: Charlene S. Dezzutti Date: 11-22-04
Name: Charlene S. Dezzutti, Ph.D.
Title: Microbiologist

Authorized Signatory Official for Recipient:

Date: 12/1/04 Janet L. Collins Acting ADLS for
Janet L. Collins, Ph.D.
Director
National Center for HIV, STD and TB Prevention

Recipient's Mailing Address Centers for Disease Control and Prevention
1600 Clifton Road, N.E.
Atlanta, Georgia 30333
Attn: Technology Transfer Liaison (Mail Stop E-51)

Authorized Signature for Provider and Title:

Date: 7 January 2005 Mick Hitchcock
Mick Hitchcock, Ph.D.
Vice President, Medical Affairs

Provider's Mailing Address Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

 **GILEAD**
Approved by Legal Department
[Signature]

Using cervical and colorectal explant models to evaluate antiretroviral drugs for the prevention of HIV-1 infection

Principle investigator: Charlene S. Dezzutti, PhD

Co-investigators: Kelly Hancock, PhD, Patricia Guenthner, Thomas Folks, PhD

Microbicide and Mucosal Virology Section, HIV and Retrovirology Branch, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA

Introduction

Because approximately 75% of newly acquired HIV-1 infections occur via sexual transmission, additional prevention measures are needed to halt the spread of HIV-1 through mucosal exposure. Currently, condoms are the only approved prevention method. However, condoms have limited effectiveness due to leakage of seminal fluid or improper usage. While topical microbicides offer an alternative to prevent acquisition of HIV-1 and other sexually transmitted pathogens, these products are still in development.

Peripheral blood levels of HIV-1 RNA are correlated to mucosal levels HIV-1 RNA. Several studies have shown that elevated peripheral blood HIV-1 RNA levels are more likely to transmit HIV-1 to their uninfected partner. Antiretroviral therapy (ART) reduces viral load in the peripheral blood as well as in mucosal secretions. In deed, ART is being used to prevent mother-to-child transmission and is being explored as a pre-exposure prophylaxis (PrEP). To systematically evaluate antiretroviral drugs that may be absorbed by the mucosal tissues and prevent HIV-1 infection, cervical and colorectal explant models will be used.

Materials and Methods

Human cervical explant culture. After obtaining informed consent, normal ectocervix is obtained within 4 hours of surgery from pre-menopausal women undergoing hysterectomy. Tissues are transported to the lab on ice in L15 medium. The cervix is washed twice with sterile PBS and placed in a petri dish. Excess submucosal tissue is removed to produce a flat piece (approximately 3 mm thick) containing both epithelium and stromal tissue. Dermal biopsy punches are used to cut full-thickness tissue specimens (5-mm diameter). Each explant is inserted through a 4-mm diameter hole in a transwell insert with the epithelium oriented on top in the apical chamber. After placement in a 24-well plate, the epithelial surface of the explant is surrounded with 2% agarose to maintain tissue orientation. In the basolateral chamber, the stroma is cultured in 0.6 mL of complete DMEM. Tissues are cultured at 37°C in a humidified incubator containing 7% CO₂. Explants are activated for 2 days in DMEM containing phytohemagglutinin-P (PHA) and human interleukin-2 (IL-2).

Human colorectal explant culture. After obtaining informed consent, normal tissue is obtained from HIV-1 negative patients undergoing surgical resection of cancerous lesions or other noninflammatory conditions in the colon and rectum. Tissues are transported to the laboratory on ice in L15 medium. Following longitudinal cutting and excision of the mesentery, the tissue is pinned down (mucosal side up) on filter paper on styrofoam. Dermal biopsy punch devices are used to cut full-thickness tissue specimens (5-mm diameter) that are transferred to a Petri dish containing L15 medium. The outer muscle layer is excised using scalpel and forceps. The remaining mucosa (epithelium and lamina propria) is positioned on pre-shrunk plugs of gelfoam (gelatin sponges) inside transwells in which holes are cut in the membranes to facilitate saturation of gelfoam and tissue with culture medium. To approximate the in vivo polarized state, Matrigel™ is applied to form a gelatinous seal around the explant to ensure that only the apical tissue surfaces are exposed to treatments. The basolateral compartment contains 1 mL of complete RPMI and human interleukin-2 (IL-2). For tissue activation, explants are treated with PHA on the first day of culture. Explants are incubated at 37°C in a modular incubator chamber purged with a mixture of 95% O₂ and 5% CO₂ that is refreshed every other day.

Antiretroviral therapy. Initially, antiretroviral drugs proposed for PrEP use are titrated starting at 50 µg/mL and cultured in duplicate explants in the basolateral medium for 4 hours prior to virus addition. After the treatment, the basolateral medium is washed 3 times with medium and replenished. A laboratory adapted or primary HIV-1 isolate (100 tissue culture infectious dose [TCID₅₀]) is added to the apical surface and cultured overnight. Alternatively, the virus used in the non-human primate studies, SHIV_{SF162p} (100 TCID₅₀) is added to the apical surface and cultured overnight. In either case, the explants are washed 3 times and cultures are monitored for two weeks for viral replication using p24gag or p27gag ELISA. When the effective concentration is determined, pre-exposure timing is planned. Tenofovir is added for 16, 8, 4, 2, or 1 hour to the explants. After washing 3 times, basolateral medium is replenished and HIV-1 or SHIV is added to the apical surface overnight and followed as described above.

Histology. Tissues are fixed in 10% buffered formalin, paraffin embedded, sectioned, and stained with hematoxylin and eosin to evaluate general tissue architecture, cell integrity and necrosis over a 2 week culture period and after an overnight exposure to each product.

MTT assay. Viability of the tissue explants and assessment of antiretroviral drug toxicity is determined using the reduction of the tetrazolium salt, MTT [1-(4,5-dimethylthiazol-2-yl)-3,5-diphenylformazan], to a methanol-soluble formazan product. Explants (5-mm diameter) are cultured without or with drug overnight. After 5 washes with PBS, the explants will be incubated in RPMI containing MTT (250 µg/mL) for 3 h at 37°C. Explants are removed from the medium and submerged overnight in 1 mL of methanol to extract the formazan product. Tissue viability is determined by dividing the optical density of the formazan product at 570 nm by the dry weight of the explant. The effect of the antiretrovirals on tissue viability is determined by a ratio between treated and untreated tissue explants.

This work is expected to determine the effective concentration in mucosal tissues to prevent HIV-1/SHIV infection. This information will be used in conjunction with the PrEP work being conducted in non-human primates.

EXHIBIT D

PUBLIC HEALTH SERVICE MATERIAL TRANSFER AGREEMENT

This Material Transfer Agreement ("MTA") has been adopted for use by the National Institutes of Health, the Food and Drug Administration and the Centers for Disease Control and Prevention, collectively referred to herein as the Public Health Service ("PHS") in all transfers of research material (Research Material) whether PHS is identified below as its Provider or Recipient.

Recipient: Centers for Disease Control and Prevention

Provider: Gilead Sciences, Inc. ("Gilead")

1. Provider agrees to transfer to Recipient's Investigator named below the following Research Material: **FTC (emtricitabine, powder form) 250 gm.**

2. THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS. The Research Material will only be used for research purposes by Recipient's investigator in his/her laboratory, for the research project described below, under suitable containment conditions. This Research Material will not be used by Recipient or its Investigator for commercial purposes such as screening, production or sale, for which a commercialization license may be required nor will Recipient or its Investigator replicate, modify, formulate, analyze or otherwise use the Research Material in any manner that is not expressly permitted by this Agreement without the advance written consent of Gilead. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and the handling of the Research Material.

2(a). Are the Research Materials of human origin?

☐ Yes

☒ No

2(b). If Yes in 2(a), were Research Materials collected according to 45 CFR Part 46, "Protection of Human Subjects"?

☐ Yes (Please provide Assurance Number:)

☒ No

3. This Research Material will be used by Recipient's investigator solely in connection with the following research project ("Research Project") described with specificity as follows (use an attachment page if necessary):

Project Description:

Pre-exposure prophylaxis with FTC in combination with one or two drugs for the prevention of simian human immunodeficiency virus (SHIV) infection in a repeat low-dose challenge model in *Macaca mulatta*.

Unprotected sexual exposure, especially among women at high risk for acquiring human immunodeficiency virus (HIV) has resulted in very high rates of infection in sub-Saharan Africa and southeast Asia. The lack of an efficacious vaccine for HIV emphasizes the urgency for developing a simple, safe and effective strategy to prevent sexual transmission.

As a model for human treatment, FTC will be used to treat female *Macaca mulatta* (Rhesus macaques) in a low-dose (10TCID₅₀) SHIV (RT-SHIV) vaginal challenge that more closely approximates virus exposures in humans. Tenofovir and FTC will be delivered subcutaneously each at 20 mg/kg. Efavirenz will be given orally at 60mg/kg.

Method: The study will be conducted using the format described below. The maximum length of virus exposures in all arms will be 20 weeks. After conclusion of pre-determined virus exposure periods, all uninfected animals will be monitored for 24 weeks. The emergence of drug resistance will be monitored in breakthrough viruses from treated animals.

Arm number	Description of Arm	Number of Animals	Treatment Regimen	Virus challenge (vaginal, RT-SHIV, 10TCID ₅₀)	Follow-up
1	Control; no pre-exposure prophylaxis (NO-PREP)	4	None	Weekly	Detectable virus anticipated around week 5
2	Two-drug prophylaxis (2D-PREP)	4	Daily treatment FTC/TNF for 20 weeks	First challenge 7 days after drug treatment and then weekly for up to 20 exposures	24 weeks f/u
3	Three-drug prophylaxis (3D-PREP)	4	Daily treatment TNF/FTC/efavirenz for 20 weeks	First challenge 7 days after drug treatment and then weekly for up to 20 exposures	24 weeks f/u

4. In all oral presentations or written publications concerning the Research Project, Recipient and Recipient's Investigator will acknowledge Provider's contribution of this Research Material unless requested otherwise. To the extent permitted by law, Recipient agrees to treat in confidence, for a period of five (5) years from the date of its disclosure, any of Provider's written information about this Research Material that is stamped "CONFIDENTIAL," or "PROPRIETARY" or some similar designation marking such documentation as confidential to Gilead except for information that was previously known to Recipient or that is or becomes publicly available or which is disclosed to Recipient without a confidentiality obligation. Recipient may publish or otherwise publicly disclose the results of the Research Project, but if Provider has given CONFIDENTIAL information to Recipient such public disclosure may be made only after Provider has had thirty (30) days to review the proposed disclosure to determine if it includes any CONFIDENTIAL information, except when a shortened time period under court order or the Freedom of Information Act pertains.

5. This Research Material represents a significant investment on the part of Provider and is considered proprietary to Provider. Provider retains all right, title and interest in and to the Research Materials. This

Agreement does not give Recipient any right or license to any Research Material or intellectual property rights of Provider. Recipient's investigator therefore agrees to retain control over this Research Material and further agrees not to transfer the Research Material to other people not under her or his direct supervision without advance written approval of Provider. Provider reserves the right to distribute the Research Material to others and to use it for its own purposes. Upon Providers reasonable requests for any reason or when the Research Project is completed or three (3) years have elapsed, whichever occurs first, the Recipient will cease use of and the Research Material will be disposed of as directed by Provider.

6. This Research Material is provided as a service to the research community. IT IS BEING SUPPLIED TO RECIPIENT WITH NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. Provider makes no representations that the use of the Research Material will not infringe any patent or proprietary rights of third parties.

7. When Provider is the PHS: Recipient shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. Recipient agrees not to claim, infer, or imply Governmental endorsement of the Research Project, the institution or personnel conducting the Research Project or any resulting product(s). Unless prohibited by law from doing so, recipient agrees to hold the United States Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of Recipient's use for any purpose of the Research Material.

8. When Recipient is the PHS: Recipient will promptly disclose to Provider all results, data, and other information or materials derived from Recipient's use of Research Material and Provider's Confidential Information ("Results"). Provider may freely use the Results solely for internal research purposes. Provider may use Results for other purposes only with Recipient's express prior written consent, which shall not be unreasonably withheld. The ownership of any inventions, discoveries and ideas that are made, conceived or reduced to practice under this Agreement ("Inventions") either solely by Recipient's Investigator or jointly by Provider and Recipient's Investigator, and whether patentable or not, shall be determined in accordance with U.S. patent law on inventorship. Recipient agrees to promptly notify Provider of any Inventions. The PHS shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. The PHS is not authorized to promise rights in advance for inventions developed under this Agreement, however, PHS agrees to give serious and reasonable consideration to Provider's request for a non-exclusive or exclusive license on commercially reasonable terms under PHS's intellectual property rights in or to any Inventions. It is the intention of NIAID that Provider not be liable to NIAID for any claims or damages arising from NIAID's use of the Research Material; however, no indemnification for any loss, claim, damage, or liability is intended or provided by NIAID under this Agreement. NIAID shall be liable for any loss, claim, damage or liability it incurs as a result of its activities under this Agreement, except that NIAID, as an agency of the United States, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. §§ 2671 *et seq*

9. The undersigned Provider and Recipient expressly certify and affirm that the contents of any statements made herein are truthful and accurate.

10. This MTA shall be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

11. Any additional terms: None.

CDC Ref. NCHSTP-V053471-00

Signatures Begin on Next Page

AGREED AND ACCEPTED BY :

Recipient Investigator

Signature: _____

Date: _____

Name: Walid Heneine, Ph.D.

Title: Chief, HIV Drug Resistance and Retroviral Zoonoses Laboratory

Authorized Signatory Official for Recipient:

Date: _____

1/12/2005

for

Janet L. Collins, Ph.D.

Acting Director

National Center for HIV, STD and TB Prevention

Acting Assoc Dir for Lab. Science.

Recipient's Mailing Address

Centers for Disease Control and Prevention

1600 Clifton Road, N.E.

Atlanta, Georgia 30333

Attn: Technology Transfer Liaison (Mail Stop E-51)

Authorized Signature for Provider and Title:

Date: _____

31 Jan 2005

Mick Hitchcock

Mick Hitchcock, Ph.D.

Vice President, Medical Affairs

Provider's Mailing Address

Gilead Sciences, Inc.

333 Lakeside Drive

Foster City, CA 94404

EXHIBIT E

CDC Ref.

Gilead Sciences, Inc.
NCHSTP-V053649-00**PUBLIC HEALTH SERVICE MATERIAL TRANSFER AGREEMENT**

This Material Transfer Agreement ("MTA") has been adopted for use by the National Institutes of Health, the Food and Drug Administration and the Centers for Disease Control and Prevention, collectively referred to herein as the Public Health Service ("PHS") in all transfers of research material (Research Material) whether PHS is identified below as its Provider or Recipient.

Recipient: Centers for Disease Control and Prevention

Provider: Gilead Sciences, Inc. ("Gilead")

1. Provider agrees to transfer to Recipient's Investigator named below the following Research Material: **420 grams of PMPA ((R)-9-(2- Phosphonylmethoxypropyl)adenine, powder form.**

2. THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS. The Research Material will only be used for research purposes by Recipient's investigator in his/her laboratory, for the research project described below, under suitable containment conditions. This Research Material will not be used by Recipient or its Investigator for commercial purposes such as screening, production or sale, for which a commercialization license may be required nor will Recipient or its Investigator replicate, modify, formulate, analyze or otherwise use the Research Material in any manner that is not expressly permitted by this Agreement without the advance written consent of Gilead. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and the handling of the Research Material.

2(a). Are the Research Materials of human origin?

____ Yes

XX No

2(b). If Yes in 2(a), were Research Materials collected according to 45 CFR Part 46, "Protection of Human Subjects"?

____ Yes (Please provide Assurance Number: ____)

XX No

3. This Research Material will be used by Recipient's investigator solely in connection with the following research project ("Research Project") described with specificity as follows (use an attachment page if necessary):

Project Description:

EVALUATION OF MULTIDRUG CHEMOPROPHYLAXIS FOR THE PREVENTION OF SIMIAN HUMAN IMMUNODEFICIENCY VIRUS INFECTION USING THE REPEAT-EXPOSURE MACAQUE MODEL.

Gilead Sciences, Inc.
NCHSTP-V053649-00

Unprotected sexual exposure results in very high rates of HIV-1 transmission among individuals at high risk for acquiring the virus. Given the current lack of an efficacious vaccine or microbicide, there is an urgent need for evaluation of other biomedical approaches for HIV-prevention. Macaque models of HIV-infection are useful to evaluate intervention modalities and advance the more promising products into human clinical trials.

In a recently concluded macaque study, we evaluated chemoprophylaxis with oral tenofovir for protection against multiple rectal challenges with SHIV. Infection was delayed in tenofovir-treated animals for up to an average of 6 weeks. While the observed delay in infection is encouraging, infection was ultimately not prevented. It may be a single drug may not deliver the antiviral potency required to effectively prevent transmission.

In the current study, drug combinations will be evaluated for chemoprophylaxis. PHHS recommended drug combinations for treatment of HIV-1 infection in humans include

- a) 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and 1 protease inhibitor (PI)
- b) 2 NRTIs and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI).

In this study we plan to use these combinations for the prevention of infection in the repeat exposure macaque model.

Study Design:

Arm	Drug	Virus (10 TCID ₅₀)	Total F/U
Control; n=6	No drug	SHIV _{SF162P3} or (RT-SHIV if EFV used)	20 weeks
3-drug; n=6	PMPA + emtricitabine + kaletra (or EFV*)	SHIV _{SF162P3} or (RT-SHIV if EFV used)	20 weeks**
***2-drug; n=6	[PMPA + Kaletra (or EFV*)]/ [PMPA + FTC]/ [FTC + Kaletra (or EFV*)]	SHIV _{SF162P3} or (RT-SHIV if EFV used)	20 weeks **

* If in-vitro data indicate that Kaletra does not show significant antiviral activity against SHIV, then, efavirenz (EFV) will be used. If EFV is used, then the virus inoculations will be done with RT-SHIV, which has a HIV-1 RT gene susceptible to the action of EFV.

** Protected animals in the 3-drug and 2-drug arms will be subjected to a "wash-out" period free of drugs and virus inoculations for up to 4 weeks. Following the "wash-out", animals will be evaluated on single drug regimens.

*** For logistical reasons, the 2-drug arm will be staggered to start about 8 weeks after the 3-drug arm has started.

CDC Ref. 1

4. In all oral presentations or written publications concerning the Research Project, Recipient and Recipient's Investigator will acknowledge Provider's contribution of this Research Material unless requested otherwise. To the extent permitted by law, Recipient agrees to treat in confidence, for a period of five (5) years from the date of its disclosure, any of Provider's written information about this Research Material that is stamped "CONFIDENTIAL," or "PROPRIETARY" or some similar designation marking such documentation as confidential to Gilead except for information that was previously known to Recipient or that is or becomes publicly available or which is disclosed to Recipient without a confidentiality obligation. Recipient may publish or otherwise publicly disclose the results of the Research Project, but if Provider has given CONFIDENTIAL information to Recipient such public disclosure may be made only after Provider has had thirty (30) days to review the proposed disclosure to determine if it includes any CONFIDENTIAL information, except when a shortened time period under court order or the Freedom of Information Act pertains.

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Gilead Sciences, Inc.
NCHSTP-V053649-00

inventions made by its employees in the course of the Research Project. The PHS is not authorized to promise rights in advance for inventions developed under this Agreement, however, PHS agrees to give serious and reasonable consideration to Provider's request for a non-exclusive or exclusive license on commercially reasonable terms under PHS's intellectual property rights in or to any Inventions. It is the intention of NIAID that Provider not be liable to NIAID for any claims or damages arising from NIAID's use of the Research Material; however, no indemnification for any loss, claim, damage, or liability is intended or provided by NIAID under this Agreement. NIAID shall be liable for any loss, claim, damage or liability it incurs as a result of its activities under this Agreement, except that NIAID, as an agency of the United States, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. §§ 2671 *et seq*

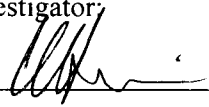
9. The undersigned Provider and Recipient expressly certify and affirm that the contents of any statements made herein are truthful and accurate.

10. This MTA shall be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

11. Any additional terms: None.

Signatures Begin on Next Page

CDC Ref.

Gilead Sciences, Inc.
NCHSTP-V053649-00**AGREED AND ACCEPTED BY :****Recipient Investigator:**Signature: Date: 4/1/05Name: Walid Heneine, Ph.D.Title: Chief, HIV surveillance, Drug Resistance, and Chemoprophylaxis Laboratory**Authorized Signatory Official for Recipient:**Date: 4/11/05Victoria Pope Ph.D for (Acting ADAS)

Janet L. Collins, M.D.

Director

National Center for HIV, STD and TB Prevention

Recipient's Mailing Address

Centers for Disease Control and Prevention

1600 Clifton Road, N.E.

Atlanta, Georgia 30333

Attn: Technology Transfer Liaison (Mail Stop E-51)

Authorized Signature for Provider and Title:Date: 25 April 2005Mick Hitchcock

Mick Hitchcock, Ph.D.

Vice President, Medical Affairs

Provider's Mailing Address

Gilead Sciences, Inc.

333 Lakeside Drive

Foster City, CA 94404

EXHIBIT F

Doc Code:

PTO/SB/16 (10-05)

Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET - Page 1 of 2

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. ED 490297095 US

INVENTOR(S)					
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)			
Walid	HENEINE	Atlanta, GA			
J. Gerardo	GARCIA-LERMA	Decatur, GA			
Thomas	FOLKS	Snellville, GA			
Robert	JANSSEN	Atlanta, GA			
Ronald	OTTEN	Villa Rica, GA			
☐ Additional inventors are being named on the _____ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
METHODS AND COMPOSITIONS FOR CHEMOPROPHYLAXIS					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
☒ The address corresponding to Customer Number:		52567			
OR					
☐ Firm or Individual Name					
Address					
City		State		ZIP	
Country		Telephone		Email	
ENCLOSED APPLICATION PARTS (check all that apply)					
☐ Application Data Sheet. See 37 CFR 1.76		☐ CD(s), Number of CDs _____			
☒ Specification Number of Pages 20		☐ Other (specify) _____			
☐ Drawing(s) Number of Sheets _____					
Total # of sheets 20		= Application Size Fee		\$0.00	
Fees Due: Filing Fee of \$200. If the specification and drawings exceed 100 sheets of paper, an application size fee is also due, which is \$250 for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).					
METHOD OF PAYMENT OF THE FILING FEE AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT					
☐ A check or money order is enclosed to cover the filing fee and application size fee (if applicable).				\$200.00	
☒ Payment by credit card. Form PTO-2038 is attached.				TOTAL FEE AMOUNT (\$)	
☐ The Director is hereby authorized to charge filing fee and application size fee (if applicable) or credit any overpayment to Account Number: _____				A duplicative copy of this form is enclosed for fee processing.	

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PROVISIONAL APPLICATION COVER SHEET

Page 2 of 2

PTO/SB/16 (10-05)

Approved for use through 07/31/2006. OMB 0651-0032

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States

☐ No.☒ Yes, the name of the U.S. Government agency and the Government contract number are: _____**Centers for Disease Control and Prevention****WARNING:**

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SIGNATURE

Sumita Chowdhury-Ghosh

Date

February 3, 2006

TYPED or PRINTED NAME

Sumita Chowdhury-Ghosh

REGISTRATION NO.

50,476

(if appropriate)

TELEPHONE

770-488-8612

Docket Number:

I-022-06US1P

020306

Doc Code:

PTO/SB/17 (01-06)

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818). FEE TRANSMITTAL for FY 2006		Complete if Known	
☐ Applicant claims small entity status. See 37 CFR 1.27		Application Number	To be assigned
TOTAL AMOUNT OF PAYMENT (\$) \$200.00		Filing Date	February 3, 2006
		First Named Inventor	Walid HENEINE
		Examiner Name	N/A
		Art Unit	N/A
		Attorney Docket No.	I-022-06US1P

METHOD OF PAYMENT (check all that apply)
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☐ Deposit Deposit Account Number: _____ Deposit Account Name: _____

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☒ Charge fee(s) indicated below☐ Charge fee(s) indicated below, except for the filing fee☒ Charge any additional fee(s) or any underpayments of fee(s) under 37 CFR 1.16 and 1.17☒ Credit any overpayments**WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**FEE CALCULATION** (All the fees below are due upon filing or may be subject to a surcharge.)**1. BASIC FILING, SEARCH, AND EXAMINATION FEES**

Application Type	FILING FEES		SEARCH FEES		EXAMINATION FEES		Fees Paid(\$)
	Fee (\$)	Small Entity Fee (\$)	Fee (\$)	Small Entity Fee (\$)	Fee (\$)	Small Entity Fee (\$)	
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	\$200.00

2. EXCESS CLAIM FEES

Fee Description	Fee (\$)	Small Entity Fee (\$)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee (\$)	Fee Paid (\$)
17	- 20 or HP = 0	x \$50.00	= \$0.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee (\$)	Fee Paid (\$)
5	- 3 or HP =	x \$200.00	= \$0.00

HP = highest number of independent claims paid for, if greater than 3.

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listing under 37 CFR 1.52(e)), the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee (\$)	Fee Paid (\$)
20	- 100 = 0	/ 50 0 (round up to a whole)	x \$250.00	= \$0.00

4. OTHER FEE(S)

Non-English specification, \$130 fee (no small entity discount)

Other (e.g., late filing surcharge): _____

SUBMITTED BY

Signature	<i>Sumita Chowdhury Ghosh</i>	Registration No. (Attorney/Agent)	50,476	Telephone	770-488-8612
Name (Print/Type)	Sumita Chowdhury-Ghosh			Date	February 3, 2006

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CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)Applicant(s): **HENEINE et al.**

Docket No.

I-022-06US1P

Application No.

To be assigned

Filing Date

February 3, 2006

Examiner

N/A

Customer No.

52567

Group Art Unit

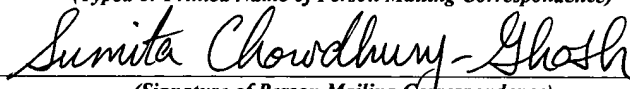
N/A

Invention: **METHODS AND COMPOSITIONS FOR CHEMOPROPHYLAXIS**

I hereby certify that the following correspondence:

Provisional Patent Application (20 sheets), Provisional Patent Application Cover Sheet, Credit Card Payment Form, Fee Transmittal, Acknowledgment Postcard*(Identify type of correspondence)*

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

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*(Signature of Person Mailing Correspondence)*ED 490297095 US*("Express Mail" Mailing Label Number)***Note: Each paper must have its own certificate of mailing.**

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Customer No. 52567

Prevention of rectal SHIV transmission in macaques by tenofovir/FTC combination

J. Gerardo García-Lerma, Ronald Otten, Shoukat Qari, Eddie Jackson, Wei Luo, Caryn Kim, Debra Adams, Michael Monsour, Raymond Schinazi, Robert Janssen, Thomas Folks, Walid Heneine

Background: Chemoprophylaxis with antiretrovirals as a strategy to prevent the transmission of human immunodeficiency virus (HIV) is being explored, although information on the most effective antiretroviral intervention is not yet known. Available data on tenofovir using macaque models of simian HIV (SHIV) mucosal infection suggest that tenofovir is not sufficiently protective at concentrations equivalent to those currently used in humans. Here, we investigated whether tenofovir/5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine(FTC, emtricitabine) combination protects macaques from rectal SHIV challenge, and whether this protection is sustained during repeated virus exposures.

Methods: One group of six Rhesus macaques was injected subcutaneously with 22mg tenofovir/20mg FTC per kg once daily. The FTC dose is comparable to that approved for humans. Six control animals did not receive any antiretroviral treatment. All animals were subjected to weekly rectal exposures with a low dose of SHIV_{SF162p3} (10 TCID₅₀; 3.8×10^5 virus particles) which expresses an R5 tropic HIV-1 envelope that resembles naturally transmitted HIV-1 strains. Infection was monitored by serology and PCR amplification of SHIV gag and pol sequences from plasma and peripheral blood lymphocytes, respectively. Historic data on control macaques using this repeat exposure model shows that four virus challenges infect ~75% of the animals.

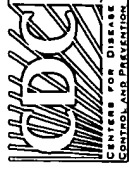
Results: Four of six controls (67%) became infected after four challenges (median = 2.5; range = 2-4). In contrast, all six animals treated with tenofovir/FTC were fully protected. After ten additional virus challenges, one of two remaining controls became infected while all six tenofovir/FTC-treated animals remained uninfected.

Conclusions: Tenofovir/FTC combination provides a high level of protection against repeated virus challenges, demonstrating that chemoprophylaxis with potent antiretrovirals is an effective strategy for preventing sexual HIV transmission.

Prevention of Rectal SHIV Transmission in Macaques by Tenofovir/FTC Combination

Walid Heneine

Laboratory Branch
Division of HIV/AIDS Prevention



Introduction

- In the absence of an effective vaccine, chemoprophylaxis with antiretrovirals has considerable potential for preventing HIV-1 transmission
- Macaque models show that tenofovir can provide substantial protection against parenteral or mucosal virus exposures
- However, this protection may be reduced at lower drug doses equivalent to those used in humans
- Current human trials with tenofovir will ultimately determine the efficacy of this intervention

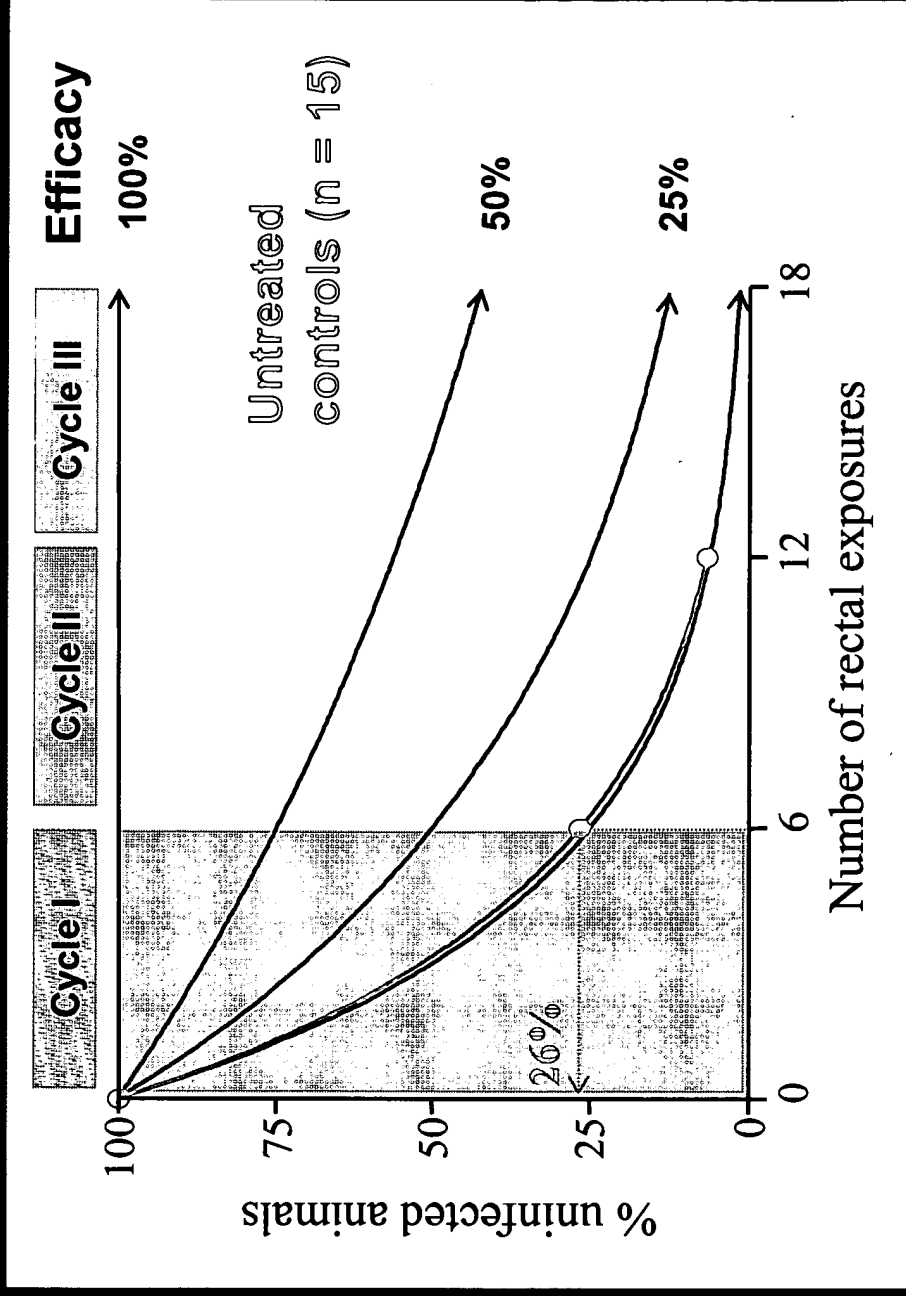
Introduction

- Many potent antiretrovirals with favorable safety and pharmacodynamic profiles are now available and are good candidates for chemoprophylaxis
- Can these drugs fully protect against sexual transmission?
- What is the relationship between drug potency and protection?
- Higher drug potency provides more protection?
- We determined whether the increased potency in a combination of 2 RT inhibitors, tenofovir and FTC, protects macaques from repeated virus exposures

Materials and Methods

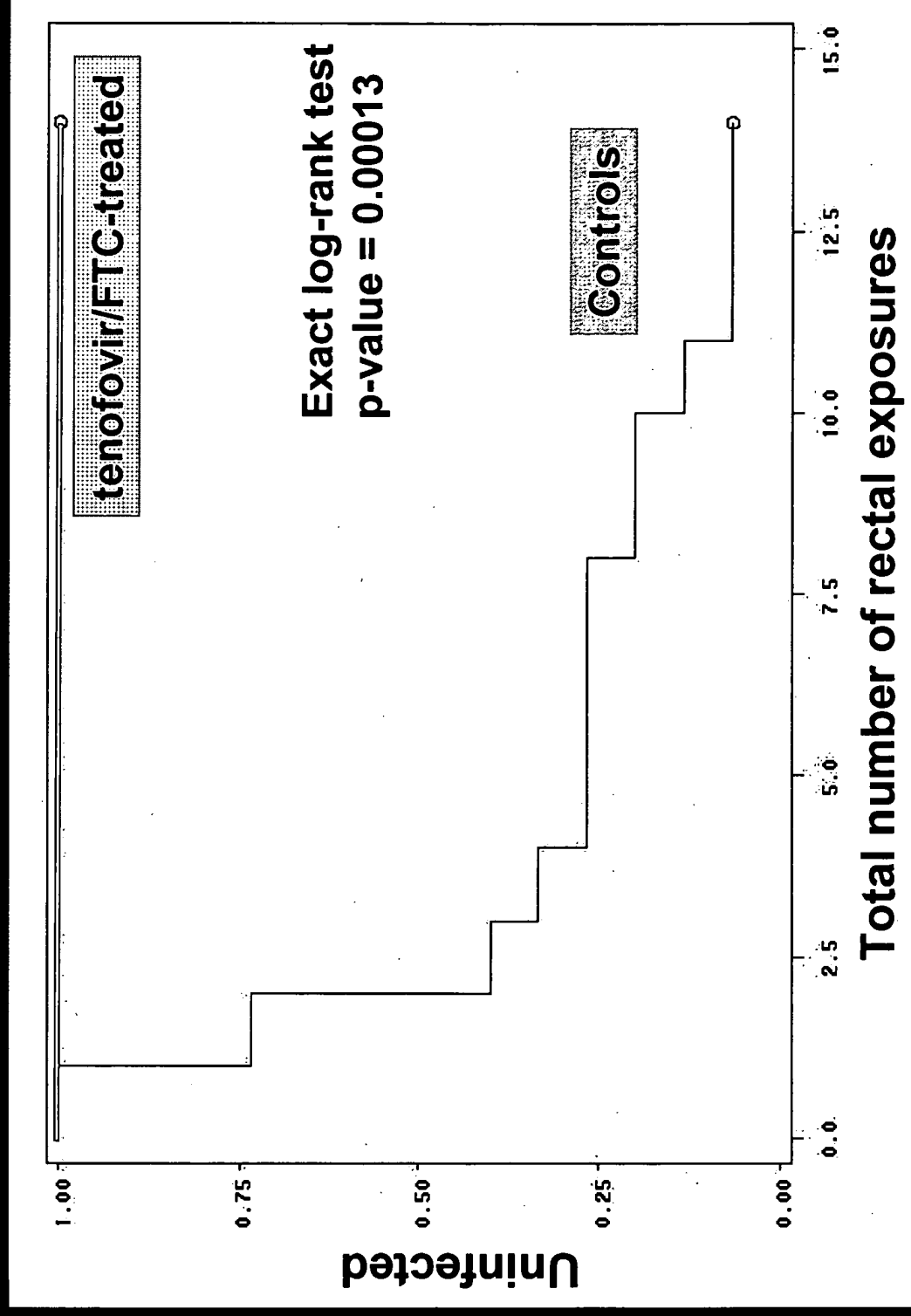
- Six male Rhesus macaques injected subcutaneously with tenofovir 22 mg/kg and FTC 20 mg/kg once daily
- Six controls received no drug treatment
- Repeated rectal exposures once weekly with SHIV162p3 that contains an HIV-1 R5 env; 14 total virus exposures
- Virus inoculum: 10 TCID (3.8 10⁵ virus particles equivalent)
- Infection was monitored by serology, RT-PCR of plasma and proviral PCR of PBMC
- Animals considered protected if seronegative and PCR negative

Repeat low-dose model



Controls, median 2 exposures (range 1-11)

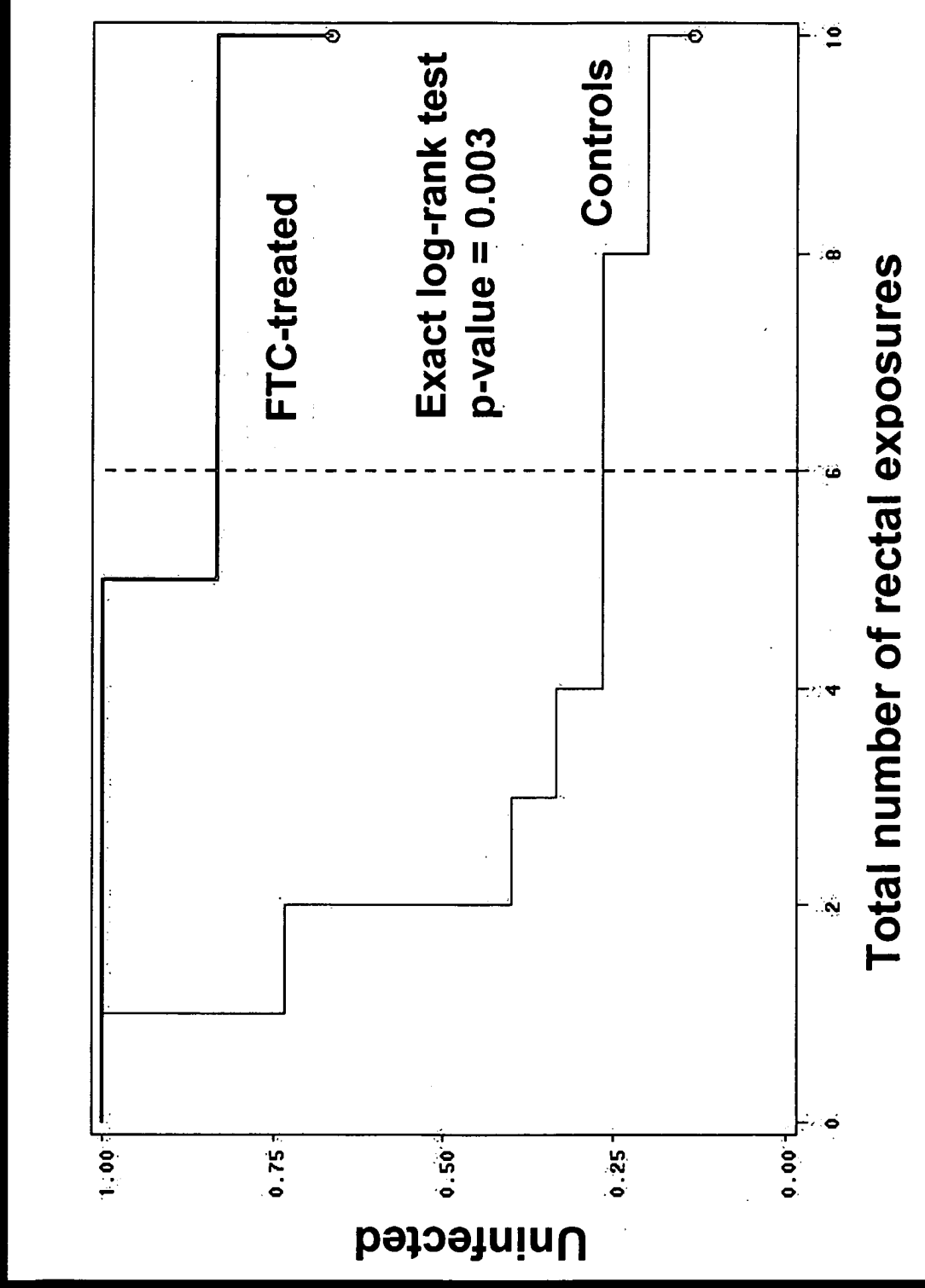
Prevention of rectal SHIV transmission in macaques by tenofovir/FTC combination



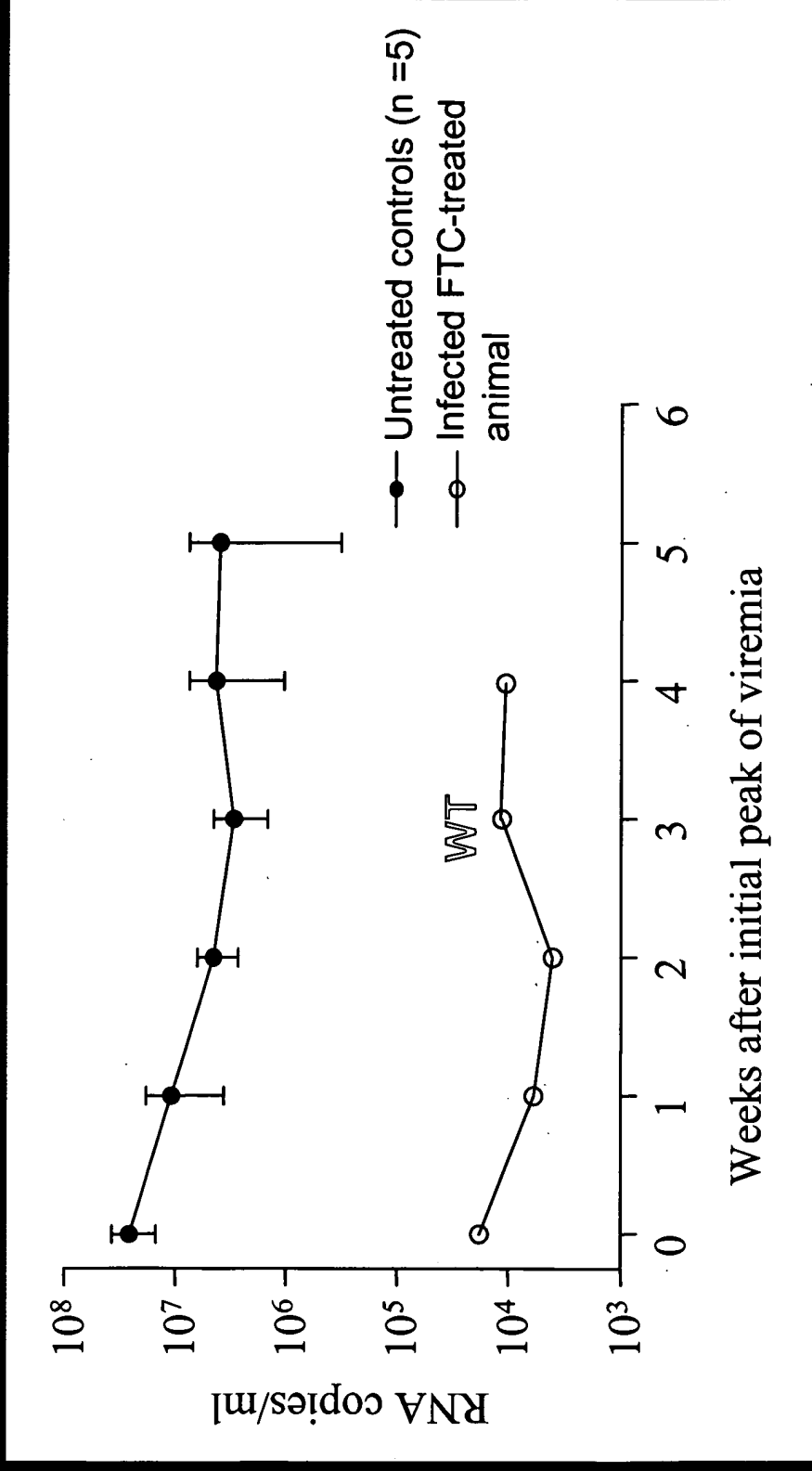
Chemoprophylaxis with FTC only

- How much FTC (Emtricitabine, Emtriva) contributes to the observed protection?
- FTC is very potent (~1.8 decrease in virus load)
- Well tolerated, good safety profile, once daily dosing, long intracellular half-life (40 h)
- Pharmacokinetic analysis suggests that 20 mg/kg/day in rhesus macaques is equivalent to the dose used in humans
- Evaluated protection by FTC in six Rhesus macaques

High level protection of rectal SHIV transmission by FTC alone



Decreased peak viremia and viral set point in an infected FTC-treated macaque



Summary and Conclusions

- Tenofovir/FTC combination protected all 6 treated animals from infection after 14 repeated rectal SHIV exposures
- Treated animals remained uninfected despite receiving seven times more exposures than controls (median exposures to infect controls is 2)
- Data suggest that chemoprophylaxis with a potent antiretroviral drug combination can be highly effective in preventing sexual HIV transmission
- The observed protection by tenofovir and FTC may not reflect that of Truvada, because a higher dose of tenofovir was used

Summary and Conclusions

- Ongoing study suggests that FTC alone at a dose similar to that used in humans shows a predicted efficacy of ~75%.
- In the Cox proportional hazards model control monkeys are 5.7 times more likely to become infected than treated monkeys (p-value is 0.024)
- Single-drug prophylaxis with FTC appears very effective. Conclusive data when study is completed.
- Adding tenofovir to FTC at a dosing similar to that in Truvada may enhance further the protection
- Drug potency matters for preventing sexual infection by chemoprophylaxis



Acknowledgments

CDC

J. Gerardo Garcia-Lerma

Ron Otten

Shoukat Qari

Eddie Jackson

Wei Luo

Caryn Kim

Debra Adams

Michael Monsour

Robert Janssen

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Walid Heneine

Emory University/VA Hospital

Raymond F Schinazi

Gilead

Jim Rooney

UC Davis

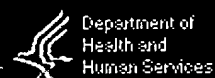
Koen van Rompay

Thomas North





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current October 2005

Drugs Used in the Treatment of HIV Infection

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Brand Name	Generic Name	Manufacturer Name	Approval Date	Time to Approval
Combivir	lamivudine and zidovudine	GlaxoSmithKline	27-Sep-97	3.9 months
Emtriva	FTC, emtricitabine	Gilead Sciences	02-Jul-03	10 months
Epivir	lamivudine, 3TC	GlaxoSmithKline	17-Nov-95	4.4 months
Epzicom	abacavir/ lamivudine	GlaxoSmithKline	02-Aug-04	10 months
Hivid	zalcitabine, ddC, dideoxycytidine	Hoffmann-La Roche	19-Jun-92	7.6 months
Retrovir	zidovudine, AZT, azidothymidine, ZDV	GlaxoSmithKline	19-Mar-87	3.5 months
Trizivir	abacavir, zidovudine, and lamivudine	GlaxoSmithKline	14-Nov-00	10.9 months
Truvada	tenofovir disoproxil/emtricitabine	Gilead Sciences, Inc.	02-Aug-04	5 months
Videx EC	enteric coated didanosine	Bristol Myers-Squibb	31-Oct-00	9 months
Videx	didanosine, ddl, dideoxyinosine	Bristol Myers-Squibb	9-Oct-91	6 months
Viread	tenofovir disoproxil fumarate	Gilead	26-Oct-01	5.9 months
Zerit	stavudine, d4T	Bristol Myers-Squibb	24-Jun-94	5.9 months
Ziagen	abacavir	GlaxoSmithKline	17-Dec-98	5.8 months

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Brand Name	Generic Name	Manufacturer Name	Approval Date	Time to Approval
Rescriptor	delavirdine, DLV	Pfizer	4-Apr-97	8.7 months
Sustiva	efavirenz	Bristol Myers-Squibb	17-Sep-98	3.2 months
Viramune	nevirapine, BI-RG-587	Boehringer Ingelheim	21-Jun-96	3.9 months

Protease Inhibitors (PIs)

Brand Name	Generic Name	Manufacturer Name	Approval Date	Time to Approval
Agenerase	amprenavir	GlaxoSmithKline	15-Apr-99	6 months
Aptivus	tipranavir	Boehringer Ingelheim	22-Jun-05	6 months
Crixivan	indinavir, IDV, MK-639	Merck	13-Mar-96	1.4 months
Fortovase	saquinavir	Hoffmann-La Roche	7-Nov-97	5.9 months
Invirase	saquinavir mesylate, SQV	Hoffmann-La Roche	6-Dec-95	3.2 months
Kaletra	lopinavir and ritonavir	Abbott Laboratories	15-Sep-00	3.5 months
Lexiva	Fosamprenavir Calcium	GlaxoSmithKline	20-Oct-03	10 months
Norvir	ritonavir, ABT-538	Abbott Laboratories	1-Mar-96	2.3 months
Reyataz	atazanavir sulfate	Bristol-Myers Squibb	20-Jun-03	6 months
Viracept	nelfinavir mesylate, NFV	Agouron Pharmaceuticals	14-Mar-97	2.6 months

Fusion Inhibitors

Brand Name	Generic Name	Manufacturer Name	Approval Date	Time to Approval
Fuzeon	enfuvirtide, T-20	Hoffmann-La Roche & Trimeris	13-Mar-03	6 months

Generic drugs used in the Treatment of HIV Infection

Drugs Used in the Treatment of Pediatric HIV Infection

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Generic Drugs Used in the Treatment of HIV Infection

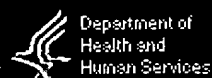
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Generic Name	Manufacturer Name	Approval Date	Time to Approval
didanosine (ddI) Delayed Release capsules	Barr Laboratories, Inc.	03-Dec-04	6 months
Oral Solution -zidovudine, AZT, azidothymidine, ZDV (Pediatric formulation)	Aurobindo Pharma Limited	19-Sep-05	6 months
zidovudine, AZT, azidothymidine, ZDV	Aurobindo Pharma Limited	19-Sep-05	10 months
zidovudine, AZT, azidothymidine, ZDV	Ranbaxy Laboratories Limited	19-Sep-05	11 months
zidovudine, AZT, azidothymidine, ZDV	Roxane Laboratories	19-Sep-05	24 months

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Drugs Used in the Treatment of Pediatric HIV Infection

Brand Name	Generic Name	Manufacturer	Adult Approval Date	Pediatric Approval Date
Agenerase	amprenavir	GlaxoSmithKline	15-Apr-99	15-Apr-99
Combivir	zidovudine and lamivudine	GlaxoSmithKline	26-Sep-97	no pediatric labeling*
Crixivan	indinavir	Merck	13-Mar-96	no pediatric labeling*
Emtriva	emtricitabine	Gilead Sciences	02-Jul-03	09-28-05
Epivir	lamivudine, 3TC	GlaxoSmithKline	17-Nov-95	17-Nov-95
Fortovase	saquinavir	Roche	7-Nov-97	no pediatric labeling*
Hivid	zalcitabine, ddC	Roche	19-Jun-92	no pediatric labeling*
Invirase	saquinavir	Roche	6-Dec-95	no pediatric labeling*
Kaletra	lopinavir, ritonavir	Abbott Laboratories	15-Sep-00	15-Sep-00
Norvir	ritonavir	Abbott Laboratories	1-Mar-96	14-Mar-97
Rescriptor	delavirdine	Pfizer	4-Apr-97	no pediatric labeling*
Retrovir	zidovudine, AZT, ZDU	GlaxoSmithKline	19-Mar-87	1-May-90
Sustiva	efavirenz	Bristol Myers-Squibb	21-Sep-98	21-Sep-98
Videx	didanosine, ddl	Bristol Myers-Squibb	9-Oct-91	9-Oct-91
Viracept	nelfinavir	Agouron Pharmaceuticals	14-Mar-97	14-Mar-97
Viramune	nevirapine	Boehringer Ingelheim	21-Jun-96	11-Sep-98
Viread	tenofovir disoproxil fumarate	Gilead	26-Oct-01	no pediatric labeling*
Zerit	stavudine, d4T	Bristol Myers-Squibb	24-Jun-94	6-Sep-96
Ziagen	abacavir	GlaxoSmithKline	17-Dec-98	17-Dec-98

* "While some of these drugs may, in practice, be used in the treatment of children of various ages, the sponsors have not submitted data to support a labeled pediatric indication at this time."

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We claim:

1. A composition for the prevention of HIV transmission comprising a plurality of antiretroviral compounds.
2. The composition of Claim 1 further comprising derivatives of said plurality of antiretroviral compounds.
3. A composition for the prevention of HIV transmission comprising a plurality of antiretroviral compounds in sufficient amounts to prevent viral infection in a subject.
4. The composition of Claim 1, wherein at least one of the plurality of antiretroviral compounds is selected from the group consisting of tenofovir, FTC, United States Food and Drug Administration approved drugs used in the treatment of HIV infection, generic drugs used in the treatment of HIV infection, United States Food and Drug Administration approved drugs used in the treatment of pediatric HIV infection and derivatives thereof.
5. The composition of Claim 1, wherein the plurality of antiretroviral compounds are in particle form and tableted with pharmaceutically acceptable carriers or tableting agents.
6. The composition of Claim 1, wherein the plurality of antiretroviral compounds are in combination with a pharmaceutically acceptable liquid carrier.
7. The composition of Claim 1, wherein the plurality of antiretroviral compounds are in combination with a pharmaceutically acceptable gel carrier.
8. A method of preventing HIV transmission in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising a plurality of antiretroviral compounds in sufficient amounts to prevent viral infection in the subject.
9. The method of Claim 8, further comprising derivatives of said plurality of antiretroviral compounds.
10. The method of Claim 8, wherein the wherein at least one of the plurality of antiretroviral compounds is selected from the group consisting of tenofovir, FTC United States Food and Drug Administration approved drugs used in the treatment of HIV infection, generic drugs used in the treatment of HIV infection, United States Food and Drug Administration approved drugs used in the treatment of pediatric HIV infection and derivatives thereof.
11. The method of Claim 8, wherein the plurality of antiretroviral compounds are in particle form and tableted with pharmaceutically acceptable carriers or tableting agents.
12. The method of Claim 8, wherein the plurality of antiretroviral compounds are in combination with a pharmaceutically acceptable liquid carrier.

13. The method of Claim 8, wherein the plurality of antiretroviral compounds are administered at least once.
14. The method of Claim 8, wherein administration of the plurality of antiretroviral compounds is selected from the group consisting of topical, oral and injectable.
15. A method of antiviral chemoprophylaxis, comprising administering to the subject a therapeutically effective amount of a composition comprising a plurality of antiviral compounds in sufficient amounts to prevent viral infection in the subject.
16. A composition for the prevention of viral transmission comprising a plurality of antiviral compounds.
17. A method of preventing HIV transmission in a subject, comprising administering to the subject a chemoprophylactically effective amount of a composition comprising a plurality of antiretroviral compounds.

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

02/07/2006 RMEBRAHT 00000121 60764811

01 FC:1005

200.00 OP

PTO-1556

(5/87)

EXHIBIT G

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UTILITY PATENT APPLICATION TRANSMITTAL (ONLY FOR NEW NONPROVISIONAL APPLICATIONS UNDER 37 CFR 1.53(B))		Attorney Docket No. CDC-10502/38	
		First Inventor Walid Heneine	
		Title INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS	
		Express Mail Label No.	

APPLICATION ELEMENTS See MPEP chapter 600 concerning utility patent application contents.	ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450		
1. ☒ Fee Transmittal Form (e.g., PTO/SB/17) (Submit an original and a duplicate for fee processing) 2. ☐ Applicant claims small entity status. See 37 CFR 1.27. 3. ☒ Specification [Total Pages <u>28</u>] Both the claims and abstract must start on a new page (For information on the preferred arrangement, see MPEP 608.01(a)) 4. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets <u>4</u>] 5. Oath or Declaration [Total Sheets <u> </u>] a. ☐ Newly executed (original or copy) b. ☐ A copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional with Box 18 completed) i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b). 6. ☒ Application Data Sheet. See 37 CFR 1.76 7. ☐ CD-ROM or CD-R in duplicate, large table or Computer Program (Appendix) ☐ Landscape Table on CD 8. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) a. ☐ Computer Readable Form (CRF) b. Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ Paper c. ☐ Statements verifying identity of above copies	ACCOMPANYING APPLICATION PARTS 9. ☐ Assignment Papers (cover sheet & document(s)) Name of Assignee: 10. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney (when there is an assignee) 11. ☐ English Translation Document (if applicable) 12. ☐ Information Disclosure Statement (PTO/SB/08 or PTO-1449) ☐ Copies of citations attached. 13. ☐ Preliminary Amendment 14. ☐ Return Receipt Postcard (MPEP 503) (Should be specifically itemized) 15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed) 16. ☐ Nonpublication Request under 35 U.S.C. 122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent. 17. ☐ Other:		
18. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76: ☐ Continuation ☐ Divisional ☐ Continuation-In-part (CIP) of prior application No.: _____ Prior application information: Examiner _____ Art Unit: _____			
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Application Data Sheet

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INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLLAXIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority of United States Provisional Patent Application Serial No. 60/764,811 filed February 2, 2006, which is incorporated herein by reference.

GOVERNMENT INTEREST

[0002] The invention described herein may be manufactured, used, and licensed by or for the United States Government.

FIELD OF THE INVENTION

[0003] The present invention in general relates to a process for inhibiting initial infection by a retrovirus such as human immunodeficiency virus (HIV) and in particular to a combination of a nucleoside reverse transcriptase inhibitor (NRTI) and a nucleotide reverse transcriptase inhibitor (NtRTI) capable of preventing self-replicating retroviral infection, even in response to multiple viral challenges.

BACKGROUND OF THE INVENTION

[0004] Despite the fact that significant progress has been made slowing the advancement of the symptoms of AIDS associated with HIV infection, in the absence of an effective vaccine, HIV continues to spread globally. The spread of HIV persists in part because an infected individual remains a potential source of infection. It is clear that current treatment of monitoring

viral titer and in response to a titer exceeding a preselected threshold commencing treatment with highly active antiretroviral therapy (HAART) has not prevented new infections.

[0005] An attractive method of controlling the spread of HIV would be to provide an individual exposed to a potential source of HIV with a pre-exposure prophylactic treatment. As HIV and, in particular HIV-1, often begins with a comparatively small population of retroviral particles being transmitted to a new host and within a few days self-replicating into a retroviral titer detectable in host blood serum. If the establishment of a retroviral could be blocked before the HIV burden expands into a self-propagating infection, an individual could avoid contraction of HIV.

[0006] Previous attempts at pre-exposure prophylaxis have met with limited success. Prophylactic activity has been demonstrated with the NtRTI, tenofovir in monkey models challenged with simian immunodeficiency virus (SIV).¹⁻³ Unfortunately, oral daily dosing and pre-exposure prophylaxis with tenofovir at a dose equivalent to that used in humans proved to only be partially protective against rectal SHIV transmission.⁴

[0007] HAART therapy involves the administration of a combination including at least three active compounds classified by the mode of operation as an NRTI, an NtRTIs, a non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitor, and an entry inhibitor. While HAART is effective in lowering retroviral titer in a host, concerns remain as to the long term toxicity and the retained potential to infect others. It is also unknown if initiating HAART therapy in a pre-exposure prophylactic regimen would be efficacious. As a result, society remains devoid of a pre-exposure prophylactic regimen to prevent an individual from developing self-propagating retrovirus infection subsequent to initial exposure.

[0008] Thus, there exists a need for a chemoprophylactic composition and dosing regimen effective in blocking early stage infection by retrovirus in a host founder cell population. There also exists a need for a chemoprophylactic composition formulated with a vehicle amenable to user compliance.

SUMMARY OF THE INVENTION

[0009] A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided in a single dose prior to the exposure. A regime of multiple temporally spaced doses prior to retroviral exposure is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection a combination of a pharmaceutically effective nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

[0010] A kit is also provided that includes at least one combination dose of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a

pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor sufficient to protect a primate host from developing a self-replicating retroviral infection along with instructions for the administration of the at least one dose one prior to and optionally one additional dose subsequent to a potential exposure to an immunodeficiency retrovirus along with dosing modifications associated with subject characteristics and behaviors to further reduce the risk of contracting a self-replicating immunodeficiency retrovirus infection.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Fig. 1 is a schematic depicting one study of the present invention for 4 groups of macaques in which all treated macaques received known antiretroviral medications 7 to 9 days prior to the first virus inoculation and continuing throughout the study with treated animals that remained uninfected throughout the 14 viral challenges receiving 28 additional days of post-exposure prophylactics.

[0012] Fig. 2 is a survival curve graph for macaque Groups 1-4 per Fig. 1, as well as for animals receiving only tenofovir disoproxil fumarate (TDF).

[0013] Fig. 3 is a graph depicting a plot of viremia as a function of time for untreated controls (○) and breakthrough infections (●) where each point represents a mean viremia observed, 0 time indicates peak plasma virus load observed in a given animal where the arrow bars denote standard error of the mean (SEM).

[0014] Fig. 4 depicts plots of infection dynamics as a function of time during the study per Fig. 1 with plots for animals coded as AG-80, AG-46, AH-04 and AG-07 corresponding to emtricitabine (FTC) treatment alone, or FTC plus TDF treatment (AI-54 and AG-81). The arrow

indicates the first detectable antibody response. Grey circles indicate detectable M184V/I mutation; wild type sequences are shown in as black full circles. Open circles indicate the time points where no genotype was undertaken

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0015] The present invention has utility in protecting a primate host from self-propagating immunodeficiency virus infection. The use of a combination of antiretroviral agents as a prophylactic dosing regime is also provided for the manufacture of a medicament is provided for protection against a human immunodeficiency virus infection developing to a level of self-replicating infection. Retroviral transmission through most routes entails a new primate host receiving a small number of viral particles. Common routes of retrovirus transmission illustratively include sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, blood transfusions, birth canal exposure, breastfeeding, and transplacental contact between individuals. Through the administration of at least one nucleoside reverse transcriptase inhibitor (NRTI) and at least one nucleotide reverse transcriptase inhibitor (NtRTI) prior to a retrovirus exposure protection is provided against development of a self-replicating retroviral infection. As the aforementioned exposure routes are characterized by a small number of retrovirus particles being transferred to the new primate host, this initial phase of infection represents a window of opportunity to protect a host from infection. The inventive chemoprophylactic treatment is provided through a dosing regimen. A dosing regimen according to the present invention that provides retroviral protection to a host primate includes at least one single dose administered prior to initial retroviral exposure. An inventive dosing regimen also

includes a course of multiple doses administered in advance of exposure to maintain a therapeutic level of NRTI and NtRTI agents in the primate host. The timing of the at least one dose prior to retroviral exposure is dictated by the pharmacokinetics of the NRTI and NtRTI components to assure the presence of a therapeutically effective amount of inventive composition for at least 20 hours subsequent to the exposure to the communicated small retroviral particle population. Multiple doses are administered according to the present invention at regular time intervals and amounts such as for example like formulated daily doses for a period of several days, weeks, or months; or are administered in advance of a likely exposure as a cluster of doses, with the amount of NRTI and NtRTI components in each dose being independent of the amount of NRTI and NtRTI in other doses within the cluster. While most oral, topical, and parenteral existing versions of NRTIs and NtRTIs are fully absorbed and therapeutically active within 1 to 8 hours, it is appreciated that subcutaneous implants and long acting timed release formulations allow for a single dose to sustain therapeutically effective amounts of an inventive prophylactic composition for several days, weeks, or even months. Representative of sustained release compositions and implants are provided in the U.S. Patents 4,122,129; 4,927,687; 4,996,047; 5,169,642; and 5,656,296.

The combination of NRTI and NtRTI compounds administered prophylactically according to the present invention are shown to provide a dose-dependent inhibition of HIV self-replicating infection and a therapeutically effective dosing primate host protection against self-replicating HIV infection is provided, even in response to multiple viral challenges. While the present invention is largely detailed with respect to HIV-1 as a prototypical infectious and pathogenic

retrovirus, it is appreciated that other retroviruses owing to reliance on reverse transcription for replication are also protected against in a primate host according to the present invention.

[0016] As used herein, “protection” as used in the context of a host primate response to an immunodeficiency virus challenge is defined by the host primate being serologically negative and negative in response to a polymerase chain reaction (PCR) testing for viral genome.

[0017] As used herein, the term “retrovirus” is inclusive of any virus that utilizes reverse transcriptase in the viral replication cycle and therefore is susceptible to the antiviral activity of nucleoside or nucleotide analogs specifically inclusive of HIV (HIV-1 and HIV-2), HTLV-1, HTLV-2, HTLV-3, HTLV-4, and SIV. Also encompassed are viruses such as HBV that although not technically classified as retroviruses nonetheless utilize a reverse transcriptase and are therefore susceptible to the antiviral activity of nucleoside and/or nucleotide analogs.

[0018] As used herein a “primate host” is defined to include a monkey, baboon, chimpanzee, gorilla, and a human. Nonhuman primates are appreciated to themselves be susceptible to infection by retroviruses and in particular immunodeficiency viruses and represent well-established animal models as to human response with an appreciation that physiological differences often require different doses in milligrams per kilogram for a nonhuman primate animal model relative to a human.

[0019] The compositions of the present invention include administration in combination of an NRTI and NtRTI and are readily compounded by pharmaceutical composition with conventional pharmaceutically acceptable carriers or diluents. Additionally, pharmaceutically acceptable derivatives and prodrugs of active NRTIs and NtRTIs operative in the present invention include salts such as alkali metal salts; esters such as acetate, butyrate, octinoate,

palmitate, chlorobenzoates, benzoates, C₁-C₆ benzoates, succinates, and mesylate; salts of such esters; and nitrile oxides. It is appreciated that other analogs of pharmaceutically active NRTIs or NtRTIs that provide within a primate host an active antiviral metabolite residue are also suitable as part of an inventive composition. A pharmaceutically acceptable carrier or diluent includes agents that are compatible with other ingredients of a dosage and not injurious to a primate host. The identity and process for compounding a combination of at least one NRTI and at least one NtRTI into a dosage form suitable for delivery by a route with administration by oral, rectal, topical, vaginal or parenteral routes of administration are provided in Remington's Science and Practice of Pharmacology, 20th Edition, Chapters 37-47, pages 681-929, where parenteral injection includes subcutaneous, intramuscular, intravenous, and intradermal injection.

[0020] As used herein the term "prodrug" is defined to include a compound that when administered to a primate host generates an active NRTI or NtRTI as a result of spontaneous reaction under physiological conditions, enzymatic catalysis, metabolic clearance, or combinations thereof. An exemplary NtRTI prodrug currently FDA approved for HAART use is tenofovir disoproxil fumarate (TDF) and is detailed in U.S. Patent 5,935,946.

[0021] The present invention provides an alternative to conventional retroviral therapy using HAART, in response to self-propagating HIV infection by protecting a primate host against the establishment of self-replicating retroviral infection that provides an indication for such therapy. Through prophylactic prior dosing with an inventive combination including at least one NRTI and one NtRTI, replication of the comparatively low number of viral particles received by a host primate is prevented.

[0022] To achieve protection against a primate host developing a retroviral self-replicating infection, at least one dosage of an NRTI and NtRTI is administered to the primate host prior to exposure to the retrovirus. Preferably, the at least one NRTI and at least one NtRTI are administered concurrently. More preferably, the combination of reverse transcriptase inhibitors is compounded into a single formulation.

[0023] The process of the present invention demonstrates protection against retroviral self-replicating infection through administration of even a single dosage administered prior to the retroviral exposure. Owing to the known pK rates of specific NRTIs and NtRTIs, a single dosage is administered to assure a therapeutically effective amount of NRTI and NtRTI persist in the primate host for a time of more than 12 hours after viral challenge. With conventional NRTI and NtRTI formulations, currently approved for HAART, preferably an inventive dose is administered within 12 hours prior to retroviral exposure and still more preferably often within 2 hours prior to retroviral exposure. The practice of the inventive process involving the administration of a single dosage in the hours proceeding a likely retroviral exposure is particularly advantageous in assuring compliant dosing in a human and also avoids side effects associated with a regular dosing regime and is particularly well suited for a human engaging in a sporadic behavior likely to bring the person into retroviral exposure. Preferably, an additional dose or doses of a combination of at least one NRTI and at least one NtRTIs is provided subsequent to the retroviral exposure event to assure adequate antiviral reverse transcriptase inhibitor concentration during and immediately subsequent to retroviral infection of the host founder cell population so as to preclude retroviral self-replication to assure NRTI and NtRTI incorporation into a replicating virus genome. Preferably, a dose of an inventive composition

taken after retroviral exposure is administered within 24 hours subsequent to the exposure, and more preferably within 12 hours subsequent to the exposure.

[0024] Alternatively, an individual routinely subjected to retroviral exposure can be protected against the development of a self-replicating retroviral infection through administration of regular prophylactic doses of an inventive combination. As a result, an epidemiological advantage exists in controlling the outbreak and spread of a retrovirus within a population is provided through offering routine doses of an inventive composition prophylactically to high-risk persons such as sex workers and a short course prophylactic inventive composition to uninfected sex trade clientele.

[0025] It is appreciated that hybrid dosing regimes of an inventive composition are also operative herein and include multiple doses prior to retroviral exposure with multiple doses not being administered for a duration or with sufficient periodicity to arise to the level of a routine prophylactic regime.

[0026] The at least one nucleoside reverse transcriptase inhibitor has the attribute of interfering with *in vivo* viral replication. An NRTI operative in an inventive prophylactic process includes emtricitabine, lamivudine, zalcitabine, zidovudine, azidothymidine, didanosine, stavudine, abacavir; with the aforementioned specific NRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

[0027] An at least one nucleotide reverse transcriptase inhibitor (NRTI) present in an inventive composition to protect a primate from developing a self-replicating retroviral infection illustratively includes tenofovir, adefovir; 2',3'-dideoxy-3'-fluoroadenisine; 2',3'-dideoxy-3'-

fluoroguanasine; 3'deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine with the aforementioned specific NtRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

[0028]

Optionally, an inventive composition also includes within an inventive combination other antiretrovirals such as nonnucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, and combinations thereof. Representative non-nucleoside reverse transcriptase inhibitors operative herein illustratively include delavirdine, efavirenz, nevirapine, and other diarylpyrimidine (DAPY) derivatives. Representative protease inhibitors operative herein illustratively include amprenavir, tipranavir, indinavir, saquinavir, lopinavir, ritonavir, fosamprenavir calcium, ritonavir, atazanavir sulfate nelfinavir mesylate, and combinations thereof. An entry inhibitor operative herein as an optional active ingredient in an inventive composition illustratively includes enfuvirtide, Schering C (Schering Plough), S-1360 (Shionogi), and BMS806 (Bristol Myers Squibb).

[0029] The dose of individual active components of an inventive prophylactic composition is administered to create a therapeutic concentration of the active composition at the situs of retrovirus initial founder cell population infection prior to viral exposure. It is appreciated that establishing a therapeutic concentration at the time of viral replication for a given NRTI, NtRTI or optional additional active agent in the target cells, includes factors for the therapeutic agent such as the route of administration, pharmacokinetics, absorption rate based on administration route, effects of food on oral absorption, *in vivo* distribution, metabolic pathways, elimination route, race, gender, and age of the subject, single dose incident side effects, long term

administration side effects, and synergistic effects with co-administered active agents. Information related to these factors considered in dosing are available from the United States Food and Drug Administration (<http://www.fda.gov/oashi/aids/virals.html>) Preferably, NRTI and NtRTI prophylactic dosing according to the present invention uses as a starting point the maximal recommended tolerated dosing levels for the given active agent combination associated with HAART treatment protocols.

[0030] An inventive kit is provided that includes a 2-dose package of oral doses, such as tablets. In an exemplary embodiment of FDA approved NRTI and NtRTIs, each dose contains between 100 and 2500 milligrams (mg) of emtricitabine and between 100 and 2500 mg of TDF along with instructions to ingest the first dose approximately 1 to 8 hours prior to potential retroviral exposure and preferably about 2 hours therebefore, and a second dosage to be ingested 20 to 48 hours after potential retroviral exposure, preferably at about 22 hours thereafter. For an adult human, preferably each of the doses includes 200 mg of emtricitabine and 300 mg TDF. A non-human primate dose according to the present invention is typically higher on a mg per kg animal body weight basis by a factor typically ranging from 2 to 10. Additional NRTIs, NtRTIs, NNRTIs, protease inhibitors or entry inhibitors are optionally provided in concert with either or both of these doses. The kit also includes instructions as to the timing of doses, contraindications, modifications associated with food ingestion, and additional behaviors that the recipient (synonymously described herein as a human primate host) can undertake to reduce the risk of retrovirus exposure and initial infection. It is also appreciated that a carrier illustratively including a gel, jelly, cream, ointment, film, sponge, foam, suppository, vaginal ring or other delivery device is provided containing an NRTI such as emtricitabine, alone or in combination

with an NtRTI such as tenofovir or TDF. The carrier is readily applied to mucosal tissue likely to be exposed to viral transmission as an added level of protection in concert with the oral doses.

[0031] An inventive kit is also provided that includes at least one NRTI and at least one NtRTI compounded as a gel, jelly, cream, ointment, film, sponge, foam, suppository, or applied to a vaginal ring or other like antiviral barrier. To prepare such a pharmaceutical compounded form, an effective amount of each of the active agents inclusive of at least one NRTI and NtRTI is combined in admixture with the pharmaceutically acceptable carrier or applied to a surface of the barrier. It is appreciated that the residence time of such a pharmaceutical composition is maintained at the site of administration through the inclusion of an optional bioadhesive that provides adhesion to mucosal tissue or the dermis. An inventive composition compounded for application to the dermis or mucosal tissue is provided along with instructions as to the timing of doses, contraindications, modifications associated with food ingestion, and additional behaviors that the person (synonymously described herein as a human primate host) can undertake to reduce the risk of retrovirus exposure and initial infection. Optionally, a kit containing an oral dosage is combined with a composition compounded for application to the dermis, rectal mucosa or vaginal mucosa so as to assure a therapeutically effective combination of NRTI and NtRTI at the mucosal point of retroviral entry associated with sexual exposure, as well as a therapeutically effective serum circulating quantity of prophylactic antiretrovirals.

[0032] The present invention is further detailed with respect to the following non-limiting examples. These examples are intended to provide exemplary specific embodiments of the present invention and are not intended to limit the scope of the appended claims.

EXAMPLES

Example 1 – Antiretroviral Drugs and Doses

[0033] A dose of 22 mg/kg of tenofovir disoproxil fumarate (TDF) is given orally and 20 mg/kg of emtricitabine (FTC) given orally or subcutaneously to one group of adult male rhesus macaques. The 22 mg/kg TDF dose resulted in an area-under the plasma concentration-time curve over a 24 h interval (AUC) of 4.49 $\mu\text{g} \times \text{hr/ml}$ which was similar to the value of 5.02 $\mu\text{g} \times \text{hr/ml}$ observed in human receiving 300 mg of TDF. The dose of 20 mg/kg of FTC resulted in an AUC value (11 $\mu\text{g} \times \text{hr/ml}$), also similar to that observed in humans receiving 200 mg of FTC orally (10.0 $\pm$ 3.12 $\mu\text{g} \times \text{hr/ml}$)⁶. Subcutaneous administration of FTC results in plasma FTC levels comparable to those achieved during oral administration, indicating a high FTC absorption in rhesus macaques.

[0034] Oral administration of FTC and TDF to macaques is by mixing the drug powders with peanut butter or fruit. Macaques are observed to ensure ingestion.

Example 2 – Virus Inoculations

[0035] A chimeric envelope SHIV_{SF162P3} isolate is used to inoculate the macaques. SHIV_{SF162P3} is a construct that contains the *tat*, *rev*, and *env* coding regions of HIV-1_{SF162} in a background of SIV_{mac239}. This isolate was obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.^{7,8} Virus exposures are performed 2 hours after drug treatment, and involved non-traumatic inoculation of 1 mL of SHIV_{SF162P3} (10 TCID₅₀ or 7.5×10^6 viral RNA copies) into the rectal vault via a sterile gastric feeding tube.⁹ Anesthetized macaques remained recumbent for at least 15 min after each intra-rectal inoculation.

Example 3 – SHIV Viral Load Assay

[0036] Plasma RNA is quantified using a real-time PCR assay as previously described.⁵ This assay has a sensitivity of detection of 50 RNA copies/ml or 10 copies of a pVp1 plasmid carrying the SIVmac239 RT gene. HIV-1 RNA is extracted from 1 mL of plasma using the NucliSens extraction method (bioMérieux). A known amount of virus particles (3×10^5) from an HIV-1 CM240 virus stock is added to each sample prior to extraction to control for the efficiency of extraction. Reverse transcription is performed using 10 microliters (μ l) of extracted RNA and the 2-step TaqMan Gold reverse-transcriptase (RT)–PCR kit (Applied Biosystems) according to the manufacturer’s instructions. PCR reactions are performed as described using an ABI 7000 Gene Detection System (Applied Biosystems). Virus loads are calculated from a standard curve generated with known amount of virus particles. All primers and probes used for SIVmac239 and HIV-1 CM240 have been reported elsewhere.⁵ HIV-1 CM240 is obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.

Example 4 – Detection of Genotypic Resistance to FTC and Tenofovir

[0037] Emergence of FTC and tenofovir resistance is monitored by sequence analysis of SIV RT (551 bp; amino acids 52 to 234) and by a more sensitive allele-specific real-time PCR method for the K65R and M184V mutations. Sequence analysis was done from plasma viruses using an RT-PCR procedure as previously described.⁵ The Vector NTI program (Version 7, 2001) is used to analyze the data and to determine deduced amino-acid sequences. Detection of low frequency of K65R and M184V mutants in plasma by real-time PCR is performed as previously described.¹⁰ These assays have a detection limit of 0.4% of K65R and 0.6% of M184V cloned sequences in a background of wild type plasmid.

Example 5 – Virus-Specific Antibody Responses

[0038] Virus-specific serologic responses (IgG and IgM) are measured using a synthetic-peptide EIA (Genetic Systems HIV-1/HIV-2) assay.

Example 6 – Statistical Methods

[0039] The exact log-rank test is used for a discrete-time survival analysis of the treatment and control groups, with use of the number of inoculations as the time variable. The Cox proportional hazards model is used to estimate the relative hazard ratio (HR). Percent protection is calculated from the HR value using the formula: $(1 - 1/HR) \times 100$. All statistical analyses for calculation of the efficacy of the different interventions are performed using SAS software (version 9.1; SAS Institute) and StatXact software (version 6.3; Cytel).

Example 7 – Routine Dosing Experimental Design

[0040] Macaques are exposed rectally once weekly for up to 14 weeks to SHIV162p3 which contains an R5 tropic HIV-1 envelope that resembles naturally transmitted viruses. The SHIV162p3 challenge dose is 10 TCID₅₀ or 7.6×10^5 RNA copies which is similar to HIV-1 RNA levels in semen during acute infection in humans.¹¹ Virus exposures are terminated when a macaque became infected. Fig. 1 shows the study design and the interventions evaluated in each group of macaques. Three prophylactic drug treatments of increasing drug potency are each given once daily to a group of six macaques. Animals in Group 1 were treated subcutaneously with 20 mg/kg of FTC alone. Animals in Group 2 received orally a combination of FTC (20 mg/kg) and TDF (22mg/kg). Animals in Group 3 had the most protective treatment with subcutaneous 20 mg/kg of FTC and a 22 mg/kg of tenofovir (PMPA). The rate of infection in

each group is compared with that seen in 18 untreated control macaques (9 real time and 9 historical controls).

[0041] All treated macaques received the corresponding drugs 7 to 9 days prior to the first virus inoculation to achieve steady-state plasma levels. Treated animals that remained uninfected during the 14 challenges received 28 days of post-exposure prophylaxis after the last challenge. Protection was defined as absence of persistent viremia and seroconversion. Treated animals that became infected continued treatment for an average of 21 weeks (range = 13 to 29) to monitor for plasma viremia and drug resistance development.

Example 8 – Survival Curves

[0042] Fig. 2 shows the survival curves observed for each group of animals per Example 7. Data with TDF (20mg/kg) is also provided for comparison. Untreated macaques are infected after a median of 2 rectal exposures (mean = 4). The majority of the animals (13/18 or 72%) are infected during the first 4 challenges (median= 2); 4 (22%) are infected between exposures 8 and 14 (mean = 10), and only 1 (6%) remained uninfected after 14 exposures. The median 2 exposures for infection in controls suggests that an animal receiving prophylactic treatment and remaining uninfected after 14 virus challenges would have been protected against a median of 7 rounds of transmissions. Treatments of Groups 1-3 are all protective to a degree with a clear dose-response relationship being observed. All 6 macaques in Group 3 that received the most potent inventive composition remained uninfected demonstrating that full protection against repeated challenges is possible. Of the 6 macaques in Group 2, 4 were protected and only 2 (animal reference numbers AI-54 and AG-81) became infected at exposures 9 and 12. Compared to controls, infection in this group is reduced by 7.8-fold (Cox proportional hazard ratio [HR]

=7.8, $p = 0.0075$). Infection in both animals is significantly delayed compared to the untreated controls ($p = 0.0004$). These 2 macaques became seropositive 2 weeks after the first detectable viral RNA in plasma and both were proviral DNA positive at weeks 10 and 12, respectively. Of the 6 macaques in Group 1 receiving FTC only, 2 remained protected after 14 exposures and 4 had the first detectable viral RNA at exposures 5 (AG-80), 10 (AG-46), 12 (AH-04), and 13 (AG-07), respectively. Survival analysis showed a statistically significant difference from untreated controls ($p = 0.004$). Compared to controls, infection is reduced 3.8-fold macaques (Cox proportional hazard ratio [HR] = 3.8, $p = 0.021$). Infection in these 4 animals is also confirmed by PCR amplification of proviral DNA from PBMCs and by serology; antibody responses are detectable 3, 1, 2, and 6 weeks after the first detectable RNA, respectively. Fig. 2 also shows that the protection achieved with FTC alone was higher than that previously seen in 4 animals receiving TDF,⁵ consistent with the slightly higher potency of FTC, although the difference was not statistically significant ($p=0.5$).

Example 9 – Prophylactic Breakthrough Infections and Drug Resistance Emergence

[0043] Since the dynamics of breakthrough infections that occur during inventive prophylaxis and drug resistance emergence are unknown, the 6 infected animals from Groups 1 and 2 are followed under continued drug treatment. Fig. 3 compares the virus load kinetics in the 6 breakthrough infections with those in 12 untreated macaques that had sufficient follow-up samples. The mean peak viremia in the 6 treated macaques was $4.9 \pm 0.5 \log_{10}$ RNA copies/ml, $2.0 \log_{10}$ lower than in untreated controls ($6.9 \pm 0.3 \log_{10}$ RNA). Figure 3 also shows that such differences in viremia were maintained up to week 11 as indicated by similar rate of virus load decline seen in the two groups of animals ($-0.23 \pm 0.02 \log_{10}/\text{week}$ in treated vs. -0.29 ± 0.02

$\log_{10}$ /week in untreated controls). The individual virus load kinetics in the 6 breakthrough infections are shown in Figure 4. Three FTC (AG-80, AH-04, and AG-07) and one of the FTC/TDF (AG-81) failures had undetectable virus loads 3, 4, 7, and 11 weeks after the peak in viremia, respectively; viremia in these animals remained consistently low or undetectable for up to 20 weeks. In contrast, all 12 untreated macaques had detectable virus loads during a median follow-up period of 7 weeks (range = 5-36 weeks). The arrow in Fig. 4 denotes the first detectable antibody response. Grey circles indicate detectable M184V/I mutation; wild type sequences are shown in black full circles. Open circles are provided for data points not genotyped.

[0044] Drug resistance testing showed that wild type virus initiated all 6 breakthrough infections in Groups 1 and 2 reflecting residual virus replication in target cells not protected by drugs (Fig. 4). Four animals had no evidence of drug resistance despite extended treatment (median= 23 weeks). Only 2 animals had detectable M184V (AG-46, FTC-treated) or M184I (AI-54 FTC/TDF-treated) mutations associated with FTC resistance at week 4 and 10, respectively. The tenofovir-associated K65R mutation is not detected in the 2 Group 2 animals receiving FTC/TDF. Fig. 4 also shows that the 2 macaques that selected M184V/I had the highest peak viremias. Without intending to be bound to a particular theory, it is hypothesized that more virus replication in these animals may have facilitated drug resistance selection. Reductions in acute viremia are proposed to contribute at a population level to a decrease in virus transmissibility.

Example 10 – Single Dosing

[0045] The process of Example 7 is repeated in Group 3 with drugs only being administered 2 hours prior to and 22 hours subsequent to each inoculation. The resultant survival curves are comparable to those detailed in Example 8.

Example 11 – Single Dosing with Suppository

[0046]

A group of 6 macaques received the drug treatment of Group 3 per Example 7 in the form of a gel inserted rectally containing 300 mg of tenofovir and 300 mg lamuvidine (3-TC) 1 hour before viral inoculation with observation to assure that the suppository is not voided. The gel is formed by compounding tenofovir and 3-TC in 2% by weight hydroxyethyl cellulose (HEC)-based gel in both a vaginal formulation (pH 4.5) and rectal formulation (pH 6.5) containing (w/v) 3% tenofovir, and 3% 3-TC. The gels are stable at room temperature for at least five months with no loss in activity; and gels retained full activity at both pH 4.5 and pH 6.5 at levels equivalent to those observed for tenofovir and 3-TC preparations in water. Using an MT4/MTT phenotypic assay, all gels were tested for activity against wild-type HIV-1_{HXB2}, and resistant HIV-1 viruses containing the K65R or M184V mutations. No significant cytotoxicity is seen in the cervical explant model.

Viral protection of the macaques is maintained throughout the study.

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[0047] Patent documents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. These documents and publications are incorporated herein by reference to the same extent as if each individual document or publication was specifically and individually incorporated herein by reference.

[0048] The foregoing description is illustrative of particular embodiments of the invention, but is not meant to be a limitation upon the practice thereof. The following claims, including all equivalents thereof, are intended to define the scope of the invention.

CLAIMS

1. A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising: administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus.
2. The process of claim 1 wherein said combination is administered orally.
3. The process of claim 1 further comprising administering to the primate host subsequent to the exposure a second combination of a pharmaceutically effective amount of a second nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a second nucleotide reverse transcriptase inhibitor.
4. The process of claim 3 wherein said nucleoside reverse transcriptase inhibitor and said second nucleoside reverse transcriptase inhibitor are chemically identical and said nucleotide reverse transcriptase inhibitor and said second nucleotide reverse transcriptase inhibitor are chemically identical.
5. The process of claim 1 wherein said combination is administered within 24 hours prior to the exposure.

6. The process of claim 3 wherein said combination is administered within 24 hours preceding the exposure and said second combination is administered within 24 hours subsequent to the exposure.

7. The process of claim 1 wherein the immunodeficiency retrovirus is HIV-1.

8. The process of claim 1 wherein said nucleoside reverse transcriptase inhibitor is selected from the group consisting of: emtricitabine, lamivudine, zalcitabine, zidovudine, azidothymidine, didanosine, stavudine, and abacavir.

9. The process of claim 1 wherein said nucleotide reverse transcriptase inhibitor is selected from the group consisting of: tenofovir, adefovir; 2',3'-dideoxy-3'-fluoroadenisine; 2',3'-dideoxy-3'-fluoroguanasine; and 3'deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine.

10. The process of claim 1 wherein said combination further comprises at least one antiretroviral present in a therapeutically effective amount and selected from the group consisting of: a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, and an entry inhibitor.

11. The process of claim 1 wherein said pharmaceutically effective amount of said nucleoside reverse transcriptase inhibitor and said pharmaceutically effective amount of said

nucleotide reverse transcriptase inhibitor are provided in said combination, each in an amount as used in highly active antiretroviral therapy.

12. The process of claim 1 wherein said combination is administered in a plurality of doses prior to the exposure.

13. The process of claim 1 wherein said nucleoside reverse transcriptase inhibitor is emtricitabine and said nucleotide reverse transcriptase inhibitor comprises tenofovir or a tenofovir ester.

14. The process of claim 1 wherein said combination is administered through a route selected from the group consisting of: orally, topically, rectally, and vaginally.

15. A process for controlling retrovirus transmission within a population comprising: administering to a subpopulation at high risk for contracting an immunodeficiency retroviral infection a combination of a pharmaceutically effective nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to an exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of said subpopulation administered said combination.

16. The process of claim 15 further comprising monitoring said subpopulation for drug resistance emergence to said combination.

17. The process of claim 15 further comprising at least one antiretroviral selected from the group consisting of: a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, and a fusion inhibitor.

18. The process of claim 15 wherein said combination is administered through a route selected from the group consisting of: orally, topically, rectally, and vaginally.

19. A kit comprising:
a first dose containing a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor;
a second dose containing a second combination of a pharmaceutically effective amount of a second nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a second nucleotide reverse transcriptase inhibitor; and
instructions for the administration of said first dose prior to and said second dose subsequent to an exposure to an immunodeficiency retrovirus.

20. The kit of claim 19 wherein said combination is formulated for oral administration.

21. The kit of claim 20 further comprising a carrier containing a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor and formulated in a form selected from the group consisting of: a gel, jelly, cream, ointment, film, sponge, foam, suppository, vaginal ring, together with instructions for application of said carrier to a body tissue prior to the exposure to the immunodeficiency retrovirus.

ABSTRACT OF THE DISCLOSURE

A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided in a single dose within 24 hours of the exposure. A regime of regular daily doses is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection the detailed combination prior to sexual exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

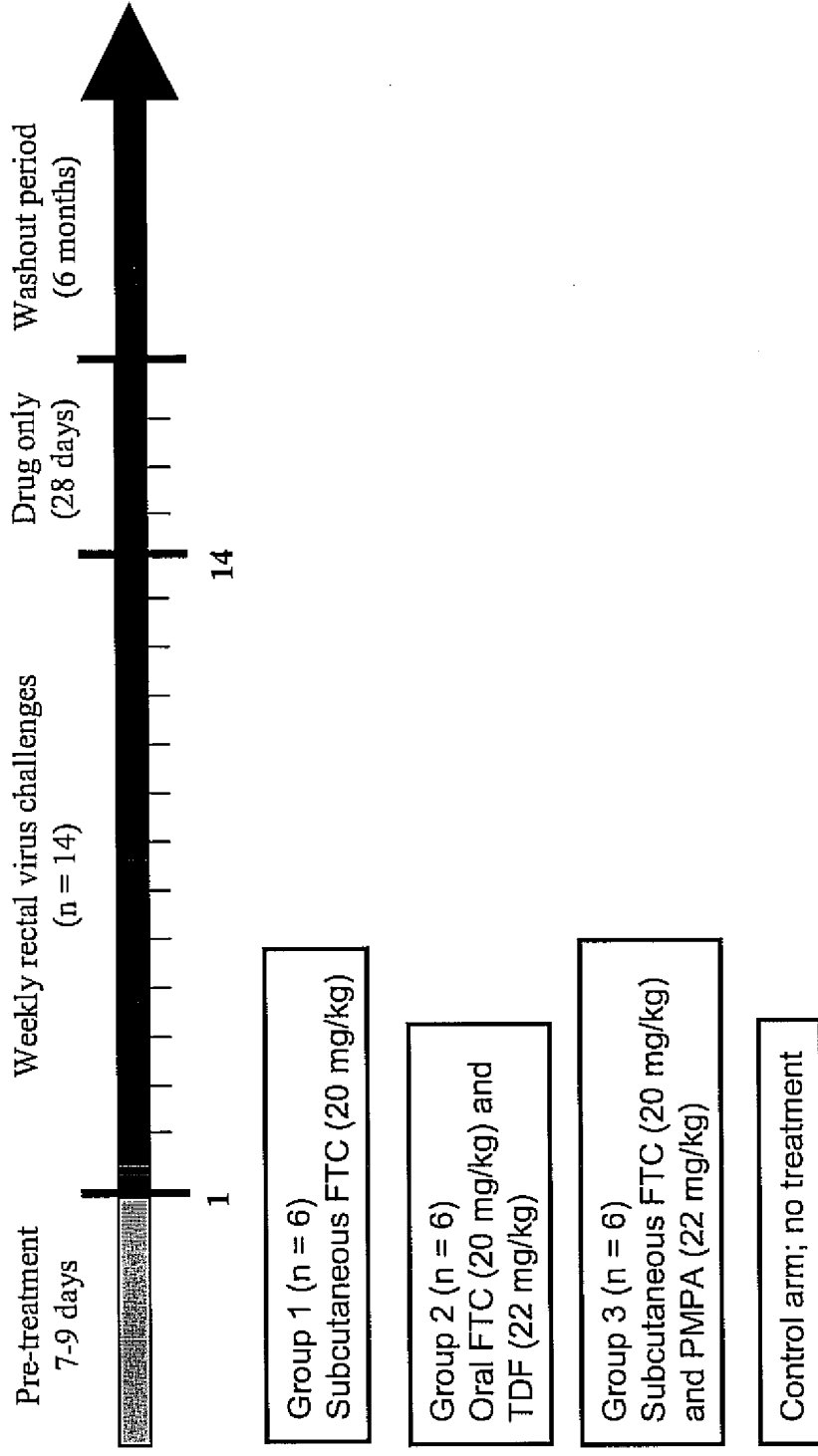


Fig 1.

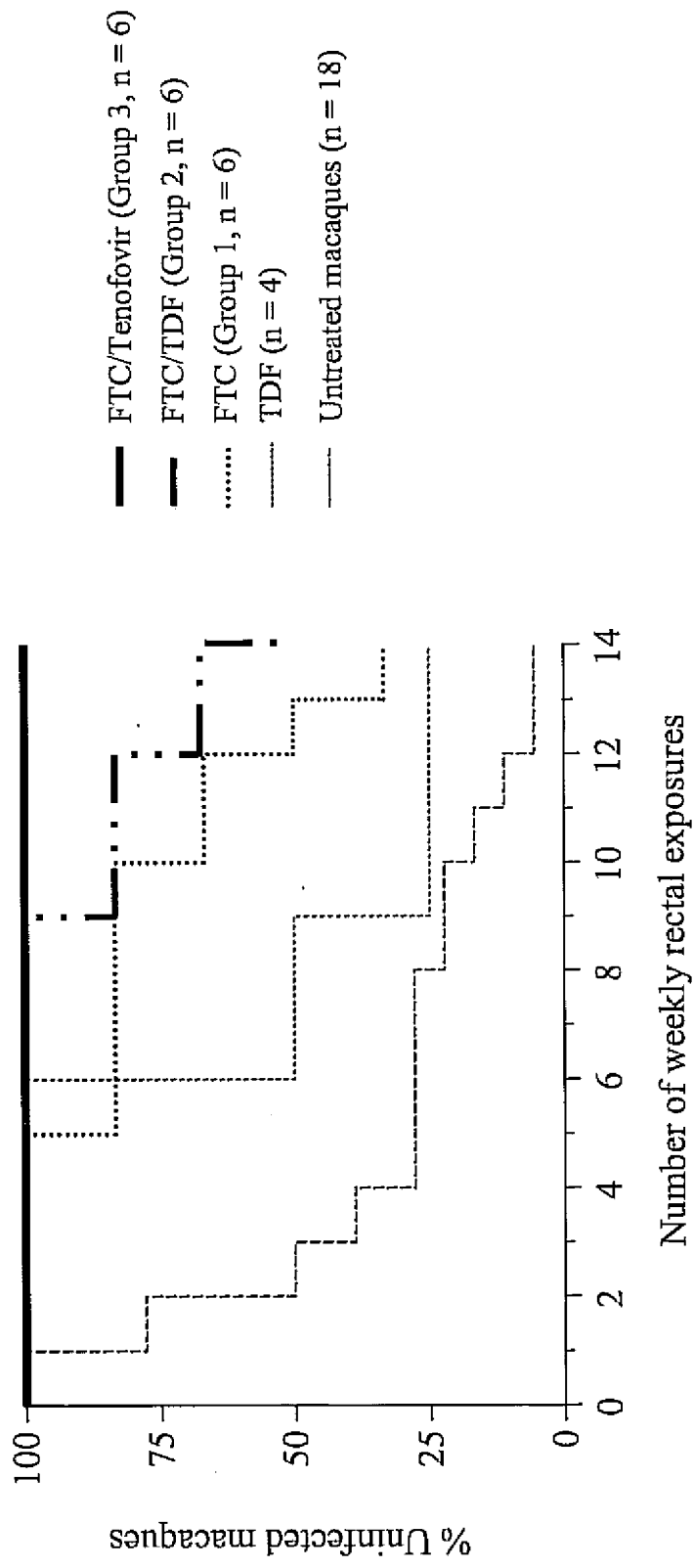


Fig 2.

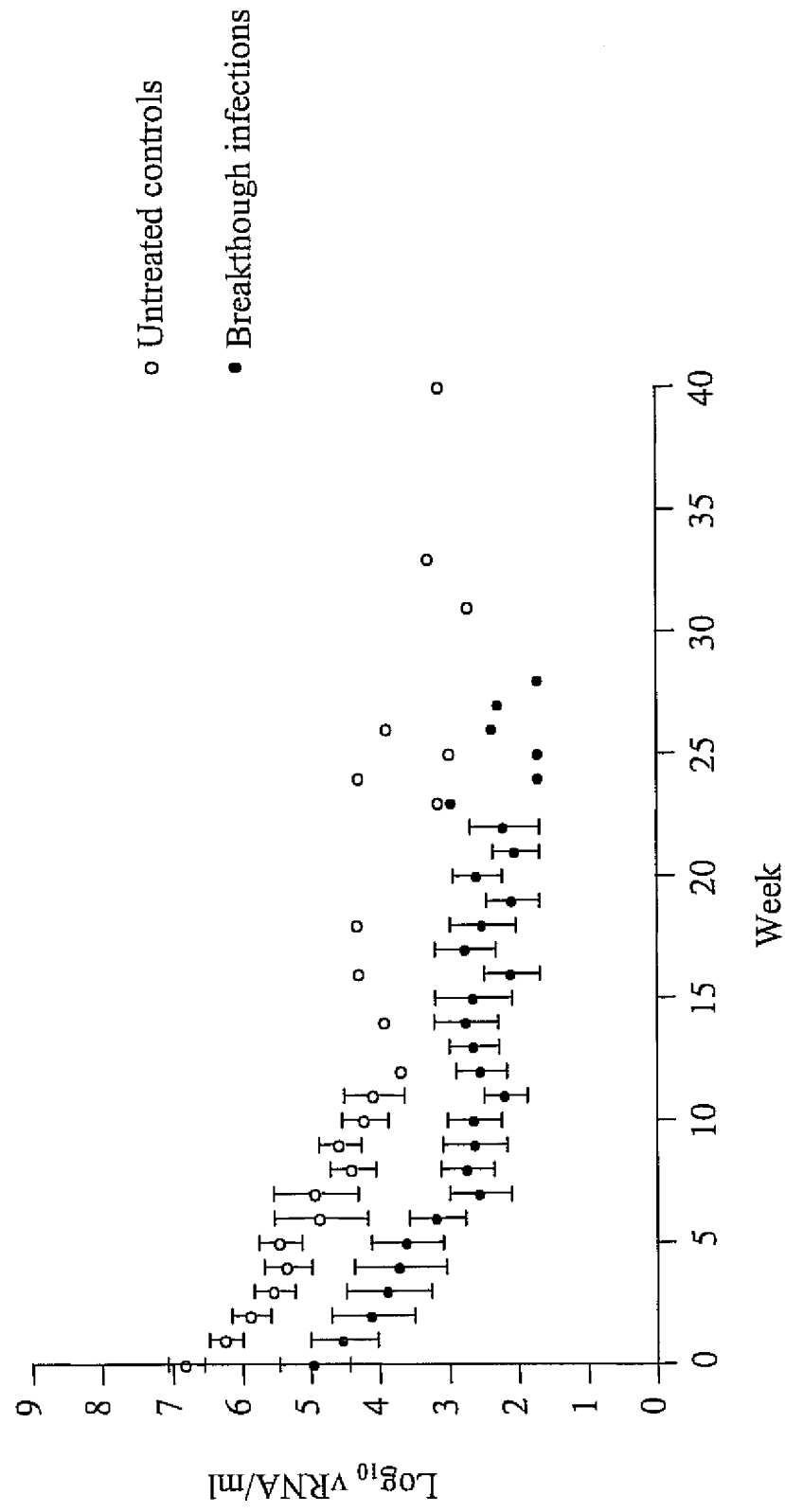


Fig. 3.

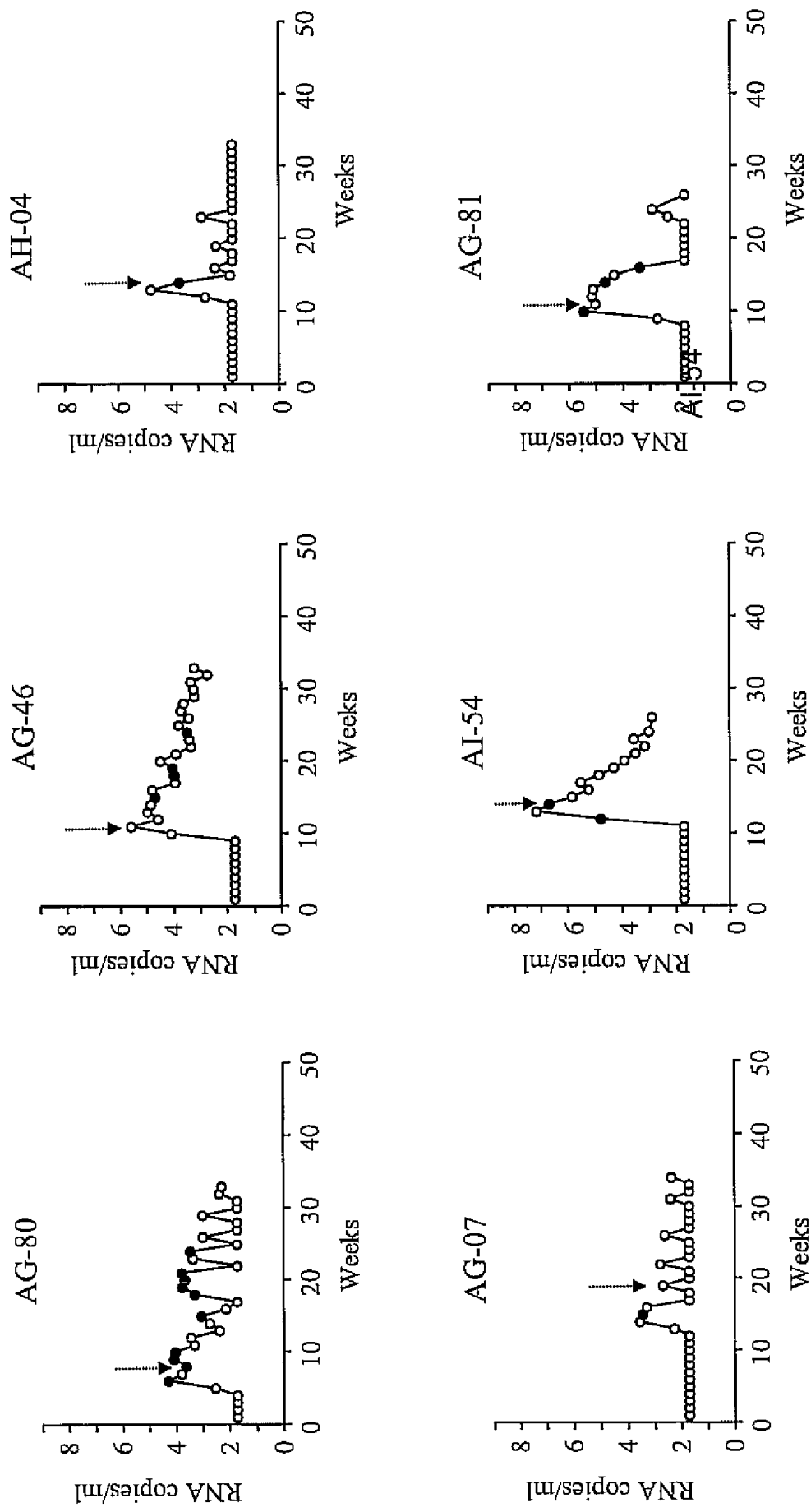


Fig. 4

Electronic Patent Application Fee Transmittal

Application Number:				
Filing Date:				
Title of Invention:	INHIBITION OF HIV INFECTION FHROUGH CHEMOPROPHYALXIS			
First Named Inventor/Applicant Name:	WALID HENEINE			
Filer:	Avery Nathan Goldstein/Gayna Lee			
Attorney Docket Number:	CDC-10502/38			
Filed as Large Entity				
Utility Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Utility application filing	1011	1	300	300
Utility Search Fee	1111	1	500	500
Utility Examination Fee	1311	1	200	200
Pages:				
Claims:				
Claims in excess of 20	1202	1	50	50
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1050

Electronic Acknowledgement Receipt

EFS ID:	1480469
Application Number:	11669547
International Application Number:	
Confirmation Number:	5582
Title of Invention:	INHIBITION OF HIV INFECTION FTHROUGH CHEMOPROPHYALXIS
First Named Inventor/Applicant Name:	WALID HENEINE
Customer Number:	59200
Filer:	Avery Nathan Goldstein/Gayna Lee
Filer Authorized By:	Avery Nathan Goldstein
Attorney Docket Number:	CDC-10502/38
Receipt Date:	31-JAN-2007
Filing Date:	
Time Stamp:	15:53:41
Application Type:	Utility

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	\$ 1050
RAM confirmation Number	266
Deposit Account	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)

1		CDC-10502FULLAPP.pdf	870892	yes	37
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal of New Application		1	1	
	Application Data Sheet		2	5	
	Specification		6	27	
	Claims		28	32	
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Warnings:					
Information:					
2	Fee Worksheet (PTO-06)	fee-info.pdf	8493	no	2
Warnings:					
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 11/669,547		
APPLICATION AS FILED – PART I							
(Column 1)		(Column 2)		SMALL ENTITY		OR	
OTHER THAN SMALL ENTITY							
FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)	RATE (\$)	FEE (\$)	
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A		N/A	300	
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A		N/A	500	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A		N/A	200	
TOTAL CLAIMS (37 CFR 1.16(i))	21	* 1	X 25=		X 50=	50	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3	minus 3 = *	X 100=		X 200=		
APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR					
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				N/A		N/A	
			TOTAL		TOTAL	1050	
* If the difference in column 1 is less than zero, enter "0" in column 2.							
APPLICATION AS AMENDED – PART II							
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
OTHER THAN SMALL ENTITY						OR	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	X =	X =	=
	Independent (37 CFR 1.16(h))	*	Minus ***	=	X =	X =	=
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))			N/A		N/A	
			TOTAL ADD'T FEE		TOTAL ADD'T FEE		
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
OTHER THAN SMALL ENTITY						OR	
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	X =	X =	=
	Independent (37 CFR 1.16(h))	*	Minus ***	=	X =	X =	=
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))			N/A		N/A	
			TOTAL ADD'T FEE		TOTAL ADD'T FEE		
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.							

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EXHIBIT H

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GILEAD SCIENCES, INC.,
Petitioner,

v.

THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES,
Patent Owner.

Case No. IPR2019-01453
Patent No. 9,044,509
Filed: January 31, 2007

PETITION FOR *INTER PARTES* REVIEW

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I. MANDATORY NOTICES

A. Real Party-In-Interest (§42.8(b)(1))

The real party-in-interest is Gilead Sciences, Inc., located at 333 Lakeside Drive, Foster City, California 94404.

B. Other Proceedings (§42.8(b)(2))

U.S. Patent No. 9,044,509 Patent (Ex. 1001) (“’509 Patent”) is not the subject of any other proceeding.

Petitioner has filed *inter partes* review petitions against three patents issued from applications claiming priority to the application from which the ’509 Patent issued; namely: (i) IPR2019-01454 (challenging U.S. Patent No. 9,579,333); (ii) IPR2019-01455 (challenging U.S. Patent No. 9,937,191); and (iii) IPR2019-01456 (challenging U.S. Patent No. 10,335,423).

C. Lead and Backup Lead Counsel (§42.8(b)(3))

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D. Service on Petitioner (§42.8(b)(4))

Service may be made by e-mail (IPRNotices@sidley.com) or by mail or hand delivery to: Sidley Austin LLP, 1501 K Street, N.W., Washington, D.C. 20005. The fax number for Counsel is 202-736-8711.

E. Fee for Petition (§42.15(a))

The Director is authorized to charge the fee specified by 37 CFR §42.15(a) to Deposit Account No. 50-1597.

II. INTRODUCTION

Since the 1990s, it has been standard practice to administer combinations of antiretroviral agents to prevent human immunodeficiency virus (“HIV”) infections in uninfected individuals who have been exposed to the virus, a regimen termed post-exposure prophylaxis (“PEP”). By 2005, PEP regimens had evolved to use newer antiretrovirals, particularly Petitioner Gilead’s Truvada®, a once-daily oral formulation of tenofovir disoproxil fumarate (“TDF”) plus emtricitabine (“FTC”). Indeed, shortly after it became available, the Centers for Disease Control and Prevention (CDC)¹ updated their widely-followed PEP guidelines (“CDC-PEP”)² to specify use of Truvada (i.e., TDF+FTC) as one of two “preferred” “backbone” regimens to prevent HIV infection after exposure.

In 2004, two California-based HIV/AIDS organizations³ published a report (“Cal-PrEP”) describing an extension of the PEP regimen for “certain people at

¹ The CDC is an agency of the Department of Health & Human Services (HHS), the Patent Owner.

² Ex. 1012 (“CDC-PEP”), 20.

³ The Center for HIV Identification, Prevention, and Treatment Services and AIDS Partnership California. See Ex. 1011 (“Cal-PrEP”), 2-3.

high risk” of HIV infection⁴—those who engage in conduct that repeatedly exposes them to HIV. Their regimen specified giving high-risk individuals antiretrovirals (particularly Truvada) before they are exposed to HIV (“pre-exposure prophylaxis” or “PrEP”), rather than after (“PEP”). Cal-PrEP justified this regimen by reasoning that any potential side-effects of using antiretrovirals for extended periods would be far outweighed by preventing infection of the high-risk individual on PrEP, and, by extension, others in that person’s community who might become exposed to HIV via that high-risk individual.

The claims of the ’509 Patent encompass both regimens—certain claims require administration of TDF+FTC before an HIV exposure (i.e., PrEP), while others cover administration after an HIV exposure (i.e., PEP). The ’509 Patent claims are thus anticipated by the methods described in Cal-PrEP and in CDC-PEP, and are obvious variants of both when considered together. Petitioner respectfully requests the Board to institute *inter partes* review of Claims 1-18 of the ’509 Patent and cancel these claims.

⁴ Cal-PrEP, 3.

III. CERTIFICATION; PROPOSED GROUNDS

Gilead Sciences, Inc. certifies it is not barred or estopped from requesting *inter partes* review of the '509 Patent. Neither Gilead, nor any party in privity with Gilead, has (i) filed a civil action challenging the validity of any claim of the '509 Patent; or (ii) been served a complaint alleging infringement of the '509 Patent more than a year prior to the present date. The '509 Patent also has not been the subject of a prior *inter partes* review. Gilead certifies that the '509 Patent is available for *inter partes* review.

Petitioner proposes three grounds:

- (i) anticipation of Claims 1-18 by Cal-PrEP under 35 U.S.C. §102(b);
- (ii) anticipation of Claims 12-18 under by CDC-PEP under 35 U.S.C. §102(b); and
- (iii) obviousness of Claims 1-18 over CDC-PEP in view of Cal-PrEP under 35 U.S.C. §103.

Petitioner submits these grounds are not redundant. The two anticipation grounds address claims with distinct requirements that are anticipated for different reasons by the disclosures of Cal-PrEP and CDC-PEP. The anticipation grounds are not redundant with the proposed obviousness ground, which rests on a different rationale for unpatentability and is presented to respond to potential arguments Patent Owner may make regarding what the prior art teaches. And because all

three grounds rely on the same two prior art references and the knowledge held by the skilled person, they are “rational, narrowly targeted, and not burdensome.”⁵

IV. KNOWLEDGE IN THE FIELD BEFORE FEBRUARY 2005

What the skilled person knew at the time of an invention is integral to the assessment of patentability. Here, the critical date is February 3, 2005—one year before the earliest priority date claimed by the ’509 Patent. The skilled person’s knowledge of HIV, antiretroviral agents, and strategies for treatment and prophylaxis of HIV by that date was extensive.

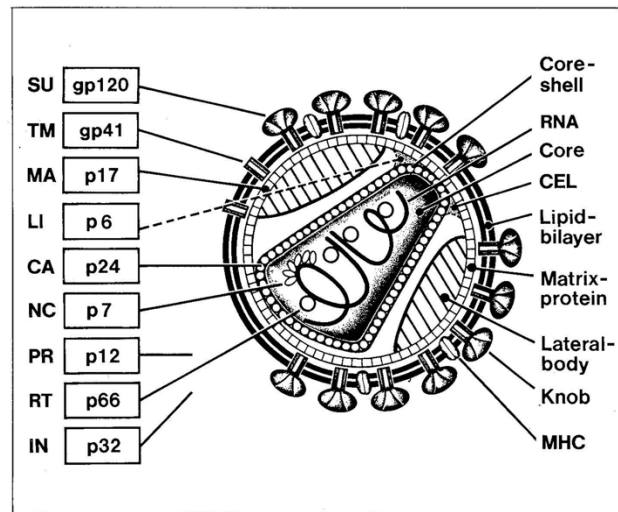
A. HIV Infections

The human immunodeficiency virus (HIV) targets and destroys the immune system’s CD4+ cells, which impedes the body’s ability to fight infections and illnesses and eventually progresses to acquired immune deficiency syndrome (“AIDS”).⁶ HIV is a retrovirus and exists outside of cells as viral particles (“virions”) (Figure)⁷:

⁵ *Great W. Cas. Co. v. Transpacific IP I Ltd.*, IPR2015-01912, Paper 10, 17-18 (P.T.A.B. Mar. 22, 2016).

⁶ *See, e.g.*, Ex. 1138 (“Janeway”), 451-57; Ex. 1147 (“Cohen-1999”), 1458-59, 1474-76

⁷ Ex. 1148 (“Gelderblom-1991”), 620.



HIV infections can result from an HIV “exposure,” which occurs when virions are transferred via bodily fluids (e.g., semen or blood) to an individual.⁸ To create a risk of infection, HIV must encounter CD4+ cells in the body and transform them to induce those cells to produce and release new virions, which can then transform other CD4+ cells. To do that, the virion binds to the CD4+ cell, which enables the HIV viral RNA to enter the cell.⁹ Then, reverse transcriptase converts the viral RNA into viral cDNA, which enters the CD4+ cell nucleus and integrates into the host genome via the action of an integrase enzyme. The infected CD4+ cell then expresses the viral cDNA to produce viral protein precursors and additional copies of the HIV RNA. Protease enzymes then process the precursor

⁸ Ex. 1009 (“Youle-Decl.”) ¶¶43-44; Gelderblom-1991, 618-20.

⁹ Gelderblom-1991, 618, 630; Ex. 1149 (“Goldsby”), 452, Fig. 19-14.

proteins, package them together with HIV RNA and release them from the HIV-infected cell as new virions.

The CD4⁺ cells transformed by the initial exposure to HIV are called “founder” cells,¹⁰ which rapidly begin producing virions that can infect other CD4⁺ cells.¹¹ The body’s immune system targets and removes the founder and other CD4⁺ cells transformed by HIV, but at some point (approximately three days after the exposure) the volume of new virions and infected CD4⁺ cells overwhelms the host’s immune system.¹² At that point, an HIV infection was considered established.¹³

B. Antiretrovirals Target Different Phases of HIV’s Life Cycle

Antiretroviral drugs inhibit replication of HIV viral RNA in CD4⁺ cells and production of new virions, which prevents additional CD4⁺ cells from being

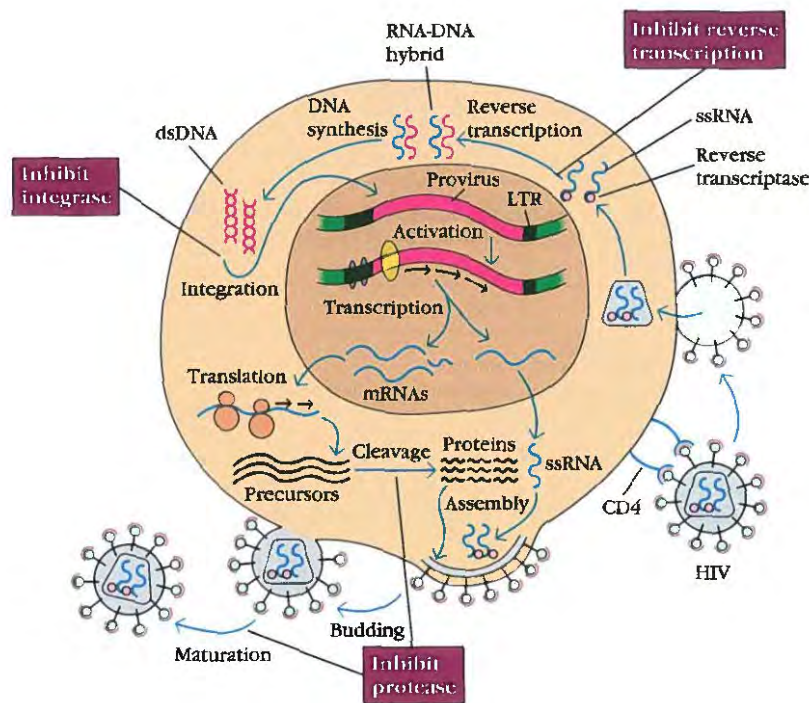
¹⁰ Ex. 1061 (“Haase-2005”), 784; Ex. 1137 (“Miller”), 9217, 9222.

¹¹ Haase-2005, 784.

¹² Youle-Decl. ¶73; Haase-2005, 784; Ex. 1156 (“Tsai-1998”), 4271 (“...short temporal window during which...treatment can block establishment of persistent infection”); Ex. 1157 (“Lifson”), 2584; Ex. 1013 (“CDC-May1998”), 5.

¹³ Youle-Decl. ¶73; Haase-2005, 784, 787; Miller, 9225-26.

transformed by HIV.¹⁴ Different classes of antiretroviral drugs were known to target different phases of HIV's life cycle (Figure).¹⁵



Agents that prevent HIV viral DNA from being created or integrated into the host cell's DNA are the most effective antiretroviral agents.¹⁶ Reverse transcriptase inhibitors ("RTIs") are particularly effective because they prevent

¹⁴ Janeway, 458-59.

¹⁵ Goldsby, 451-53; Janeway, 458-59; Lifson, 2584; Ex. 1015 ("Hu"), 6087.

¹⁶ Cal-PrEP, 11.

creation of the HIV proviral cDNA.¹⁷ Two examples of RTIs are nucleotide reverse transcriptase inhibitors (“NRTIs”) such as tenofovir and tenofovir disoproxil fumarate (TDF)¹⁸ and nucleoside reverse transcriptase inhibitors (“NRTIs”) such as emtricitabine (FTC).¹⁹

C. Combination Antiretroviral Regimens

Since the 1990s, it was known that the most effective way to “accomplish durable suppression of HIV replication” is to administer two or more different antiretroviral drugs (“combination” therapy)—one agent (“monotherapy”) does not

¹⁷ See Goldsby, 451-52; Ex. 1021 (“Barreiro”), 234; Youle-Decl. ¶95.

¹⁸ “TDF is a prodrug of tenofovir.” Cal-PrEP, 8; *see also* Youle-Decl. ¶81; Ex. 1029 (“De-Clercq-JCV”), 118-19.

¹⁹ Ex. 1025 (“Truvada®-Label”), 2-3; Ex. 1016 (“De-Clercq-IJB”), 1806-10; De-Clercq-JCV, 115-18; Ex. 1030 (“Bang”), 2413-15; *see also* Youle-Decl. ¶¶78-80, 96. A third type of RTI—non-nucleoside reverse transcriptase inhibitors (“NNRTIs”)—binds to reverse transcriptase and inhibits its functions. *See* Ex. 1067 (“Saag”), 26; De-Clercq-JCV, 118; Goldsby, 451-53; Youle-Decl. ¶83.

ensure sufficient and sustainable suppression.²⁰ Monotherapy also risks creating drug resistance if HIV mutates to overcome the inhibition of viral replication.²¹ Combination therapy minimizes that risk as it requires HIV to acquire multiple mutations to overcome the inhibitory effect of the drugs.²²

The CDC thus has recommended combinations of antiretrovirals for both treatment and prophylaxis of HIV since well before 2005, particularly two NRTIs²³ plus either a protease inhibitor (PI) or an NNRTI.²⁴ The two NRTIs are referred to

²⁰ Ex. 1014 (“CDC-ARV”), 10-11; Ex. 1017 (“Bassett”), 396; Youle-Decl. ¶¶86-87, 223.

²¹ CDC-ARV, 10; Ex. 1018 (“Coffin”), 487-88; Cal-PrEP, 11 (discussing susceptibility of TDF monotherapy to prevalent K65R mutation).

²² CDC-ARV, 10; Ex. 1019 (“Hammer”), 731; Ex. 1020 (“Gulick”), 738.

²³ NtRTIs and NRTIs are sometimes referred to generally as “NRTIs.” Youle-Decl. ¶79.

²⁴ CDC-ARV, 11 (treatment); CDC-May1998, 8-9; *see also* Ex. 1024 (“CDC-2001”), 24-27 (prophylaxis); *see also* Barreiro, 234, Youle-Decl. ¶117.

as the “backbone” of the combination regimen.²⁵ TDF+FTC is an example of a two-NRTI backbone.²⁶

D. Truvada and Its Properties

The FDA approved Truvada in August 2004 as a once-daily oral formulation of two agents, TDF+FTC, for treating HIV infection in combination with a third agent.²⁷ Truvada contains 300 mg of TDF and 200 mg of FTC, the same doses in Gilead’s single-agent formulations of FTC (Emtriva®) and TDF (Viread®).²⁸

In October 2004, zidovudine+lamivudine (Combivir®) was the prevailing backbone and when combined with efavirenz was considered “one of the most effective, thoroughly investigated, and well-tolerated regimens for the treatment of antiretroviral-naïve patients.”²⁹ Truvada’s clinical results, however, established that TDF+FTC caused fewer side-effects than Combivir (8% versus 15%) with

²⁵ Youle-Decl. ¶88.

²⁶ Ex. 1022 (“Collins”), 1, Title; Youle-Decl. ¶89.

²⁷ Truvada®-Label, 21; Ex. 1026 (“Approval-Letter”), 1, 6.

²⁸ Truvada®-Label, 1; Ex. 1027 (“Viread®-Label”), xv; Ex. 1028 (“Emtriva®-Label”), 17.

²⁹ Ex. 1034 (“DeJesus”), 1038.

comparable efficacy.³⁰ Truvada also avoided the K65R mutation seen with TDF monotherapy.³¹

Within months of its approval, skilled persons recognized Truvada's advantages over other antiretroviral combinations:

- TDF+FTC provides synergistic antiretroviral activity relative to the activity exhibited by each agent alone.³²
- TDF+FTC avoids mutual interference (when two agents compete for the same natural nucleotide/nucleoside), which decreases antiretroviral activity and increases rates of adverse events and drug-related toxicities.³³

³⁰ Ex. 1035 (“Moyer”), 3 (fewer instances of anemia, neutropenia, diarrhea, fatigue, and depression in TDF+FTC-arm patients).

³¹ *Id.* 2-3; *see also* Ex. 1039 (“Brenner”), F12; Youle-Decl. ¶101.

³² Truvada®-Label, 3; Ex. 1031 (“Vela”), Conclusions; Ex. 1032 (“Dando”), 2076; Youle-Decl. ¶¶97, 204.

³³ Barreiro, 234, 236; Youle-Decl. ¶98.

- TDF+FTC have symmetric pharmacokinetic properties³⁴— a sufficiently long half-life to be suitable for once-daily dosing and can be combined without harmful interactions, which enables Truvada to provide a prolonged exposure with less frequent dosing.³⁵

Truvada was “an important step forward”³⁶ because its once-a-day fixed-dose tablet formulation “simplif[ies] treatment regimens by reducing the number of pills and times per day patients need to take them”³⁷ “enhanc[ing] therapy adherence, and thus, the likelihood of further improvement in the success rate.”³⁸ Truvada also demonstrated superior safety,³⁹ a particularly important feature for patients using antiretrovirals for extended periods in HIV prophylaxis or who were antiretroviral-naïve.⁴⁰ Experts accurately predicted Truvada would “soon be the

³⁴ Ex. 1033 (“Back”), S3-S4; Youle-Decl. ¶104.

³⁵ Back, S2-S4; Barreiro, 235; Youle-Decl. ¶¶103-04.

³⁶ Ex. 1041 (“De-Clercq-2005”), 265.

³⁷ Ex. 1040 (“FDA-2004”), 2 (quoting Acting FDA Commissioner).

³⁸ De-Clercq-2005, 265.

³⁹ Barreiro, 238; Youle-Decl. ¶98.

⁴⁰ Cal-PrEP, 11-12; CDC-ARV, 47-48; CDC-May1998, 9.

starting treatment of choice for drug-naïve HIV patients”⁴¹ and called it “a truly recommendable drug regimen for the treatment of antiretroviral-naïve patients.”⁴²

Consequently, by 2005, a skilled person would have considered Truvada (TDF+FTC) to be a preferred option for both HIV treatment and prophylaxis.⁴³

E. HIV Chemoprophylaxis

Before February 2005, combination antiretroviral prophylaxis (including with TDF+FTC) of HIV-uninfected individuals exposed to HIV was well-established.⁴⁴ PEP was known to effectively prevent HIV infection in settings including: (i) HIV/AIDS caregivers exposed via accidental needle-sticks; (ii) uninfected infants with HIV-positive mothers exposed during childbirth or through breastfeeding; (iii) individuals engaging in unprotected sex with an infected partner; (iv) intravenous drug users; and (v) sex workers.⁴⁵

⁴¹ Moyer, 3.

⁴² De-Clercq-2005, 250.

⁴³ Youle-Decl. ¶¶102, 163, 230.

⁴⁴ CDC-PEP, 8-9; Ex. 1042 (“Youle-JIAPAC”), 103-04; Ex. 1043 (“Gayle”), 4-5; Ex. 1044 (“Chase”), 2.

⁴⁵ Youle-Decl. ¶¶111-14.

PEP regimens maintain a persistent concentration of antiretrovirals in the patient, which suppresses the CD4+ cell-mediated replication of HIV after an exposure and thereby prevents establishment of the infection.⁴⁶ Well before 2005, single-agent TDF-based regimens showed protective effects in animal testing, which reinforced the viability of using TDF in HIV prophylaxis.⁴⁷ And within months of Truvada’s approval in 2004, CDC and others published guidelines endorsing its use as a preferred agent for both post- and pre-exposure HIV prophylaxis.⁴⁸

V. THE ’509 PATENT

A. Person of Ordinary Skill in the Art

A person of ordinary skill in the art (“skilled person”) would have been an individual familiar with treatment and prophylaxis of HIV or similar viruses in individuals in a clinical and/or pre-clinical setting. The knowledge held by such a

⁴⁶ *Id.* ¶122; Janeway, 458-59.

⁴⁷ Tsai-1998, 4265, 4271 (calling TDF “PMPA,” *see* Youle-Decl. ¶81); Ex. 1045 (“Tsai-1995”), 1197, 1199 (same); Ex. 1046 (“Van Rompay-1998”), F81; Ex. 1047 (“Otten-2004”), 9772-74; Lifson, 2584, 2589.

⁴⁸ CDC-PEP, 8-10; Cal-PrEP, 11.

person would have resulted from that person’s education, training, and experience, which would have included, for example, either an M.D. or an advanced degree in an allied field (e.g., microbiology, epidemiology, public health), along with 2-3 years of experience in those fields or in treating patients.⁴⁹

B. Summary of the Disclosure

The ’509 Patent concerns methods for chemoprophylaxis of primate immune deficiency viruses by administering a “combination of antiretroviral agents.”⁵⁰ It suggests that “if the establishment of a retroviral could be blocked before the HIV burden expands into a self-propagating infection, an individual could avoid contraction of HIV.”⁵¹ The ’509 Patent identifies known antiretrovirals used in highly active antiretroviral therapy (HAART) for use in its regimen, including NRTI and NtRTI formulations,⁵² and notes an “exemplary NtRTI prodrug” is

⁴⁹ Youle-Decl. ¶16.

⁵⁰ ’509 Patent, 3:10.

⁵¹ *Id.* 1:44-47.

⁵² *See, e.g., id.* 5:16-20 (“With conventional NRTI and NtRTI formulations, currently approved for HAART....”); *id.* 5:53-60 (NRTIs); *id.* 5:61-6:2 (NtRTIs); §IV.B.

tenofovir disoproxil fumarate (TDF).”⁵³ It also indicates that subjects can be given any of a wide variety of other known antiretrovirals.⁵⁴

The ’509 Patent describes experiments in which macaques (primates) were given small doses of an engineered form of the simian immunodeficiency virus (SIV) containing components of HIV.⁵⁵ By February 2005, this was a well-known model for testing antiretroviral drugs for HIV prophylaxis.⁵⁶ The experimental results showed varying degrees of protection against infection.⁵⁷

C. Claim Construction

1. Representative Claims

Claims 1 and 12 are the independent claims; each defines a method with the same two operative steps:

- (a) selecting an uninfected primate host or an uninfected human (i.e., “a primate host not infected with the immunodeficiency retrovirus”

⁵³ ’509 Patent, 4:55-58; 1:56-60.

⁵⁴ *Id.* 6:3-17.

⁵⁵ *Id.* 7:55-8:2.

⁵⁶ *See, e.g.*, Otten-2004, 164, 166; Ex. 1048 (“Li”), 639, 642; Youle-Decl.

¶¶211, 50.

⁵⁷ ’509 Patent, 9:37-10:10.

(Claim 1) or “an uninfected human that does not have the self-replicating infection” (Claim 12)) and

- (b) administering to that subject “a combination comprising: (i) a pharmaceutically effective amount of emtricitabine [FTC] and (ii) a pharmaceutically effective amount of tenofovir” “or tenofovir disoproxil fumarate [TDF]” (Claim 1) or “tenofovir ester” (Claim 12).

Both claims specify oral administration of TDF+FTC, terminating with the clause “wherein the combination is administered orally.”

Despite having identical operative steps, the objective and desired results of the claimed methods are phrased differently:

<i>Claim 1</i>	<i>Claim 12</i>
A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:	A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:
[operative steps]	[operative steps]
wherein the combination is <u>administered prior to an exposure</u> of the primate host to the immunodeficiency retrovirus,	

thereby protecting the primate host from infection with the immunodeficiency retrovirus,	thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human,
[oral administration]	[oral administration]

2. Proposed Constructions

With four exceptions, the terms used in the claims require no interpretation.

- a. “[P]rotecting a primate host from a self-replicating infection” (Claims 1-11) / “[I]nhibiting establishment of a...self-replicating infection” (Claims 12-18)

The preamble of Claim 1 specifies “[a] process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus,” while that of Claim 12 specifies “[a] process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human.” Both repeat the substance of their preambles after reciting their “selecting” and “administering” steps; Claim 1 states “*thereby protecting the primate host from infection with the immunodeficiency retrovirus...*” while Claim 12 states “*thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human...*”

A preamble is not limiting if “the body of the claim sets out the complete invention, and the preamble is not necessary to give ‘life, meaning and vitality’ to

the claim.”⁵⁸ Also, claim language specifying the result of performing a therapeutic method is routinely found to not require that outcome in every patient, but is only the desired result of treatment.⁵⁹ And simply reciting what inherently results from performing the steps of a known therapeutic method cannot render novel a claim specifying those same steps.⁶⁰

Here, the preambles of Claims 1 and 12 do not alter how the operative steps of each claimed method are to be performed. Instead, the “selection” and “administration” steps in each claim define the complete process. Reciting the results of performing these operative steps in “thereby” clauses likewise does not limit the scope of these claims.

The specification reinforces these conclusions. For example, it states that “‘protection’ as used in the context of a host primate response to an immunodeficiency virus [HIV] challenge is defined by the host primate being serologically negative and negative in response to a polymerase chain reaction

⁵⁸ *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1373-74 (Fed. Cir. 2001).

⁵⁹ *See, e.g., id.* 1375-76.

⁶⁰ *See, e.g., In re Montgomery*, 677 F.3d 1375, 1381-82 (Fed. Cir. 2012).

(PCR) testing for viral genome.”⁶¹ The specification, however, does not suggest that these tests alter how the operative steps of the method are to be performed. Instead, it suggests that “protection” results from administering any combination of an NRTI and an NtRTI.⁶² Moreover, the specification indicates that known FDA-approved antiretroviral agents are to be used as is—it does not suggest altering the dose of the agents, or using a unique pattern of administration.⁶³ Given that the degree of viral suppression of these different agents varies widely,⁶⁴ and that the

⁶¹ ’509 Patent, 4:3-8. A host is “serologically negative” if the quantity of antiviral antibodies in a sample from the host is lower than a threshold value indicative of a “negative” result. Youle-Decl. ¶166. A negative response in PCR testing for the viral genome is when the quantity of viral DNA in a sample from the host is below a value indicative of a “negative” result. *Id.* ¶¶166-67.

⁶² ’509 Patent, 2:11-16; 4:27-58, 5:53-6:2.

⁶³ *Id.* 6:18-38.

⁶⁴ *See* Youle-Decl. ¶¶83, 85, 88, 101.

experimental examples show varying degrees of protection for even a subset of those agents,⁶⁵ “protection” must necessarily encompass a range of outcomes.

The same conclusion holds for “inhibiting establishment.” The specification nowhere defines or uses this phrase. Instead, it portrays “establishment” as the stage of progression of an HIV infection when it becomes “a self-propagating” or “self-replicating retroviral” infection.⁶⁶ None of its passages addressing “establishment” proposes altering performance of the operative steps of Claim 12, and the specification reports varying degrees of success in preventing establishment of infections.⁶⁷ “Inhibiting establishment” thus does not require success in every individual, but is simply identifying the objective of the method.

⁶⁵ See, e.g., ’509 Patent, 9:48-50 (“Treatments of Groups 1-3 are all protective to a degree with a clear dose-response relationship being observed.”) (emphasis added).

⁶⁶ *Id.* 1:44-47 (“self-propagating”), 4:59-63 (“self-replicating”); see also *id.* 1:18-19.

⁶⁷ See, e.g., *id.* 9:48-50; footnote 64, *supra*.

Consequently, the preamble and “thereby” clauses in Claims 1 and 12 are non-limiting—each specifies only an intended result of the process; neither requires 100% inhibition or prevention in any particular individual.

b. “[S]elf-replicating infection” (Claims 1 and 12)

All the claims use the phrase “self-replicating infection.”⁶⁸ There is no express definition of this phrase in the patent disclosure, and it does not have a uniform scientific meaning.⁶⁹

As used in the specification, “self-replicating infection” refers to a point in time after an HIV exposure when the body’s immune system alone cannot prevent progression of the HIV infection.⁷⁰ That was known to occur about three days (~72 hours) after an exposure, which corresponds to when infected CD4+ cells are

⁶⁸ If the Board determines the preambles and “thereby” clauses are not limiting, it need not construe “self-replicating infection.”

⁶⁹ HIV does not “self-replicate”—it enters cells and induces them to produce additional copies of HIV virions. *See supra* §IV.A.

⁷⁰ Youle-Decl. ¶¶187-88.

being produced faster than the immune system can destroy them.⁷¹ Consistent with this, the '509 Patent identifies the transition to a self-replicating infection as occurring “within a few days” and explains at that point HIV virions are “self-replicating into a retroviral titer detectable in host blood serum.”⁷²

A “*self-replicating infection*” thus means “*an HIV infection that can no longer be suppressed solely by the host’s immune system.*”

c. “[P]rior to an exposure” / “prior to a potential exposure” / “following potential exposure”

The claims use a variety of phrases (or none) to specify when a combination of an NRTI and an NtRTI is to be administered relative to an “exposure”:

- Independent Claim 1 specifies administration is “prior to an exposure”;
- Independent Claim 12 imposes no timing requirement;
- Claim 10 specifies that administration is “daily for several days, weeks or months both before and after an exposure”;
- Claim 13 specifies administration is “prior to a potential exposure” and

⁷¹ See, e.g., Haase-2005, 783-84; Ex. 1065 (“Fauci-1996”), 654; CDC-PEP, 8 (recommending treatment within 72 hours of exposure); Youle-Decl. ¶¶53-54.

⁷² '509 Patent, 1:40-44.

- Claim 16 specifies administration “following potential exposure.”

The ’509 Patent uses “exposure” to refer to HIV viral particles being introduced into an individual in a manner that can result in infection.⁷³

The ’509 Patent recognizes that certain populations of individuals will experience repeated exposures to HIV, observing that prophylaxis is “particularly well suited for a human engaging in a sporadic behavior likely to bring the person into retroviral exposure.”⁷⁴ The ’509 Patent thus recognizes what was well-known in 2005—certain “high risk” populations of uninfected individuals engage in activities that cause them to be repeatedly exposed to HIV over a defined period.⁷⁵

The ’509 Patent also recognizes that the primary benefit of PrEP is to reduce the rate of new HIV infections in a community, explaining it provides an “epidemiological advantage...in controlling the outbreak and spread of a retrovirus within a population” when provided “prophylactically to high-risk persons such as sex workers....”⁷⁶ The skilled person would recognize this epidemiological goal

⁷³ *Id.* 3:14-20, 25-29.

⁷⁴ *Id.* 5:25-27 (emphasis added).

⁷⁵ Cal-PrEP, 1; Youle-Decl. ¶144.

⁷⁶ ’509 Patent, 5:41-47 (emphasis added).

may not be realized even though the regimen will prevent HIV infection in an individual who follows it.⁷⁷

The '509 Patent also distinguishes “an exposure” from the “first exposure” of the uninfected individual to HIV—only the first HIV exposure is the “initial exposure.”⁷⁸ None of the claims uses the terms “initial” or “first” or otherwise requires agents to be administered before the first/initial “exposure.” Instead, they use the words “an exposure,” thus indicating administration of antiretroviral agents can occur after an earlier HIV exposure, as long as (i) the earlier exposure did not result in an HIV infection (i.e., the individual remains “uninfected”), and (ii) administration occurs before a future exposure.

Claim 12 makes no reference to the timing of an HIV exposure relative to administration, while Claims 13 and 16 specify administration before or after a “potential” exposure, respectively. The ordinary meaning of “potential” is that an event may, but may not necessarily, occur.⁷⁹ Claims 12, 13 and 16, thus, do not

⁷⁷ Youle-Decl. ¶¶106-07, 253.

⁷⁸ *See, e.g.*, '509 Patent, 1:64-67; 3:30-33.

⁷⁹ Ex. 1122 (“Random House Dictionary”), 1514 (defining “potential” as “possible, as opposed to actual”).

require an HIV exposure to actually occur after administration of the antiretroviral agents, which aligns with the method being prophylactic in nature.

Consequently, each of Claims 1, 12, 13 and 16 encompasses a process whereby at least one NRTI and one NtRTI are administered after an HIV exposure of the individual that did not result in an infection. Moreover, only Claim 1 affirmatively requires an administration to precede an actual HIV exposure, with Claim 10 additionally requiring an administration after an exposure.⁸⁰

VI. PRECISE REASONS FOR RELIEF REQUESTED

A. Cal-PrEP and CDC-PEP Are Prior Art to the Claims

The '509 Patent claims priority to provisional application 60/764,811, filed February 3, 2006. The prior art used in the grounds (Cal-PrEP and CDC-PEP) was published more than a year prior to that date (i.e., before February 3, 2005).

1. Cal-PrEP (Ex. 1011)

Cal-PrEP bears a publication date of November 2004.⁸¹ A December 8, 2004 archive of the website “www.aidspartnershipca.com” provides access to the

⁸⁰ See *SanDisk Corp. v. Kingston Tech. Co.*, 695 F.3d 1348, 1360 (Fed. Cir. 2012).

⁸¹ Cal-PrEP, 2.

Cal-PrEP document,⁸² and archived pages of that website announced Cal-PrEP's availability as early as November 30, 2004.⁸³ Archives of another website (www.uclaisap.org) as early as December 21, 2004 likewise provide access to the Cal-PrEP document⁸⁴ and announced Cal-PrEP's availability by November 28, 2004.⁸⁵ The Cal-PrEP authors also testified that Cal-PrEP was disseminated to the public starting in November 2004.⁸⁶

2. CDC-PEP (Ex. 1012)

CDC-PEP was published on January 21, 2005 in Volume 54, No. RR-2 of the CDC periodical Morbidity and Mortality Weekly Report Recommendations and Reports (MMWR-RR) on January 21, 2005.⁸⁷ MMWR-RR has been an

⁸² Ex. 1108 (“Wayback-Decl.”), 6-46.

⁸³ See Ex. 1126; *see also* Ex. 1127.

⁸⁴ Wayback-Decl., 47-87.

⁸⁵ *Id.* 170-71.

⁸⁶ Ex. 1103 (“Szekeres-Decl.”) ¶5; Ex. 1129 (“Coates-Decl.”) ¶10.

⁸⁷ Cal-PrEP, cover-1.

official “report[] to CDC by state health departments” since prior to 1990.⁸⁸

MMWR-RR issues are published by CDC’s Coordinating Center for Health Information and Service, “officially released to the public” and “available free of charge.”⁸⁹

CDC-PEP was publicly disseminated before February 3, 2005. A CDC website archive of past issues of MMWR-RR lists the date of publication of Vol. 54(RR-2) as January 21, 2005.⁹⁰ The Internet Archives also captured the MMWR webpage announcing the availability of CDC-PEP on January 21, 2005.⁹¹ CDC-PEP also was available in libraries at least as early as January 28, 2005.⁹² MMWR-RR publication staff also represented to Petitioner’s counsel that CDC-PEP was made available on their website as from January 21, 2005,⁹³ and the CDC

⁸⁸ *Id.* back-cover-2; Ex. 1139 (“Wayback-Decl.-II”), 6 (volumes of MMWR-RR from Volume 39, with publications dating from 1990-2003).

⁸⁹ CDC-PEP, back-cover-2.

⁹⁰ Ex. 1124 (“CDC-Archive”), 3.

⁹¹ Wayback-Decl.-II, 8.

⁹² Ex. 1128 (“UCSD-Decl.”) ¶8.

⁹³ Ex. 1140 (“Kushan-Decl.”) ¶¶6-11.

webpage announcing CDC-PEP indicates the webpage was last reviewed and converted on January 11, 2005 (below), which matches the metadata of the CDC-PEP file sent to Petitioner's counsel by MMWR-RR publication staff.⁹⁴



B. Cal-PrEP and CDC-PEP Provide Enabling Descriptions

To anticipate, a prior art reference must provide an enabling disclosure. Well-settled law holds that a prior art reference provides an enabling disclosure of a therapeutic method if it describes administering the same agent(s) in the claim,

⁹⁴ Ex. 1125 (“CDC-2005 web”), 25; Kushan-Decl. ¶¶8-10.

even without proof that doing so provided the specified therapeutic effect⁹⁵ and even if the method was not ever performed.⁹⁶

Here, Cal-PrEP and CDC-PEP each describe a method of prophylactically administering antiretroviral drugs including Truvada to individuals who are not infected with HIV in order to prevent establishment of HIV infections in those individuals. Cal-PrEP and CDC-PEP thus each teach administering the same two agents—TDF with FTC—in their same, FDA-approved amounts (200 mg FTC and 300 mg TDF) to individuals confirmed to be HIV-negative to prevent HIV infections. Following the methods described in Cal-PrEP and CDC-PEP thus necessarily yields the results specified in the claims of the '509 Patent, as the same

⁹⁵ *Bristol-Myers*, 246 F.3d at 1378 (prior art showing performance of a claimed method need not report desired therapeutic result); *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005) (prior art need not report results inherent to process); *In re Gleave*, 560 F.3d 1331, 1335-36 (Fed. Cir. 2009) (“prior art reference need not disclose ‘proof of efficacy’ to anticipate the claim.”) (citation omitted).

⁹⁶ *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003) (prior art anticipates if it provides enabling description of process).

two operative steps listed in these various claims are described in these references. Each of Cal-PrEP and CDC-PEP also provides extensive details about their methods along with citations to literature to support performing them, and thereby provides fully enabling disclosures of those methods.

C. Claims 1-18 Are Anticipated by Cal-PrEP

1. Overview of Cal-PrEP

Cal-PrEP describes a method of prophylactically administering antiretroviral drugs to “high-risk” individuals who are not infected with HIV before they have an actual or potential exposure to HIV to prevent infection:

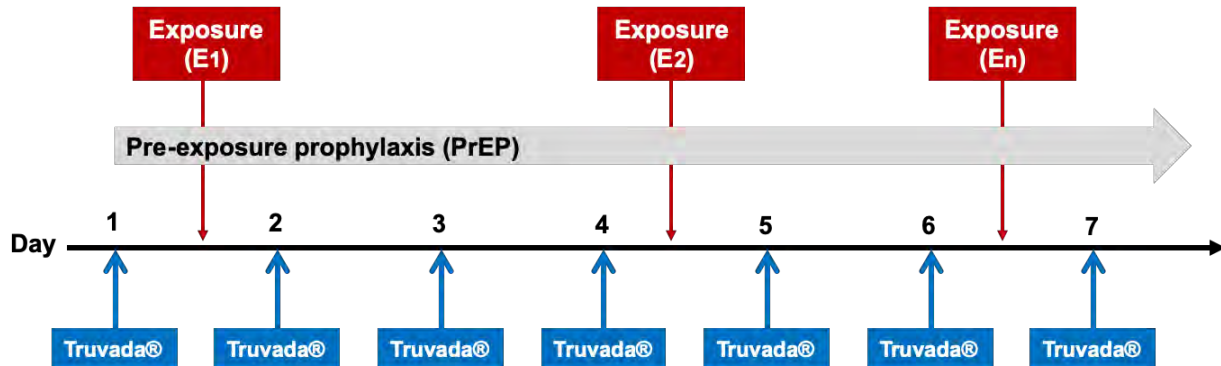
Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection. PrEP should be distinguished from postexposure prophylaxis (PEP), in which an individual takes ARVs soon after a potential HIV exposure with the goal of reducing the likelihood of infection.⁹⁷

Cal-PrEP indicates that TDF is the most suitable NRTI to use in PrEP, and identifies Truvada as one of two TDF-based drug products to use in PrEP.⁹⁸

⁹⁷ Cal-PrEP, 1, 3 (same).

⁹⁸ *Id.* 11.

Cal-PrEP's regimen when followed by a high-risk individual who has multiple HIV exposures ($E_1, E_2, \dots E_n$) is illustrated below:⁹⁹



Cal-PrEP explains that its regimen was based on prior experiences with chemoprophylaxis.¹⁰⁰ It summarizes prophylactic use of antiretrovirals to prevent HIV infections following exposures in occupational (e.g., healthcare worker) as well as non-occupational (e.g., sexual and drug use) settings,¹⁰¹ and discusses experiences using antiretrovirals to prevent transmission of HIV from an infected mother to her uninfected child through birth or breastfeeding, observing the latter

⁹⁹ Youle-Decl. ¶¶164-65.

¹⁰⁰ Cal-PrEP, 4.

¹⁰¹ *Id.* 4, 8-11.

“has been shown to dramatically reduce the odds for perinatal HIV transmission.”¹⁰²

Cal-PrEP also describes initiated or planned clinical trials for evaluating PrEP regimens in different cohorts of at-risk individuals.¹⁰³ It observes that, from an epidemiological perspective, whether PrEP will be a success (i.e., whether it reduces rates of infection in a community) depends on several factors, including the risk-taking nature of individuals,¹⁰⁴ whether PrEP alters risk-taking,¹⁰⁵ whether PrEP is supported by healthcare providers and communities,¹⁰⁶ and potential barriers to access to antiretrovirals.¹⁰⁷ Importantly, a skilled person would not have understood these epidemiological questions about whether PrEP will reduce rates of infection in a community as casting doubt that a PrEP regimen based on

¹⁰² *Id.* 5.

¹⁰³ *Id.* 6-11.

¹⁰⁴ *Id.* 19-20.

¹⁰⁵ *Id.* 20-21.

¹⁰⁶ *Id.* 22-23.

¹⁰⁷ *Id.* 24-26.

Truvada (TDF+FTC) would be effective in any individual who followed it properly.¹⁰⁸

2. Independent Claims 1 and 12

Cal-PrEP anticipates Claims 1 and 12 of the '509 Patent because it describes selecting an HIV-uninfected (HIV-seronegative) individual and administering to that individual pharmaceutically effective amounts of TDF+FTC in the form of Truvada prior to an HIV exposure.

a. Preambles

Cal-PrEP describes administering antiretroviral drugs to HIV-uninfected individuals before they are exposed to HIV in order to prevent an infection: “Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection.”¹⁰⁹ While the preambles of Claims 1 and 12 are not limiting, Cal-PrEP nonetheless describes a process that meets each.

¹⁰⁸ Youle-Decl. ¶¶150, 252; Cal-PrEP, 4; Tsai-1998, 4265.

¹⁰⁹ Cal-PrEP, 1 (emphasis added); Youle-Decl. ¶¶165-67.

- b. “[S]electing” “a primate host not infected with the immunodeficiency retrovirus” [1] / “an uninfected human that does not have the self-replicating infection” [12]

Cal-PrEP teaches administering antiretroviral agents to HIV-uninfected individuals (“*primate host*”/“*human*”).¹¹⁰ It indicates that potential candidates are to be screened for eligibility for PrEP, and must be confirmed to be HIV-negative before beginning PrEP (“Planned studies of PrEP will screen for HIV infection prior to enrollment.”)¹¹¹ Cal-PrEP also indicates that being HIV-positive is a basis for excluding individuals from PrEP clinical trials conducted in the 2004/2005-time frame.¹¹² Cal-PrEP thus teaches the “selecting” step of Claims 1 and 12.

- c. “[A]dministering...a combination comprising: (i) a pharmaceutically effective amount of emtricitabine and (ii) a pharmaceutically effective amount of tenofovir or [TDF]” [1] / “tenofovir ester” [12] “prior to an

¹¹⁰ Cal-PrEP, 3; Youle-Decl. ¶¶165, 168.

¹¹¹ Cal-PrEP, 13.

¹¹² *Id.* (“Planned studies of PrEP will screen for HIV infection prior to enrollment....”). A “seronegative” individual is HIV-negative based on a serum antibody test. *Id.*; Youle-Decl. ¶166.

exposure” [1] “wherein the combination is administered orally”

Cal-PrEP describes administering antiretroviral agents to HIV-uninfected individuals prior to an actual or potential exposure to HIV in order to prevent an HIV infection. As it states:

PrEP involves the use of antiretroviral drugs (ARVs) by an individual prior to potential HIV exposure, in order to reduce the likelihood of HIV infection.¹¹³

Cal-PrEP identifies the properties of antiretroviral agents that make them well-suited for use in PrEP, stating:

To be ideal for use as PrEP, a drug should be potent, able to be dosed once daily, have a favorable toxicity profile, and not promote development of high-level viral resistance based on a single mutation. In addition, drugs whose mechanisms of action focus on pre-integration phases of the viral life cycle (prior to completion of effective viral

¹¹³ Cal-PrEP, 3 (emphasis added); *see also id.* 1 (“Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection.”).

integration into host cell DNA) are, at least in theory, likely to be more effective than those that focus on post-integration.¹¹⁴

Cal-PrEP then explains that FTC and TDF have these features. Regarding FTC, it explains:

Of the NRTIs, several drugs have characteristics that may limit their potential as PrEP candidates. Lamivudine (3TC) and emtricitabine (FTC) cause few toxicities and may be taken once daily, but both are susceptible to a single-point mutation at codon 184 that confers resistance, especially when taken alone.¹¹⁵

Cal-PrEP's observation that FTC monotherapy can lead to resistance would have been understood by the skilled person as indicating FTC should be co-administered with another antiretroviral.¹¹⁶

Cal-PrEP then states that TDF is the “most suitable” NRTI for use in PrEP regimens, explaining that it provides the best combination of features for use in

¹¹⁴ *Id.*, 11.

¹¹⁵ *Id.* (emphasis added).

¹¹⁶ Youle-Decl. ¶¶163, 227; Saag, 29.

PrEP regimens and stating, *inter alia*, that it is “a relatively safe agent with few adverse side-effects and interactions with other drugs.”¹¹⁷

Cal-PrEP specifically identifies Truvada as one of the two TDF-based drug products that can be used in PrEP, stating:

Tenofovir disoproxil fumarate (TDF) is the NRTI that is currently most suitable for use as PrEP. TDF is potent, can be dosed once daily, and has a relatively favorable toxicity profile....TDF was approved by FDA in 2001 to treat HIV infection and is formulated as a once-daily, 300 mg oral tablet (Viread®); a once-daily, fixed-dose combination tablet of TDF and emtricitabine (Truvada™) was approved in August 2004 (both Gilead Sciences, Inc., Foster City, CA).¹¹⁸

Cal-PrEP also recommends use of FDA-approved antiretroviral products,¹¹⁹ which a skilled person would understand to mean that such drugs should be used in their FDA-approved doses.¹²⁰ Truvada contains FDA-approved doses of 200 mg

¹¹⁷ Cal-PrEP, 11-12.

¹¹⁸ *Id.*, 11 (emphasis added).

¹¹⁹ *Id.* 10-11.

¹²⁰ Youle-Decl. ¶237.

FTC and 300 mg TDF,¹²¹ the same doses in the FDA-approved single-agent formulations of TDF (Viread) and FTC (Emtriva). When Truvada is administered to a human, it will suppress HIV viral replication and exhibit potent antiviral activity against HIV.¹²² By doing so, Truvada (as well as each of its constituent agents) not only effectively treats an HIV infection but prevents establishment of an HIV infection.¹²³

The '509 Patent does not identify what amounts of TDF and FTC constitute a “pharmaceutically effective amount” of either agent, stating instead that doses should be selected to “create a therapeutic concentration of the active composition at the situs of retrovirus initial founder cell population infection prior to viral exposure.”¹²⁴ Clinical evidence demonstrates that occurs when Truvada, with its FDA-approved doses of 300 mg of TDF and 200 mg of FTC is administered.¹²⁵ The '509 Patent also observes that “[p]referably, NRTI and NtRTI prophylactic

¹²¹ Truvada®-Label, 21; Youle-Decl. ¶¶92.

¹²² See §IV.D; CDC-PEP, 8; Truvada®-Label, 2-3; Youle-Decl. ¶¶95.

¹²³ See Youle-Decl. ¶¶92, 237, 242; Dumond-PRN, 14-15.

¹²⁴ '509 Patent, 6:19-22.

¹²⁵ Truvada®-Label, 1; Viread®-Label, i; Emtriva®-Label, 5.

dosing according to the present invention uses as a starting point the maximal recommended tolerated dosing levels for the given active agent combination associated with HAART treatment protocols.”¹²⁶

Cal-PrEP also teaches “*orally*” administering TDF+FTC, given that Truvada is a tablet designed for oral ingestion.¹²⁷

Cal-PrEP thus teaches orally administering Truvada to an uninfected individual before an HIV exposure, which results in that individual being given pharmaceutically effective amounts of TDF and FTC as Claims 1 and 12 specify.

d. “Thereby” Clauses

While the “thereby” clauses of Claims 1 and 12 are not limiting (see §V.C.2.a), Cal-PrEP necessarily satisfies each. Cal-PrEP teaches administering Truvada to an HIV-uninfected individual before an HIV exposure, which results in oral administration to that individual of the same “pharmaceutically effective” amounts of TDF and FTC that the claims and ’509 Patent disclosure say will protect the host from an HIV infection or will inhibit establishment of infection.

¹²⁶ ’509 Patent, 6:34-38.

¹²⁷ Cal-PrEP, 11; Truvada®-Label, 1 (“TRUVADA Tablets are for oral administration.”).

Consequently, administering Truvada as Cal-PrEP teaches will both “*protect*” the individual from an HIV infection (“*a self-replicating infection...*”) and will “*inhibit establishment*” of an HIV infection as Claims 1 and 12 specify.

As Cal-PrEP describes every element of Claims 1 and 12, it anticipates both claims.

3. Claims 13 and 16

Claims 13 and 16 depend from Claim 12. Claim 13 specifies “*the combination is administered prior to a potential exposure of the primate host to the human immunodeficiency retrovirus*” while Claim 16 specifies administration “*following potential exposure of the primate host to the human immunodeficiency retrovirus.*”

As noted in §V.C.2.c, a “potential exposure” does not require an actual HIV exposure to occur. Regardless, the PrEP regimen described in Cal-PrEP teaches providing antiretroviral therapy to uninfected individuals before and after an actual or potential HIV exposure. First, Cal-PrEP explains that “PrEP involves the use of antiretroviral drugs (ARVs) by an individual prior to potential HIV exposure, in order to reduce the likelihood of HIV infection.”¹²⁸ Second, Cal-PrEP teaches that

¹²⁸ Cal-PrEP, 3 (emphasis added).

its PrEP regimen is to be followed for an extended period of time (e.g., 9 to 24 months)¹²⁹ by uninfected human subjects who, over that period, will engage in activities that cause multiple actual or potential HIV exposures (e.g., sex workers, men who have sex with men (“MSM”), intravenous drug users).¹³⁰ Cal-PrEP thus teaches that HIV-uninfected high risk individuals on its regimen will be given doses of recommended TDF-based drugs (e.g., Truvada) on days that precede and follow days on which that individual is actually or potentially exposed to HIV, as Claims 13 and 16 specify, respectively.

4. Claims 2-3

Claim 2 specifies the primate host is an “*adult human*,” while Claim 3 specifies the primate host is a “*male adult primate host*.” Cal-PrEP indicates that candidates for prophylaxis include, *inter alia*, MSM, i.e., adult human males.¹³¹

¹²⁹ Cal-PrEP describes clinical trials in which individuals are to be given a daily administration of a TDF-based drug for periods between 9 to 24 months. Cal-PrEP, 7-9; Youle-Decl. ¶203.

¹³⁰ Cal-PrEP, 1; *see also infra* Figures in §VI.E.1.

¹³¹ Cal-PrEP, 4, 7, Table 1.

5. Claims 4 and 14

Claims 4 and 14 specify, respectively, that TDF+FTC are administered “orally directly to the human in a combined single dosage formulation” or “into a single combination formulation suitable for oral administration.” Truvada is a tablet containing both TDF+FTC that is administered orally to humans. Cal-PrEP thus teaches oral administration of TDF+FTC as Claims 4 and 14 specify.¹³²

6. Claim 5

Claim 5 requires the “immunodeficiency retrovirus” to be a “human immunodeficiency virus.” Cal-PrEP proposes the use of PrEP for HIV.¹³³

7. Claim 6

Claim 6 specifies the “human immunodeficiency virus (HIV) is HIV-1.” The most prevalent strain of HIV in the U.S. in 2005 and today is HIV-1, with 99.9% of cases involving HIV-1.¹³⁴ Cal-PrEP focuses on Californians, and thus would be understood as teaching use of chemoprophylaxis of HIV-1 infections.¹³⁵

¹³² See *id.* 11.

¹³³ *Id.* 1.

¹³⁴ Ex. 1056 (“Torian”), 1334; Ex. 1057 (“CDC-Surveillance”), 986.

¹³⁵ Cal-PrEP, 2, 7 (Table 1); see Youle-Decl. ¶¶91, 141.

8. Claims 7 and 17

Claim 7 specifies a “*rectal and/or vaginal exposure of the primate host to the immunodeficiency retrovirus,*” while Claim 17 specifies the exposure “*comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.*”

Cal-PrEP explains that PrEP is “targeted to MSM, [and] female partners of MSM...”¹³⁶ It also describes use of PrEP in “high-risk, HIV-negative MSM” and “[f]emale commercial sex workers.”¹³⁷ Men within the MSM category are exposed to HIV rectally, orally, and through the reproductive organs, while women who are partners of MSM and female sex workers are exposed to HIV vaginally, orally, and rectally.¹³⁸ Thus, Cal-PrEP teaches use of HIV chemoprophylaxis to prevent HIV infection in one or more of the manners of exposure in Claims 7 and 17.

¹³⁶ Cal-PrEP, 1.

¹³⁷ *Id.* 8-9; *see also id.* 7 (Table 1).

¹³⁸ *See Youle-Decl.* ¶143.

9. Claim 8

Claim 8 specifies “*administering 200 milligrams (mg) of emtricitabine and 300 mg of tenofivir [sic] disoproxil fumarate to a human host.*” Cal-PrEP teaches use of Truvada in PrEP which results in administration of 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate to the individual.¹³⁹

10. Claim 9

Claim 9 specifies that TDF+FTC is to be “*administered daily for several days, weeks or months.*” Because the claim is written with the disjunctive “or,” it encompasses administrations that last as few as “*several days.*”¹⁴⁰

Cal-PrEP describes PrEP regimens being tested in clinical studies in which TDF is administered to subjects for a period of 9 to 24 months.¹⁴¹ A skilled person would understand from Cal-PrEP’s description of these clinical trials that study participants will take the TDF drug (e.g., Truvada) daily for the specified period

¹³⁹ Truvada®-Label, 21.

¹⁴⁰ *SkinMedica, Inc. v. Histogen Inc.*, 727 F.3d 1187, 1199 (Fed. Cir. 2013).

¹⁴¹ Cal-PrEP, 8-9, 12 (“The PrEP studies described in Section II are providing participants with 300 mg TDF tablets (or placebo) to be taken once daily during the study period.”); Youle-Decl. ¶203.

(e.g., 9, 12 or 24 months).¹⁴² Cal-PrEP also explains that “individuals take PrEP throughout their sexual lifetimes.”¹⁴³

Cal-PrEP also indicates that FDA-approved antiretroviral products are to be used, and identifies two such products: Viread (TDF) and Truvada (TDF+FTC).¹⁴⁴ A skilled person would understand from Cal-PrEP that these products should be used in their FDA-approved forms.¹⁴⁵

Cal-PrEP thus anticipates Claim 9.

11. Claim 10

Claim 10 specifies the combination is “*administered daily for several days, weeks or months both before and after an exposure of the primate host to the immunodeficiency retrovirus,*” and, like Claim 9, encompasses administrations that last “*several days*” before and after an exposure.

¹⁴² Youle-Decl. ¶203.

¹⁴³ Cal-PrEP 22; Youle-Decl. ¶145.

¹⁴⁴ Cal-PrEP, 11.

¹⁴⁵ *Id.*; Truvada®-Label, 20; Youle-Decl. ¶¶159, 201.

Cal-PrEP describes clinical trials in which antiretroviral agents are administered for extended periods (i.e., 9 to 24 months) to high-risk individuals.¹⁴⁶ Cal-PrEP justifies its PrEP regimen by reasoning that high-risk individuals are likely to engage in conduct that repeatedly exposes them to HIV during any particular period of time, and that if such individuals are on PrEP when those exposures occur, that will decrease the likelihood of infection.¹⁴⁷ When HIV exposures might occur after any individual's commencement of PrEP, and how frequently they may occur while that individual is on PrEP, will depend on that individual's conduct. Consistent with this, Cal-PrEP instructs that while patients are on the PrEP regimen, they are to be continuously counseled on ways to decrease high-risk activity, are to be repeatedly tested for HIV infection,¹⁴⁸ and are not to suspend taking antiretrovirals after an initial exposure.¹⁴⁹

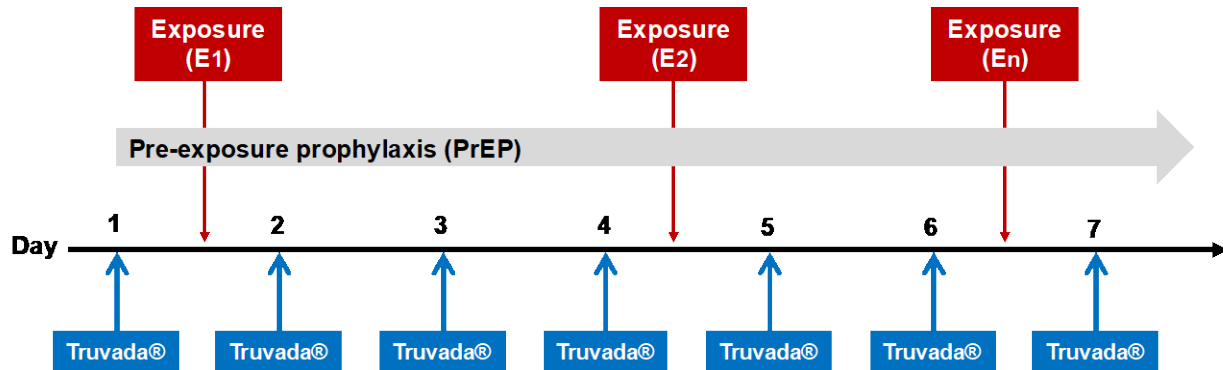
¹⁴⁶ Cal-PrEP, 8-9, 12.

¹⁴⁷ *Id.* 6-10; Youle-Decl. ¶149.

¹⁴⁸ Cal-PrEP, 9, 13-14; Youle-Decl. ¶260.

¹⁴⁹ Cal-PrEP, 8-9, 12 (“[T]ablets (or placebo) [are] to be taken once daily during the study period.”) (emphasis added); Youle-Decl. ¶¶149, 201, 203.

Cal-PrEP thus describes a regimen in which, relative to any of the daily administrations of antiretrovirals, some HIV exposures will occur in a high-risk individual several days before and several days after that HIV exposure (as illustrated below).¹⁵⁰



Cal-PrEP also cites Tsai-1995, a study in which antiretrovirals were administered for multiple days, both before and after exposure to the virus.¹⁵¹

Cal-PrEP thus teaches administration of Truvada (TDF+FTC) to high-risk individuals that will occur several days before and several days after any individual HIV exposures, as Claim 10 specifies.

¹⁵⁰ Youle-Decl. ¶164.

¹⁵¹ Tsai-1995, 1197.

12. Claims 11 and 15

Claims 11 and 15 each specify that the administration of TDF+FTC results in “*an absence of persistent viremia and seroconversion.*”

The PrEP regimen described in Cal-PrEP is designed to prevent HIV infection after exposure in an uninfected human subject.¹⁵² Before February 2005, physicians considered the absence of viremia and seroconversion to demonstrate an absence of HIV infection.¹⁵³ Viremia was conventionally determined by evaluating the presence or absence of HIV in the patient (i.e., “viral load”), while seroconversion was determined by detection of a minimum quantity of anti-HIV antibodies in the patient’s blood.¹⁵⁴

Cal-PrEP teaches testing for viremia and seroconversion to determine if a subject has become infected with HIV under PrEP. For example, it points to the absence of viremia and seroconversion in animals exposed to SIV as evidence that PrEP was effective to prevent infection.¹⁵⁵ A skilled person would understand

¹⁵² See *supra* §VI.C.1.

¹⁵³ Youle-Decl. ¶¶183, 166-67.

¹⁵⁴ *Id.*; see also Ex. 1110 (“Fearon”), 26-29.

¹⁵⁵ Cal-PrEP, 8, n.32-33 (citing Tsai-1995, Van-Rompay-1998).

from Cal-PrEP that negative test results for persistent viremia and seroconversion indicates successful prophylaxis.¹⁵⁶

13. Claim 18

Claim 18 specifies the “*tenofovir ester is tenofovir disoproxil fumarate.*” Cal-PrEP teaches using Truvada in PrEP. Truvada contains tenofovir disoproxil fumarate (TDF), a tenofovir ester.¹⁵⁷

D. Claims 12-18 Are Anticipated by CDC-PEP

1. Overview of CDC-PEP

CDC-PEP describes a regimen of daily administrations of combinations of antiretroviral agents for an extended period following an HIV exposure to prevent an HIV infection:

A 28-day course of HAART¹⁵⁸ is recommended for persons who have had nonoccupational exposure to blood, genital secretions, or other

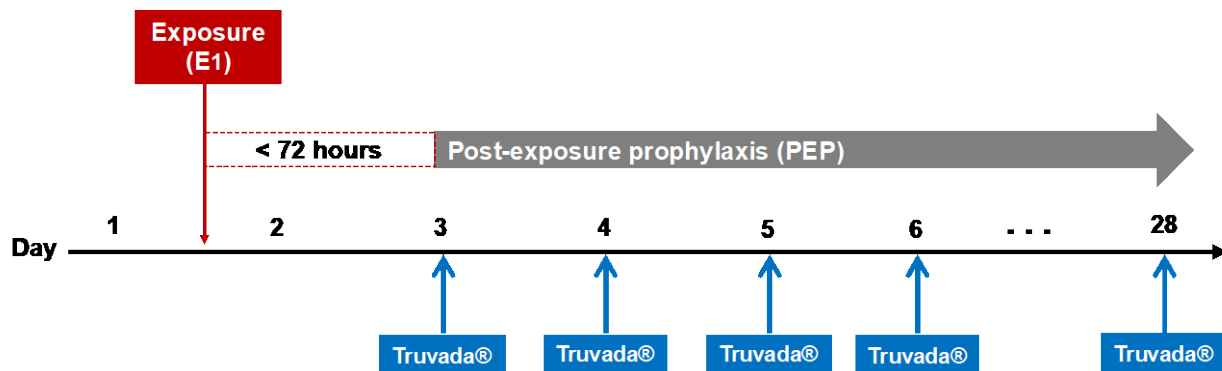
¹⁵⁶ Youle-Decl. ¶¶166-67.

¹⁵⁷ Truvada®-Label, 2; Youle-Decl. ¶92.

¹⁵⁸ Highly active antiretroviral therapy (HAART) involves daily administrations of two or more antiretroviral agents. See CDC-PEP, 8; '509 Patent, 5:11-20.

potentially infected body fluids of a person[] known to be HIV infected.¹⁵⁹

CDC-PEP identifies TDF+FTC as one of two “preferred” backbone combinations to use in PEP, and notes that Truvada is an oral formulation containing 300 mg of TDF and 200 mg of FTC.¹⁶⁰ PEP is illustrated below:¹⁶¹



CDC-PEP indicates the PEP regimen is based on “[e]vidence from animal studies and human observational studies [which] demonstrate that [PEP] administered within 48-72 hours and continued for 28 days might reduce the risk for acquiring HIV infection after mucosal and other nonoccupational

¹⁵⁹ CDC-PEP, 8.

¹⁶⁰ *Id.* 9-10.

¹⁶¹ Youle-Decl. ¶174.

exposures.”¹⁶² CDC-PEP also identifies non-clinical and clinical evidence supporting the efficacy of PEP in HIV prophylaxis:

[D]ata are available from animal transmission models, perinatal clinical trials, studies of health-care workers receiving prophylaxis after occupational exposures, and from observational studies.¹⁶³

CDC-PEP notes that PEP in an occupational setting “was associated with an 81% decrease in the risk for acquiring HIV.”¹⁶⁴

CDC-PEP encourages use of PEP “as soon as possible” after exposure, and no later than 72 hours after exposure, because “[t]he sooner []PEP is administered after exposure, the more likely it is to interrupt transmission.”¹⁶⁵ CDC-PEP also explains PEP is warranted despite side-effects of antiretrovirals, explaining:

¹⁶² CDC-PEP, 8.

¹⁶³ *Id.* 2.

¹⁶⁴ *Id.* 3.

¹⁶⁵ *Id.* 8 (“A 28-day course of HAART is recommended for persons who have had nonoccupational exposure...when the person seeks care within 72 hours of exposure.”); *see also id.* 9, 15 (“Accumulated data from animal and human clinical and observational studies demonstrate that antiretroviral therapy initiated as soon

Because HIV is an incurable transmissible infection that affects the quality and duration of life, HAART should be used to maximally suppress local viral replication that otherwise might occur in the days after exposure and potentially lead to a disseminated, established infection.¹⁶⁶

CDC-PEP likewise observes that “[i]nitial concerns about severe side effects and toxicities have been ameliorated by experience with health-care workers who have taken PEP after occupational exposures.”¹⁶⁷

The use of combinations of antiretrovirals also was known to mitigate the risk of viral resistance.¹⁶⁸ In addition, physicians prefer backbones based on a single pill because they facilitate compliance, which is critically important in preventing HIV.¹⁶⁹

as possible within 48-72 hours...and continued for 28 days might reduce the likelihood of transmission.”).

¹⁶⁶ *Id.* 8.

¹⁶⁷ *Id.* 4.

¹⁶⁸ *Id.* 5; Youle-Decl. ¶¶222, 224, 116; Gerberding, 828.

¹⁶⁹ Youle-Decl. ¶103.

2. Independent Claim 12

a. Preamble

As described in §V.C.2.a, the preamble of Claim 12 is not limiting.

Regardless, CDC-PEP teaches that the purpose of commencing a PEP regimen is to prevent the HIV infection from being established in an individual exposed to HIV, and emphasizes its effectiveness depends on how rapidly after the exposure it is commenced.¹⁷⁰ That is consistent with the understanding that HIV infections become established in an individual approximately three days after the HIV exposure. CDC-PEP thus teaches the same objective as the preamble of Claim 12.

b. *“[S]electing an uninfected human that does not have a self-replicating infection”*

CDC-PEP teaches selecting individuals that are HIV-negative for receiving PEP, explaining that PEP is to be used in humans who have an “exposure [that] represents a substantial risk for HIV transmission (Figure 1) and when the person

¹⁷⁰ CDC-PEP, 8 (“[]PEP administered within 48-72 hours and continued for 28 days might reduce the risk for acquiring HIV infection after mucosal and other nonoccupational exposures. The sooner []PEP is administered after exposure, the more likely it is to interrupt transmission.”).

seeks care within 72 hours of exposure.”¹⁷¹ A patient who is “at risk” does not yet have an established infection but may have been exposed to HIV.¹⁷² CDC-PEP also teaches use of a “baseline” test to ensure the at-risk patient is not infected, followed by recurring testing to ensure that the prophylaxis is effective.¹⁷³

- c. “[A]dministering to the uninfected human...a combination comprising: (i) a pharmaceutically effective amount of emtricitabine; and (ii) a pharmaceutically effective amount of tenofovir or tenofovir ester”

CDC-PEP teaches that “[a] 28-day course of HAART is recommended for persons who have had nonoccupational exposure.”¹⁷⁴ CDC-PEP notes “no evidence indicates that any specific antiretroviral medication...is optimal,” but indicates certain regimens are “preferred.”¹⁷⁵ CDC-PEP then recommends two

¹⁷¹ *Id.*, 6, 8.

¹⁷² Youle-Decl. ¶43.

¹⁷³ CDC-PEP, 7, 12; Youle-Decl. ¶¶182-83.

¹⁷⁴ CDC-PEP, 8.

¹⁷⁵ *Id.* 8.

“NNRTI-based” backbone regimens: efavirenz plus either (i) lamivudine plus zidovudine or (ii) emtricitabine plus tenofovir.¹⁷⁶

TABLE 2. Antiretroviral regimens for nonoccupational postexposure prophylaxis of HIV infection

Preferred regimens	
NNRTI*-based	Efavirenz [†] plus (lamivudine or emtricitabine) plus (zidovudine or tenofovir)
Protease inhibitor (PI)-based	Lopinavir/ritonavir (co-formulated as Kaletra) plus (lamivudine or emtricitabine) plus zidovudine

The word “plus” after efavirenz (an NNRTI) in Table 2 indicates this agent is to be combined with one of the two backbone regimens: either two NRTIs (lamivudine plus zidovudine) or one NRTI (emtricitabine) and one NtRTI (tenofovir).¹⁷⁷

Table 3 of CDC-PEP indicates that both backbones can be provided through administration of a single combination formulation, either: (i) “Combivir®” for the lamivudine plus zidovudine backbone or (ii) Truvada for emtricitabine plus tenofovir (in the form of TDF) backbone. CDC-PEP labels Truvada (TDF+FTC)

¹⁷⁶ *Id.* 9, Table 2.

¹⁷⁷ Youle-Decl. ¶176.

one of two “preferred regimens for prophylaxis,”¹⁷⁸ specifying use of “1 tablet once daily 200 mg emtricitabine/300 mg tenofovir” in the form of Truvada.¹⁷⁹

TABLE 3. Highly active antiretroviral therapy medications, adult dosage, cost, and side effects

Medication	Adult dosage*	Cost (in dollars) for 4 weeks*	Side effects and toxicities
Combination tablets			
Lopinavir/ritonavir (Kaletra [®]) ⁵	3 tablets twice daily 400 mg lopinavir/100 mg ritonavir	650	Diarrhea, nausea, vomiting; asthenia; elevated transaminases; hyperglycemia; fat redistribution; lipid abnormalities; possible increased bleeding in persons with hemophilia; and pancreatitis
→ Zidovudine/lamivudine (Combivir [®])	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine	640	See following individual medications
Zidovudine/lamivudine/abacavir (Trizivir [®])	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine/ 300 mg abacavir	1,020	See following individual medications
Lamivudine/abacavir (Epzicom [®])	1 tablet once daily 300 mg lamivudine/600 mg abacavir	760	See following individual medications
→ Emtricitabine/tenofovir (Truvada [®])	1 tablet once daily 200 mg emtricitabine/300 mg tenofovir	800	See following individual medications

While CDC-PEP proposes use of a third ARV, it elsewhere explains that “[n]o evidence indicates that a three-drug HAART regimen is more likely to be effective than a two-drug regimen” in prophylaxis.¹⁸⁰ CDC-PEP also recommends use of only two agents—one NRTI and one NtRTI—in situations where the clinician or patient has concerns over the individual taking three antiretroviral agents.¹⁸¹ Claim 12 encompasses administration of a third agent in addition to TDF and FTC by its use of “comprising” language.

¹⁷⁸ CDC-PEP, 9, Table 2.

¹⁷⁹ *Id.*, 10, Table 3; Youle-Decl. ¶¶171, 176.

¹⁸⁰ CDC-PEP, 8.

¹⁸¹ *Id.*, 8; Youle-Decl. ¶177.

A skilled person who follows CDC-PEP will administer Truvada *orally* to an HIV uninfected individual as required by the claims. Doing that orally administers to the individual the FDA-approved doses of 200 mg TDF and 300 mg FTC, which are pharmaceutically effective amounts of each agent.¹⁸² The '509 Patent acknowledges these amounts are effective in preventing HIV infection.¹⁸³ CDC-PEP thus discloses the “administering” step of Claim 12.

CDC-PEP also teaches that commencing PEP using the recommended regimens as soon as possible after an exposure can prevent an HIV infection.¹⁸⁴ It credits animal studies and human clinical evidence as supporting this conclusion.¹⁸⁵ For example, it notes that prophylactic use of a less potent single-agent ARV (i.e., zidovudine) in a health-worker prophylaxis study “was associated with an 81% decrease in the risk for acquiring HIV.”¹⁸⁶

¹⁸² CDC-PEP, 10, Table 3; Youle-Decl. ¶¶174-75.

¹⁸³ '509 Patent, 6:48-49, 7:36-50.

¹⁸⁴ CDC-PEP, 2, 8.

¹⁸⁵ *Id.* 8-9.

¹⁸⁶ *Id.* 3.

d. “Thereby” Clause

As explained in §V.C.2.a, Claim 12’s “thereby” clause is not limiting. Nevertheless, CDC-PEP discloses methods that meet this requirement. Most notably, because CDC-PEP teaches administering a daily oral dose of the same, FDA-approved and pharmaceutically effective amounts of TDF+FTC as the claims, it must yield the same result specified in the claims.¹⁸⁷ CDC-PEP also repeatedly states that PEP regimens are effective in preventing HIV infection if commenced early enough after an exposure. CDC-PEP thus discloses the “thereby” clause of Claim 12.

3. Claims 13 and 16

Claims 13 and 16 specify that administration is to occur “*prior to*” or “*following*” a “*potential*” exposure, respectively. As explained in §V.C.2.c, a “potential” exposure does not have to actually occur. Both claims are anticipated for the same reason that Claim 12 is anticipated.

¹⁸⁷ *Id.* 10, Table 3; Youle-Decl. ¶175.

CDC-PEP also expressly teaches administration of TDF+FTC following potential non-occupational HIV exposure, such as unprotected sex, and thus anticipates Claim 16.¹⁸⁸

CDC-PEP further indicates that in a non-occupational setting, PEP is to be followed for at least a 28-day period.¹⁸⁹ CDC-PEP also explains that certain categories of individuals engage in activity that may repeatedly expose them to HIV, and teaches that these “high-risk” individuals are to be counseled to refrain from such activities during the 28-day PEP regimen.¹⁹⁰ Such individuals, however, are likely to nonetheless engage in activities that may expose them to HIV during the 28-day PEP period.¹⁹¹ Such individuals who have remained HIV-negative after a prior exposure will be administered TDF+FTC prior to the next (i.e., “a”) potential exposure as Claim 13 specifies.

¹⁸⁸ CDC-PEP, 8.

¹⁸⁹ *Id.*

¹⁹⁰ *Id.* 8-9, 12; Youle-Decl. ¶180.

¹⁹¹ Youle-Decl. ¶135, 180.

4. Claim 14

CDC-PEP teaches use of “Emtricitabine/tenofovir (Truvada)” as one of its two preferred PEP backbone regimens.¹⁹² Truvada is formulated as a single dosage oral tablet.¹⁹³ CDC-PEP thus describes use of TDF+FTC that “*is compounded into a single combination formulation suitable for oral administration.*”

5. Claim 15

CDC-PEP teaches use of HIV antibody tests (which assess seroconversion) and viral load tests (which assess persistent viremia) after the conclusion of prophylaxis to confirm that an infection has not occurred.¹⁹⁴ “HIV viral load” testing and “HIV antibody testing” are accepted ways of confirming a lack of persistent viremia and an absence of seroconversion.¹⁹⁵ Table 4 of CDC-PEP provides guidance on using these tests to confirm that prophylaxis was successful

¹⁹² CDC-PEP, 10, Table 3.

¹⁹³ Truvada®-Label, 1; Youle-Decl. ¶92.

¹⁹⁴ CDC-PEP, 13, Table 4.

¹⁹⁵ Youle-Decl. ¶183, 166-67; Fearon, 26.

in a subject.¹⁹⁶ CDC-PEP thus teaches determining “*an inhibition of infection in the host*” “*by an absence of persistent viremia and seroconversion in the human following the exposure to the immunodeficiency retrovirus.*”

6. Claim 17

CDC-PEP recommends a 28-day course of ARVs in the case of “[e]xposure of vagina, rectum....[w]ith...semen, vaginal secretions....”¹⁹⁷ These are all forms of exposure via sexual intercourse recited in Claim 17, which lists those exposures as alternatives. CDC-PEP thus teaches that “*the potential exposure to the human immunodeficiency retrovirus comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.*”

7. Claim 18

CDC-PEP teaches use of Truvada in prophylaxis for HIV. Truvada contains tenofovir disoproxil fumarate (TDF), which is a tenofovir ester.¹⁹⁸ CDC-PEP thus describes “*wherein the tenofovir ester is tenofovir disoproxil fumarate.*”

¹⁹⁶ CDC-PEP, 13, Table 4.

¹⁹⁷ *Id.* 8, Fig. 1.

¹⁹⁸ Youle-Decl. ¶81.

E. Claims 1 to 18 Would Have Been Obvious

Patent Owner may contend that Cal-PrEP does not describe the method of Claims 1 to 18, pointing to Cal-PrEP's observation that clinical trials to test its effectiveness were underway but not completed. But Cal-PrEP describes administering the same agents in the same doses to the same subjects for the same purpose as the contested claims, and thus necessarily describes the same process.¹⁹⁹

Regardless, a skilled person would have found Cal-PrEP to provide a specific motivation (i.e., the need to decrease rates of HIV infections in high-risk individuals and within their communities) to modify the PEP regimen described in CDC-PEP by administering Truvada (TDF+FTC) to high-risk individuals before (rather than after) an actual HIV exposure. A skilled person thus would have found it obvious to administer Truvada to an uninfected individual before an HIV exposure to prevent an HIV infection and would have reasonably expected doing so to be effective based on, *inter alia*, experiences with PEP. Consequently, each of the claimed methods would have been obvious based on CDC-PEP in view of Cal-PrEP in February 2005.

¹⁹⁹ See, e.g., *Bristol-Myers*, 246 F.3d at 1378; *Rasmussen*, 413 F.3d at 1326.

1. A Skilled Person Would Have Been Motivated to Commence Prophylaxis Before an Exposure Based on Cal-PrEP

By February 2005, a skilled person would have known from CDC-PEP and their own experiences using the PEP regimen that starting administration of TDF+FTC within 72 hours after an HIV exposure can prevent establishment of an HIV infection.²⁰⁰ As CDC-PEP teaches, commencing ARV administration as soon as possible after the HIV exposure is a key factor influencing success of that regimen.²⁰¹ Indeed, CDC-PEP emphasizes that “[t]he sooner []PEP is administered after exposure, the more likely it is to interrupt transmission.”²⁰²

The skilled person also would have known that antiretrovirals “interrupt transmission” of HIV by actively suppressing HIV viral replication at the initial site of HIV exposure in the body.²⁰³ That person likewise knew that antiretrovirals

²⁰⁰ CDC-PEP at 8-12; Youle-Decl. ¶¶175, 179.

²⁰¹ CDC-PEP, 8.

²⁰² *Id.* 8, 15 (“Accumulated data from animal and human clinical and observational studies demonstrate that antiretroviral therapy initiated as soon as possible within 48-72 hours....”); Youle-Decl. ¶¶246, 129-30; CDC-2001, 26.

²⁰³ CDC-PEP, 8; Youle-Decl. ¶¶247-48.

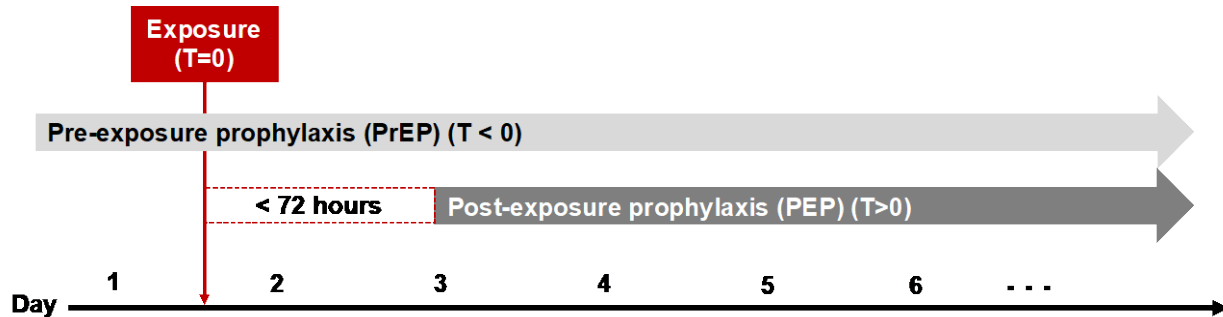
require time after ingestion to transit to the sites of an HIV exposure (e.g., the mucosa) and create drug concentrations at those sites sufficient to suppress HIV replication—at least two hours for TDF and FTC.²⁰⁴ The skilled person thus would have recognized that the theoretically optimal time to administer TDF+FTC to prevent HIV infection under the PEP regimen would be several hours before an HIV exposure. Doing that would create the maximally suppressive effect of antiretrovirals at the site of the exposure starting at the exact moment of the HIV exposure, and, if maintained without interruption, would maximally inhibit HIV replication within the founder cell population.²⁰⁵ The skilled person, thus, would have been motivated to administer antiretrovirals even before an HIV exposure to maximize the effectiveness of antiretroviral prophylaxis.

The skilled person further would have recognized that the PrEP regimen in Cal-PrEP differs from the PEP regimen described in CDC-PEP solely with respect to timing: the PrEP regimen effectively shifts the start of a PEP regimen from a

²⁰⁴ Ex. 1079 (“Dumond-PRN”), 15; Youle-Decl. ¶¶244, 131.

²⁰⁵ Youle-Decl. ¶¶131-33; Saag, 28.

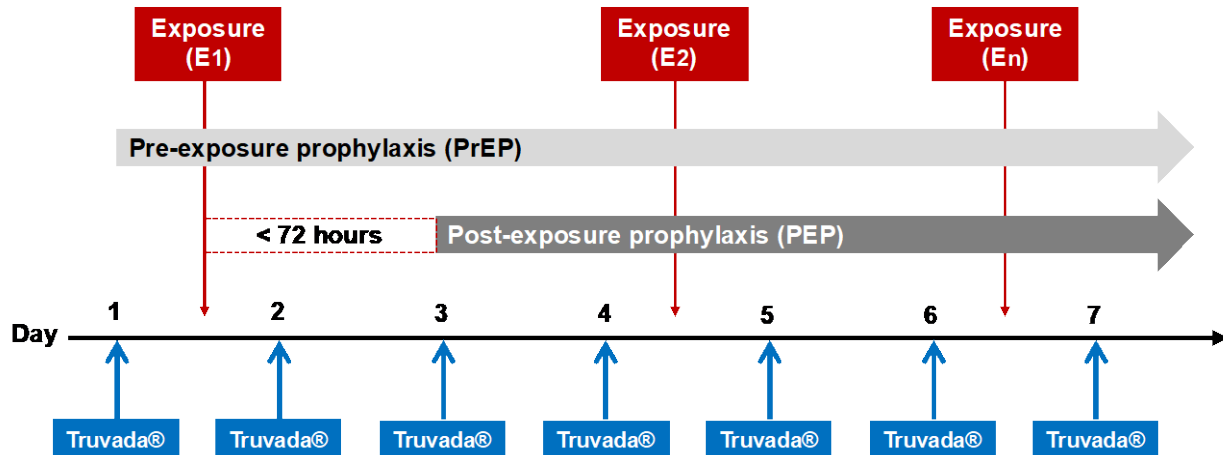
time immediately after ($T > 0$) an HIV exposure to a time prior to that exposure ($T < 0$).²⁰⁶



Indeed, the skilled person would have recognized that a “high risk” individual, such as a sex worker, placed on a 28-day PEP regimen after a first exposure to HIV cannot be meaningfully differentiated from the same individual on a PrEP regimen—in both, the high-risk individual during that 28-day period will have “an exposure” to HIV multiple times ($E_2, \dots E_n$), both before and after taking daily doses of the antiretroviral agents, as illustrated below.²⁰⁷

²⁰⁶ Youle-Decl. ¶¶245, 134.

²⁰⁷ See *id.* ¶¶202, 135.



Before 2005, the guidance in Cal-PrEP provided a specific motivation to the skilled person to alter the PEP regimen in CDC-PEP by administering, *inter alia*, Truvada to “high-risk,” HIV-uninfected individuals before an exposure to HIV (rather than after).²⁰⁸ As Cal-PrEP explains, high-risk individuals (e.g., commercial sex workers, intravenous drug users, MSM) engage in conduct that repeatedly exposes them to HIV, and such exposures significantly increase the risks of HIV infection to not only those individuals but to others in their community with whom they interact.²⁰⁹ Cal-PrEP thus proposes to administer combinations of antiretrovirals (including Truvada) to such high-risk individuals for periods that will span when those individuals are likely to have multiple

²⁰⁸ *Id.* ¶136.

²⁰⁹ Cal-PrEP, 3; Youle-Decl. ¶146; Youle-JIAPAC, 104.

exposures to HIV due to their conduct. Certainly, Cal-PrEP recognizes that antiretrovirals can cause side-effects, and that continued use of them presents risks for individuals who take them for extended periods.²¹⁰ But the skilled person would have understood that by nonetheless recommending chemoprophylaxis for these high-risk individuals for extended periods (e.g., 9 to 24 months), Cal-PrEP teaches that the individual and community benefits of preventing HIV infections (i.e., a lifelong, incurable disease) outweigh those risks of potential side-effects.²¹¹

Cal-PrEP justifies its regimen as being part of a broader strategy for reducing the rate of HIV infection in communities—it proposes administering antiretrovirals to uninfected high-risk individuals to not only prevent those individuals from contracting HIV, but to prevent those individuals from infecting others in their community. For example, Cal-PrEP advocates antiretroviral prophylaxis as a supplement to “intensive risk-reduction interventions” proposed in CDC-PEP to prevent HIV infections in high-risk uninfected individuals.²¹² Cal-PrEP also observes that behavioral interventions alone have not meaningfully

²¹⁰ Cal-PrEP, 10-11.

²¹¹ Youle-Decl. ¶146; Cal-PrEP, 6-10.

²¹² CDC-PEP, 6; see Youle-Decl. ¶¶145, 147.

reduced HIV infection rates in communities with high-risk individuals in them, and observes that effective epidemiological strategies were urgently needed in such communities.²¹³

Cal-PrEP thus justifies its recommendation to alter the known PEP strategy by administering Truvada to uninfected high-risk individuals to advance its community-focused goal of reducing the spread of HIV via these individuals in communities where they are active.²¹⁴ Indeed, whether PrEP could reduce HIV infection rates in communities was one of the objectives of the clinical trials referenced in Cal-PrEP.²¹⁵

2. CDC-PEP and Cal-PrEP Both Recommended Truvada for Prophylaxis of HIV-Uninfected Individuals

CDC-PEP and Cal-PrEP each specifically identify Truvada as a “preferred”²¹⁶ or “optimal”²¹⁷ product to use in their respective chemoprophylaxis

²¹³ CDC-PEP, 3; Cal-PrEP, 3; Youle-Decl. ¶250.

²¹⁴ Youle-Decl. ¶¶147, 149, 250.

²¹⁵ *Id.* ¶261.

²¹⁶ CDC-PEP, 8-9, Table 2; 10, Table 3; *see also supra* §VI.D.2.c.

²¹⁷ Cal-PrEP, 11; *see also supra* §VI.C.2.c.

regimens for HIV-uninfected individuals. By February 2005, a skilled person also would have been motivated to use Truvada given its favorable side-effects profile relative to Combivir and other antiretrovirals,²¹⁸ and to minimize risks of viral resistance that can arise from TDF or FTC monotherapy.²¹⁹

For example, Cal-PrEP notes the “possible emergence of resistance due to selection of the K65R mutation” for TDF monotherapy and that FTC is “susceptible to a single-point mutation at codon 184 that confers resistance, especially when taken alone.”²²⁰ Truvada’s clinical trial results showed no instances of viral resistance.²²¹ The skilled person thus would have understood that monotherapy-linked risks could be minimized by using Truvada, which combines TDF with FTC.²²²

²¹⁸ Moyer, 1; Youle-Decl. ¶237.

²¹⁹ See, e.g., Cal-PrEP, 11 (“To be ideal for use as PrEP, a drug should...not promote development of high-level viral resistance based on a single mutation.”); Youle-Decl. ¶¶87, 163.

²²⁰ Cal-PrEP, 11 (emphasis added).

²²¹ Moyer, 1.

²²² Youle-Decl. ¶¶163, 222, 224.

Thus, before February 2005, CDC-PEP taught that Truvada was a “preferred” agent to use in the PEP regimen and Cal-PrEP taught that Truvada met every feature of the “ideal” PrEP agent.²²³ Consequently, a skilled person would have found it obvious to use Truvada in the PrEP regimen suggested by CDC-PEP and Cal-PrEP.

3. A Skilled Person Would Reasonably Expect PrEP Using Truvada to be Effective in Preventing HIV Infection

During examination, Patent Owner represented to the Patent Office that a skilled person in February 2005 would have doubted that a pre-exposure HIV chemoprophylaxis regimen based on TDF+FTC would have been effective in preventing HIV infection.²²⁴ That assertion has no basis in fact. It also ignores that the claims do not require any particular degree of success, given that the preamble and “thereby” clauses of Claims 1 and 12 are non-limiting.²²⁵ And the

²²³ CDC-PEP, 9, Table 2; Cal-PrEP, 11; Youle-Decl. ¶¶241, 96, 161.

²²⁴ Ex. 1002 (“’509 File History”), 116-18.

²²⁵ *See supra* §V.C.2.a.

law only requires a reasonable expectation of success, not certainty, a standard more than met by the scientific evidence known before February 2005.²²⁶

a. Extensive Experiences with PEP Established a Reasonable Expectation of Success

More than 15 years of experience before February 2005 established that combinations of antiretroviral agents can prevent HIV infections in uninfected individuals after they have been exposed to HIV. Indeed, the CDC's own guidelines (CDC-PEP) rest on the principle that aggressively suppressing HIV viral replication by administering combinations of antiretroviral agents shortly after an HIV exposure will prevent establishment of an HIV infection.²²⁷

CDC-PEP identifies timing, not viral inhibition by ARVs, as the most critical factor in successful prophylaxis, explaining that delays in starting administration of ARVs makes the chemoprophylactic regimen less effective.²²⁸ That observation also makes it clear that administering antiviral agents before an

²²⁶ *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367-68 (Fed. Cir. 2016).

²²⁷ CDC-PEP, 2-4; Youle-Decl. ¶¶130-31.

²²⁸ CDC-PEP, 2.

HIV exposure yields the maximum prophylactic effectiveness, as it will create effective concentrations of the antiretroviral agents at the site of exposure the moment an HIV exposure occurs.²²⁹ PrEP, in essence, is the most optimal form of the PEP regimen.

CDC-PEP also catalogs the extensive scientific evidence known before 2005 that supports the effectiveness of antiretroviral-based prophylaxis in preventing HIV infection in uninfected individuals. That evidence includes animal studies, experiences with mother-to-child prophylaxis, observational studies of PEP, and case reports.²³⁰ CDC-PEP, for example, refers to data showing an 81% reduction in infections in needle-stick settings using antiretroviral therapy with zidovudine.²³¹ CDC's own reliance on this evidence to support its PEP guidelines directly refutes Patent Owner's assertions during examination that a skilled person would not have expected administration of Truvada before an HIV exposure to effectively prevent establishment of an HIV infection in an uninfected

²²⁹ Youle-Decl. ¶133; Saag, 28.

²³⁰ CDC-PEP, 2-4.

²³¹ *Id.* 3.

individual.²³² And expectations of success could only increase with the advances of the early 2000s, particularly clinical experiences with TDF+FTC, which showed effective suppression of viral replication with fewer side-effects than Combivir.²³³

b. PrEP and PEP Regimens Have the Same Pharmacological Mechanism and Cause the Same Result

A skilled person familiar with how antiretroviral agents such as TDF and FTC work in treatment and in post-exposure prophylaxis would have expected the same pharmacological effect to be observed if the agents are administered before an HIV exposure. That is because the same agents when administered to a human subject at the same doses will cause the same effects—they will create a drug concentration at the site of the exposure that maximally suppresses HIV replication.²³⁴ The skilled person thus would have recognized that the way Truvada prevents HIV infection in the human body in the PEP regimen is identical

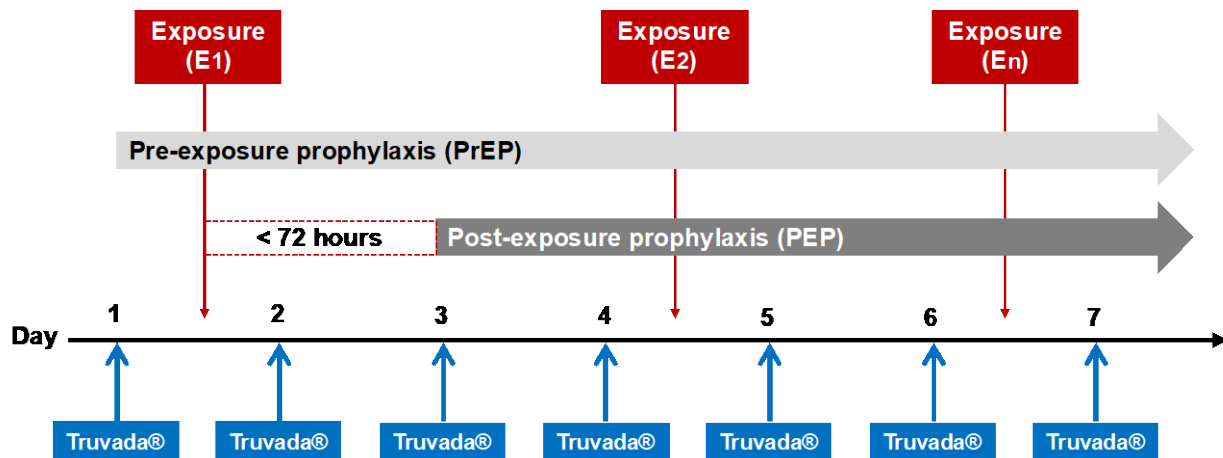
²³² See, e.g., '509 File History, 115 (“The art teaches that use of an anti-HIV agent to treat HIV infection does not reasonably predict the ability of that agent to protect against HIV infection.”).

²³³ Moyer, 1.

²³⁴ Youle-Decl. ¶¶242-43, 248.

to the way it does so in a PrEP regimen, and the reasons why PEP is effective in preventing HIV infection are the same reasons it is effective in PrEP.

CDC-PEP and Cal-PrEP also describe performing the same operative steps—orally administering once a day at least 300 mg of TDF and 200 mg of FTC (i.e., Truvada) to an uninfected individual—with the only difference being when those steps are performed. Indeed, a high-risk uninfected individual placed on a Truvada-based PEP regimen who does not become infected and who experiences an additional HIV exposure during the 28-day or longer regimen will meet all the requirements of the contested claims. That is because the HIV-uninfected individual will be given pharmaceutically effective amounts of TDF and FTC before an HIV exposure (i.e., at exposures E_2 or later).²³⁵



²³⁵ *Id.* ¶¶135-36.

A skilled person thus would have reasonably expected pre-exposure administration of Truvada to prevent establishment of an HIV infection in an uninfected individual (i.e., PrEP with Truvada), given that post-exposure administration of the same dose of the same two agents (i.e., PEP with Truvada) does.²³⁶

c. Cal-PrEP Described Clinical Trials Focused on Decreasing Community Rates of HIV Infection

Patent Owner may contend that Cal-PrEP's indication that clinical trials were needed to prove the effectiveness of PrEP, coupled with its identification of factors that could limit the effectiveness of PrEP, would have led a skilled person to doubt that Truvada, when administered to an HIV uninfected individual before an HIV exposure, would “protect” a host from a HIV infection or “inhibit establishment” of an infection per Claims 1 and 12. Such contentions have no merit.

Initially, the claims do not require the successful prevention of HIV in every individual—they only require performing the steps of administering pharmaceutically effective amounts of TDF and of FTC to one uninfected

²³⁶ *Id.* ¶¶245, 248.

individual before an HIV exposure. That is precisely what is taught or suggested by both Cal-PrEP and CDC-PEP.

Moreover, nothing in the '509 Patent answers the questions supposedly raised in Cal-PrEP about the feasibility of PrEP. Most notably, the macaque studies reported in the '509 Patent do not address any of the human behavioral factors that Cal-PrEP identifies as potentially limiting the effectiveness of PrEP in slowing the rate of infection. Those factors include, *inter alia*, compliance (i.e., whether patients take the pills each day at the right time), access to drugs, and a variety of societal and behavioral factors.²³⁷ A skilled person reading Cal-PrEP would have instead recognized that in its ideal implementation (i.e., an individual with a steady supply of Truvada who takes it every day as prescribed), PrEP would be effective in preventing HIV infection in that individual.²³⁸

More generally, both Cal-PrEP and CDC-PEP recognize that reducing the rate of HIV infections within a community can be best achieved by a combination of interventions. For example, CDC-PEP instructs caregivers to counsel

²³⁷ *Id.* ¶¶262, 258.

²³⁸ *Id.* ¶¶251-52.

individuals to avoid high-risk activities while on the PEP regimen.²³⁹ Cal-PrEP likewise explains that to “reduce the occurrence of future HIV exposures,” individuals on PrEP should be continuously counseled on ways to decrease high-risk activity (e.g., abstinence, protective behaviors, and being repeatedly tested for HIV infection).²⁴⁰ Cal-PrEP, however, recognized that some patients will not follow advice to reduce high-risk activities, be exposed to HIV, and create risks for the broader community. Cal-PrEP thus portrayed the risk-benefit assessment as tilting in favor of administering antiretroviral agents to HIV-uninfected individuals to span periods of their “high-risk” activities.²⁴¹

Ultimately, the relevant question for obviousness is whether a skilled person would reasonably believe that administering TDF+FTC to one uninfected individual will prevent establishment of an HIV infection in that individual.²⁴² More than substantial evidence shows that to be true.

²³⁹ CDC-PEP, 5.

²⁴⁰ Cal-PrEP, 27.

²⁴¹ *Id.* 3.

²⁴² Youle-Decl. ¶¶251, 253, 259.

d. HIV Chemoprophylaxis Was Not “Highly Unpredictable”

During examination, Patent Owner claimed HIV chemoprophylaxis was “highly unpredictable” for various reasons.²⁴³ Patent Owner’s assertions are contradicted by the literature and/or are legally irrelevant.

First, Patent Owner cited results from a PrEP trial using a CCR5 inhibitor.²⁴⁴ Besides involving an agent with a different mechanism of action than TDF+FTC, those results could not have influenced expectations of a skilled person in February 2005 because they were not published until 2013.²⁴⁵

Second, Patent Owner portrayed Subbarao-2006 as showing that prophylaxis using TDF monotherapy in animal studies was unsuccessful. But skilled persons—including the CDC and the authors of Subbarao-2006—portrayed these same TDF monotherapy animal studies as being positive clinical results supporting PrEP.²⁴⁶ Notably, Subbarao-2006 reported that even after 14 weekly exposures,

²⁴³ ’509 File History, 82, 116-17.

²⁴⁴ *Id.* 116; Youle-Decl. ¶¶83, 207.

²⁴⁵ ’509 File History, 116.

²⁴⁶ Youle-Decl. ¶¶216-19, 233-36.

“[o]ne macaque (RQ4180) in the daily-TDF group remained uninfected,” and credited that to TDF’s effectiveness, stating “oral TDF must have played a role in preventing infection in this macaque.”²⁴⁷ Subbarao-2006 also stated “that oral TDF prophylaxis of macaques in our study resulted in a 60% decrease in the per-exposure probability of infection,” thereby providing at least “partial protection” when administered prior to exposure.²⁴⁸ And Subbarao-2006 not only reported that “tenofovir prophylaxis may be of benefit” in a pre-exposure setting (noting it delayed median times to infection), but stated this in the paper’s title.²⁴⁹ Moreover, a commentary published in the same issue of *Science* cited Subbarao-2006’s experimental results as supporting the viability of TDF-based PrEP *combination* therapy, stating “combinations of agents may be more suited for PrEP” than TDF alone, and specifically recommended use of Truvada in PrEP.²⁵⁰ And other

²⁴⁷ Ex. 1050 (“Subbarao-2006”), 907, 909; Youle-Decl. ¶217.

²⁴⁸ Subbarao-2006, 907; Youle-Decl. ¶216.

²⁴⁹ See Subbarao-2006, 910; see also *id.* 907.

²⁵⁰ Grant-2006, 875; see also Ex. 1053 (“Grant-2005”), 2170; Youle-Decl.

¶¶220-21; *supra* §IV.D.

contemporaneous publications cited other TDF-based PrEP animal studies as supporting the viability of TDF PrEP monotherapy in humans.²⁵¹

Post-filing publications from the CDC also directly contradict Patent Owner's assertions. Most notably, in its 2014 PrEP guidelines, the CDC cited Subbarao-2006 as *supporting* the efficacy of TDF in PrEP, stating:

Evidence from these human studies of blood-borne and perinatal transmission as well as studies of vaginal and rectal exposure among animals [FN17-19] *suggested that PrEP (using antiretroviral drugs) could reduce the risk of acquiring HIV infection* from sexual and drug-use exposures.²⁵²

The last assertion made by Patent Owner was that Cambodian TDF PrEP clinical trials were cancelled due to concerns over therapeutic efficacy.²⁵³ That too is incorrect: one report identified concerns over trial participants being unfairly

²⁵¹ *E.g.*, Ex. 1051 (“Grant-2006”), 874 (observing that Subbarao’s results “advance[]...the use of antiretroviral drugs in...PrEP...for HIV disease); Ex. 1052 (“Subbarao-2007”), 241 (follow-up publication stating “oral TDF can be initially effective for a while”); Youle-Decl. ¶209.

²⁵² Ex. 1123 (“CDC-2014”), 14 (emphasis added) (FN17 is Subbarao-2006).

²⁵³ ’509 File History, 114.

exploited as the reason, and that same report observed that tenofovir “has a better safety profile than any anti-HIV drug on the market” and “already has proven to be extremely effective as an HIV preventative in monkey experiments.”²⁵⁴

And while Patent Owner asserted during examination that “the prior art does not disclose or suggest...selecting a subject not infected with the immunodeficiency retrovirus, and administering a pharmaceutically effective amount of emtricitabine and a pharmaceutically effective amount of tenofovir” for PEP or PrEP,²⁵⁵ that statement is demonstrably incorrect. As shown in §§VI.B-VI.D, CDC-PEP and Cal-PrEP each are based on the proposition that HIV prophylaxis with Truvada is effective. Critically, neither of those publications was provided to the Examiner during examination of the ’509 Patent and each is far more relevant to patentability than the references that were actually considered.

F. There Are No Secondary Indicia of Non-Obviousness

Patent Owner may contend that evidence of secondary considerations, such as unexpected results or commercial success, warrant finding the claims non-

²⁵⁴ Ex. 1054 (“Cohen-2004”), 1092.

²⁵⁵ ’509 File History, 114.

obvious.²⁵⁶ But to be pertinent to obviousness, the secondary considerations evidence must have a nexus to *the invention*. “[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent.”²⁵⁷

Here, the evidence shows that any unexpected results or commercial success of using TDF+FTC in PrEP regimens are attributable to the prior art, not the ’509 Patent. That prior art clearly identifies not only the process of administering Truvada to HIV-uninfected individuals before an HIV exposure to prevent HIV infections but also identifies the characteristics of drugs “ideal for use as PrEP” and explains that “drugs [like NRTIs] whose mechanisms of action focus on pre-integration” are likely to be effective.²⁵⁸ Indeed, at best, the ’509 Patent provided simply a confirmation of what scientists knew and expected from the prior art.

Likewise, if “market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence

²⁵⁶ Secondary considerations are irrelevant to anticipation.

²⁵⁷ *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006).

²⁵⁸ *See, e.g., Cal-PrEP*, 10-11.

of commercial success, is weak.”²⁵⁹ Gilead holds patents claiming once-daily oral formulations of TDF, FTC, and their combination, which cover all uses of the compounds.²⁶⁰ Because market entry for third parties was blocked by Gilead’s patents on the Truvada product, any inference of non-obviousness for commercial success of the claimed methods (which concern a use of Truvada) is weak at best.

Other secondary considerations are absent. For example, by February 2005, there was no failure of others or skepticism in the field with respect to Truvada’s use in PrEP. Instead, by then, the CDC had recommended its use in both treatment and prophylaxis²⁶¹ and skilled persons proposed using it in large-scale PrEP trials.²⁶² Physicians also had begun recommending Truvada for PrEP to high-risk patients and such individuals began obtaining Truvada from friends to take in

²⁵⁹ *Merck & Co. v. Teva Pharmaceuticals USA*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

²⁶⁰ *E.g.*, U.S. Patent Nos. 5,922,695 (TDF); 6,703,396 (FTC); 8,592,397 (TDF+FTC).

²⁶¹ Ex. 1075 (“DHHS-2004”), 14; CDC-PEP, 9 (Table 2).

²⁶² Youle-Decl. ¶¶230-32; *see also* Ex. 1135 (“Grant-Proposal”), 3-4.

prophylaxis before and after high-risk behavior.²⁶³ And Truvada’s more recent success in PrEP is not due to anything disclosed in the ’509 Patent, but to the efforts of the CDC and Gilead to promote its use.

Thus, no secondary indicia have a nexus to the claimed methods, and none supports the non-obviousness of the contested claims. Petitioner also submits any evidence of secondary indicia advanced by Patent Owner in its response should be addressed after institution, where that evidence and its relevance can be contested.

VII. THE BOARD SHOULD NOT EXERCISE ITS DISCRETION UNDER 35 U.S.C. §325(D)

Under the relevant factors identified in *Becton Dickinson & Co. v. B. Braun Melsungen AG* and in the Board’s July 2019 Trial Practice Guide Update, the Board should not exercise its discretion under §325(d).²⁶⁴ Neither Cal-PrEP nor CDC-PEP was cited during examination of the ’509 Patent, and neither is

²⁶³ Youle-Decl. ¶241.

²⁶⁴ Trial Practice Guide, 84 Fed. Reg. 33,925 (July 2019 Update) (“Trial Practice Guide”), 29-30 (factors 1 to 4) (citing *Becton Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (P.T.A.B. Dec. 15, 2017) (precedential)).

cumulative or equivalent to the prior art used during its examination. Both references also are far more relevant than the art considered during examination.²⁶⁵ This petition also proposes different grounds (including anticipation), and presents new evidence not considered by the Office—a declaration from Dr. Michael Youle (Ex. 1009), a noted expert in the field of HIV therapy and prevention.²⁶⁶ This Petition therefore does not present the “same or substantially the same prior art or arguments” raised or considered during examination of the ’509 Patent.

Patent Owner may nonetheless contend the Board should not institute trial because Cal-PrEP and CDC-PEP were considered during examination of a subsequently filed application, U.S. Application No. 15/406,344, which issued as U.S. Patent No. 9,937,191 (Ex. 1005) (“’191 Patent”). But the examination record of the ’191 Patent reveals that “the Office erred in evaluating the asserted prior art”

²⁶⁵ *Microsoft Corp. v. Parallel Networks Licensing, LLC*, IPR2015-00486, Paper 10, 14-15 (P.T.A.B. July 15, 2015); *Becton Dickinson*, IPR2017-01586, Paper 8, 17-18; Trial Practice Guide, 29-30.

²⁶⁶ *Apotex Inc. v. Novartis AG*, IPR2017-00854, Paper 11, 13-14 (P.T.A.B. July 18, 2017).

during its examination, which, if anything, justifies the Board not exercising its discretion under §325(d) here.²⁶⁷

What the '191 Patent file wrapper shows is that the Examiner rejected claims similar to those in the '509 Patent as being obvious over seven prior art references, two of which were Cal-PrEP and CDC-PEP. The Examiner correctly observed that Cal-PrEP (also referred to as “Szekeres”) identified (1) the need for biomedical approaches to HIV prevention including PrEP and that (2) TDF was well-suited for PrEP.²⁶⁸ The Examiner also correctly observed that CDC-PEP disclosed Truvada for use in PEP and that it would have been obvious to treat uninfected individuals who are exposed to or at risk of exposure to HIV with Truvada.²⁶⁹

Rather than address the merits of this rejection, Patent Owner secured an interview with the Examiner, proposed an amendment to add a “tablet” limitation

²⁶⁷ Trial Practice Guide, 30 (factor 5).

²⁶⁸ Ex. 1006 (“’191 File History), 60. The Examiner consequently did not observe that Cal-PrEP also identified Truvada as one of two TDF options to use in PrEP.

²⁶⁹ *Id.*, 60-61.

to the '509 Patent claims, and appeared to convince the Examiner this amended claim would be patentable for the same reasons that the Examiner had found the '509 Patent claims patentable. As the Examiner's interview summary states:

Applicants' attorney indicates that applicants will pursue subject matter within the scope of allowed claim in parent application (now US 9,044,509).... Particularly, claims 1 herein will be amended to the same as claim 1 in '509, but with a further limitation of the oral dosage form: a tablet. The examiner indicates that such a claim would be allowable for reasons as set forth in the parent application.²⁷⁰

Then, when Patent Owner presented this amended "tablet" claim, it stated the Examiner had "confirmed that it was not necessary to address the rejection under 35 U.S.C. §103 if the proposed claim amendments were made in the response."²⁷¹

But neither Cal-PrEP nor CDC-PEP was ever cited during examination of the '509 Patent, much less were the basis of rejections that were imposed and overcome during its examination.²⁷² Thus, the statement in the Examiner's

²⁷⁰ *Id.*, 53 (emphasis added).

²⁷¹ *Id.* 40 (emphasis added).

²⁷² The same Examiner examined all four patents that issued from this family of applications.

interview summary form (and reinforced by Patent Owner's response) that the '191 Patent claims were patentable *for the same reasons the Examiner had found the '509 Patent claims patentable* was and is demonstrably false—the '509 Patent claims were never even considered in connection with Cal-PrEP or CDC-PEP because Patent Owner did not provide those references to the Office until years after the '509 Patent granted.

The examination record of the '191 Patent thus shows that Patent Owner never addressed, much less overcame, any rejection that relied on the substantive teachings of Cal-PrEP and CDC-PEP. What it shows instead is that the Examiner mistakenly equated the basis of the rejections of the '191 Patent claims with a rejection imposed over different and much less relevant prior art (i.e., not Cal-PrEP or CDC-PEP) during examination of the '509 Patent claims, and relied on that mistake to find the '191 Patent claims patentable. That mistake would warrant the Board not exercising its discretion in proceedings against the '191 Patent. And, if the examination record of the '191 Patent were somehow relevant to the earlier-examined '509 Patent at issue in this petition, the Office's later error would (if anything) support the Board not exercising its §325(d) discretion here.

Consequently, because the patentability issues presented in this petition were not considered during examination of the '509 Patent, the Board should not exercise its discretion under §325(d).

VIII. CONCLUSION

Petitioner respectfully requests that trial be instituted and that the claims be held unpatentable for the reasons set forth above.

Dated: August 21, 2019

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CERTIFICATE OF COMPLIANCE

I hereby certify that this Petition complies with the type-volume limitations of 37 C.F.R. §42.24, because it contains 13,917 words (as determined by the Microsoft Word word-processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §42.6(e), I hereby certify that on this 21st day of August, 2019, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by Federal Express on the following counsel:

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 9,044,509 (“509 Patent”)
1002	File History of U.S. Patent No. 9,044,509 (“509 File History”)
1003	U.S. Patent No. 9,579,333 (“333 Patent”)
1004	File History of U.S. Patent No. 9,579,333 (“333 File History”)
1005	U.S. Patent No. 9,937,191 (“191 Patent”)
1006	File History of U.S. Patent No. 9,937,191 (“191 File History”)
1007	U.S. Patent No. 10,335,423 (“423 Patent”)
1008	File History of U.S. Patent No. 10,335,423 (“423 File History”)
1009	Declaration of Michael Youle, MB, ChB (“Youle-Decl.”)
1010	Curriculum Vitae of Michael Youle, MB, ChB
1011	Szekeres et al., “Anticipating the Efficacy of HIV Pre-Exposure Prophylaxis (PrEP) and the Needs of At-Risk Californians,” Center for HIV Identification, Prevention and Treatment Services (2004) (“Cal-PrEP”)
1012	Centers for Disease Control and Prevention, “Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States,” Recommendations from the U.S. Department of Health and Human Services, Morbidity and Mortality Weekly Report 54(2) (Jan. 21, 2005) (“CDC-PEP”)
1013	Centers for Disease Control and Prevention, “Public Health Service Guidelines for the Management of Health-Care Worker Exposures to HIV and Recommendations for Postexposure Prophylaxis,” Morbidity and Mortality Weekly Report 47(7) (1998) (“CDC-May1998”)
1014	Centers for Disease Control and Prevention, “Report of the NIH Panel to Define Principles of Therapy of HIV Infection and Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and

	Adolescents,” Morbidity and Mortality Weekly Report 47(5) (1998) (“CDC-ARV”)
1015	Hu et al., “Simian Immunodeficiency Virus Rapidly Penetrates the Cervicovaginal Mucosa after Vaginal Inoculation and Infects Intraepithelial Dendritic Cells,” J. Virol. 74(13): 6087–95 (2000) (“Hu”)
1016	De Clercq, “HIV-chemotherapy and -prophylaxis: new drugs, leads and approaches,” Int’l J. Biochem. Cell Bio. 36(9): 1800–22 (2004) (“De Clercq-IJB”)
1017	Bassett et al., “Two Drugs or Three? Balancing Efficacy, Toxicity, and Resistance in Postexposure Prophylaxis for Occupational Exposure to HIV,” Clin. Infect. Dis. 39(3): 395–401 (2004) (“Bassett”)
1018	Coffin, “HIV Population Dynamics in Vivo: Implications for Genetic Variation, Pathogenesis, and Therapy,” Science 267(5197): 483–9 (1995) (“Coffin”)
1019	Hammer et al., “A Controlled Trial of Two Nucleoside Analogues plus Indinavir in Persons with Human Immunodeficiency Virus Infection and CD4 Cell Counts of 200 per Cubic Millimeter or Less,” N. Engl. J. Med. 337(11): 725–33 (1997) (“Hammer”)
1020	Gulick et al., “Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy,” N. Engl. J. Med. 337(11): 734–39 (1997) (“Gulick”)
1021	Barreiro et al., “Combinations of Nucleoside/Nucleotide Analogues for HIV Therapy,” AIDS Rev. 6(4): 234–43 (2004) (“Barreiro”)
1022	Collins, “Tenofovir/FTC Backbone Outperforms AZT/3TC (Combivir) with Efavirenz in Treatment Naive Patients; Reduced Toxicity Drives ITT Viral Efficacy,” HIV i-Base (Jan. 29, 2005), http://i-base.info/htb/7665 (“Collins”)
1023	Gerberding, “Occupational Exposure to HIV in Health Care Settings,” N. Engl. J. Med. 348(9): 826–33 (2003) (“Gerberding”)

1024	Centers for Disease Control and Prevention, “Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis,” Morbidity and Mortality Weekly Report 50(11) (2001) (“CDC-2001”)
1025	Truvada® Label, FDA.gov (Aug. 2004), https://web.archive.org/web/20041014005516/http://www.truvada.com:80/fpi.pdf (“Truvada®-Label”)
1026	Truvada® Approval Letter, FDA.gov (Aug. 2, 2004), http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2004/21752ltr.pdf (“Approval-Letter”)
1027	Viread®-Label, FDA.gov (Oct. 2001), https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21356lbl.pdf (“Viread®-Label”)
1028	Emtriva®-Label, FDA.gov (July 2003), https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21500_emtriva_lbl.pdf (“Emtriva®-Label”)
1029	De Clercq, “Antiviral Drugs in Current Clinical Use,” J. Clin. Virol. 30(2): 115–33 (2004) (“De-Clercq-JCV”)
1030	Bang & Scott, “Emtricitabine: An Antiretroviral Agent for HIV Infection,” Drugs 63(22): 2413–24 (2003) (“Bang”)
1031	Vela et al., “In Vitro Evaluation of the Anti-HIV Activity and Metabolic Interactions of Emtricitabine and Tenofovir,” HIV DART 2004 – Frontiers in Drug Development for Antiretroviral Therapies, Dec. 12-16, 2004, Montego Bay, Jamaica (“Vela”)
1032	Dando & Wagstaff, “Emtricitabine/Tenofovir Disoproxil Fumarate,” Drugs 64(18): 2075–82 (2004) (“Dando”)
1033	Back et al., “The Pharmacology of Antiretroviral Nucleoside and Nucleotide Reverse Transcriptase Inhibitors: Implications for Once-Daily Dosing,” J. Acquir. Immune Defic. Syndr. 39(1): S1–23 (Aug. 1, 2005) (“Back”)

1034	DeJesus et al., “Abacavir versus Zidovudine Combined with Lamivudine and Efavirenz, for the Treatment of Antiretroviral-Naive HIV-Infected Adults,” Clin. Infect. Dis. 39(7): 1038–46 (2004) (“DeJesus”)
1035	Moyer, “Combined Tenofovir, Emtricitabine, Efavirenz May Be More Tolerable Than Standard First-Line HIV,” Medscape Medical News (Nov. 3, 2004), https://www.medscape.com/viewarticle/492968 (“Moyer”)
1036	Feinberg, “Tenofovir + Emtricitabine vs. AZT + 3TC,” AIDS Clin. Care 17(1): 7 (Jan. 1, 2005) (“Feinberg”)
1037	Mascolini, “Truvada Goes Toe-to-Toe with Combivir,” ICAAC Report: Evolving Antiretroviral Strategies, Conference Report for the National AIDS Treatment Advocacy Project (2004) (“Mascolini”)
1038	Gallant et al., “Efficacy and Safety of Tenofovir DF vs. Stavudine in Combination Therapy in Antiretroviral Naïve Patients: A 3-Year Randomized Trial,” JAMA 292(2): 191–201 (2004) (“Gallant”)
1039	Brenner et al., “HIV-1 Subtype C Viruses Rapidly Develop K65R Resistance to Tenofovir in Cell Culture,” AIDS 20(9): F9–F13 (Jun. 12, 2006) (“Brenner”)
1040	Food and Drug Administration, “Treatment Options for HIV, AIDS,” FDA Consumer Magazine, Nov.–Dec. 2004 (“FDA-2004”)
1041	De Clercq, “Emerging Anti-HIV Drugs,” Expert Opin. Emerg. Drugs 10(2): 241–73 (May 10, 2005) (“De-Clercq-2005”)
1042	Youle & Wainberg, “Pre-Exposure Chemoprophylaxis (PREP) as an HIV Prevention Strategy,” J. Int’l Assoc. Physicians AIDS Care 2(3): 102–5 (2003) (“Youle-JIAPAC”)
1043	Helene Gayle, Prepared Remarks, “Prevention Now! A Vision for the Future,” Bill & Melinda Gates Foundation (July 9, 2002), https://www.gatesfoundation.org/Media-Center/Speeches/2002/07/Helene-Gayle-2002-Prevention-Now (“Gayle”)

1044	Marilyn Chase, “Trials Will Test Whether AIDS Drug Can Also Prevent HIV,” Wall St. J., Dec. 4, 2003 (“Chase”)
1045	Tsai et al., “Prevention of SIV Infection in Macaques by (R)-9-(2-Phosphonylrr-ethoxypropyl)adenine,” Science 270(5239): 1197–9 (1995) (“Tsai-1995”)
1046	Van Rompay et al., “Two Doses of PMPA Protect Newborn Macaques Against Oral Simian Immunodeficiency Virus Infection,” AIDS 12(9): F79–83 (1998) (“Van-Rompay-1998”)
1047	Otten et al., “Multiple Vaginal Exposures to Low Doses of R5 Simian-Human Immunodeficiency Virus: Strategy to Study HIV Preclinical Interventions in Nonhuman Primates,” J. Inf. Dis. 191(2): 164–73 (Dec. 9, 2004) (“Otten-2004”)
1048	Li et al., “Infection of Cynomolgus Monkeys with a Chimeric HIV-1/SIVmac Virus that Expresses the HIV-1 Envelope Glycoproteins,” J. Acquir. Immune Defic. Syndr. 5(7): 639–46 (1992) (“Li”)
1049	Gazzard et al., “The Combination of Tenofovir (TDF), Emtricitabine (FTC) and Efavirenz (EFV) has Significantly Greater Responses vs. Fixed-Dose Zidovudine/Lamivudine (CBV) and EFV in Antiretroviral Naive Patients: A 24-Week Preliminary Analysis,” ARV Update: 44th ICAAC Highlights (Dec. 2004), http://www.thebodypro.com/content/art34001.html (“Gazzard”)
1050	Subbarao et al., “Chemoprophylaxis with Tenofovir Disoproxil Fumarate Provided Partial Protection Against Infection with Simian Human Immunodeficiency Virus in Macaques Given Multiple Virus Challenges,” J. Infect. Dis. 194(7): 904–11 (Oct. 1, 2006) (“Subbarao-2006”)
1051	Grant & Wainberg, “Chemoprophylaxis of HIV Infection: Moving Forward with Caution,” J. Infect. Dis. 194(7): 874–876 (Oct. 1, 2006) (“Grant-2006”)
1052	Subbarao et al., “Direct Stringency Comparison of Two Macaque Models (Single-high vs. Repeat-low) for Mucosal HIV Transmission

	Using an Identical Anti-HIV Chemoprophylaxis Intervention,” J. Med. Primatol. 36(4–5): 238–43 (2007) (“Subbarao-2007”)
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1054	Cohen, “Cambodian Leader Throws Novel Prevention Trial Into Limbo,” AIDS Research News of the Week, Science 305(5687): 1092 (2004) (“Cohen-2004”)
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1057	Centers for Disease Control and Prevention, “HIV-2 Infection Surveillance – United States, 1987–2009,” Morbidity and Mortality Weekly Report 60(29): 985–988 (July 29, 2011) (“CDC-Surveillance”)
1058	Ruthie Blum, “Promoting Prophylaxis,” The Jerusalem Post (Jan. 11, 2007) (“Blum”)
1059	“Family Health International Receives Grant to Evaluate Once-Daily Antiretroviral as a Potential Method of HIV Prevention,” Bill & Melinda Gates Foundation (Oct. 28, 2002) (“Gates-Foundation”)
1060	Youle & Wainberg, “Could Chemoprophylaxis Be Used as an HIV Prevention Strategy While We Wait for an Effective Vaccine?” AIDS 17(6): 937–8 (2003) (“Youle-AIDS”)
1061	Haase, “Perils at Mucosal Front Lines for HIV and SIV and Their Hosts,” Nature Rev. Immunol. 5(10):783–92 (Oct. 2005) (“Haase-2005”)
1062	Pope & Haase, “Transmission, Acute HIV-1 Infection and the Quest for Strategies to Prevent Infection,” Nat. Med. 9(7): 847–52 (2003) (“Pope”)

1063	Chakraborty, “Viral Burden in Genital Secretions Determines Male-to-Female Sexual Transmission of HIV-1: A Probabilistic Empiric Model,” AIDS 15(5): 621–7 (2001) (“Chakraborty”)
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EXHIBIT I

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GILEAD SCIENCES, INC.,
Petitioner,

v.

THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES,
Patent Owner.

Case No. IPR2019-01454
Patent No. 9,579,333
Filed: April 6, 2015

PETITION FOR *INTER PARTES* REVIEW

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I. MANDATORY NOTICES

A. Real Party-In-Interest (§42.8(b)(1))

The real party-in-interest is Gilead Sciences, Inc., located at 333 Lakeside Drive, Foster City, California 94404.

B. Other Proceedings (§42.8(b)(2))

U.S. Patent No. 9,579,333 (Ex. 1003) (“’333 Patent”) is not the subject of any other proceeding.

Petitioner has filed *inter partes* review petitions against three patents issued from applications claiming priority to the application from which the ’333 Patent issued; namely: (i) IPR2019-01453 (challenging U.S. Patent No. 9,044,509); (ii) IPR2019-01455 (challenging U.S. Patent No. 9,937,191); and (iii) IPR2019-01456 (challenging U.S. Patent No. 10,335,423).

C. Lead and Backup Lead Counsel (§42.8(b)(3))

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D. Service on Petitioner (§42.8(b)(4))

Service may be made by e-mail (IPRNotices@sidley.com) or by mail or hand delivery to: Sidley Austin LLP, 1501 K Street, N.W., Washington, D.C. 20005. The fax number for Counsel is 202-736-8711.

E. Fee for Petition (§42.15(a))

The Director is authorized to charge the fee specified by 37 CFR §42.15(a) to Deposit Account No. 50-1597.

II. INTRODUCTION

Since the 1990s, it has been standard practice to administer combinations of antiretroviral agents to prevent human immunodeficiency virus (“HIV”) infections in uninfected individuals who have been exposed to the virus, a regimen termed post-exposure prophylaxis (“PEP”). By 2005, PEP regimens had evolved to use newer antiretrovirals, particularly Petitioner Gilead’s Truvada®, a once-daily oral formulation of tenofovir disoproxil fumarate (“TDF”) plus emtricitabine (“FTC”). Indeed, shortly after it became available, the Centers for Disease Control and Prevention (CDC)¹ updated their widely-followed PEP guidelines (“CDC-PEP”)² to specify use of Truvada (i.e., TDF+FTC) as one of two “preferred” “backbone” regimens to prevent HIV infection after exposure.

In 2004, two California-based HIV/AIDS organizations³ published a report (“Cal-PrEP”) describing an extension of the PEP regimen for “certain people at

¹ The CDC is an agency of the Department of Health & Human Services (HHS), the Patent Owner.

² Ex. 1012 (“CDC-PEP”), 20.

³ The Center for HIV Identification, Prevention, and Treatment Services and AIDS Partnership California. See Ex. 1011 (“Cal-PrEP”), 2-3.

high risk of HIV infection”⁴—those who engage in conduct that repeatedly exposes them to HIV. Their regimen specified giving high-risk individuals antiretrovirals (particularly Truvada) before they are exposed to HIV (“pre-exposure prophylaxis” or “PrEP”), rather than after (“PEP”). Cal-PrEP justified this regimen by reasoning that any potential side-effects of using antiretrovirals for extended periods would be far outweighed by preventing infection of the high-risk individual on PrEP, and, by extension, others in that person’s community who might become exposed to HIV via that high-risk individual.

The claims of the ’333 Patent encompass both regimens—certain claims require administration of TDF+FTC before an HIV exposure (i.e., PrEP), while others also cover administration after an HIV exposure (i.e., PEP). All or some of the ’333 Patent claims are thus anticipated by the methods described in Cal-PrEP and in CDC-PEP, and all are obvious variants of both when considered together. Petitioner respectfully requests the Board to institute *inter partes* review of Claims 1-17 of the ’333 Patent and cancel these claims.

⁴ Cal-PrEP, 3.

III. CERTIFICATION; PROPOSED GROUNDS

Gilead Sciences, Inc. certifies it is not barred or estopped from requesting *inter partes* review of the '333 Patent. Neither Gilead, nor any party in privity with Gilead, has (i) filed a civil action challenging the validity of any claim of the '333 Patent; or (ii) been served a complaint alleging infringement of the '333 Patent more than a year prior to the present date. The '333 Patent also has not been the subject of a prior *inter partes* review. Gilead certifies that the '333 Patent is available for *inter partes* review.

Petitioner proposes three grounds:

- (i) anticipation of Claims 1-17 by Cal-PrEP under 35 U.S.C. §102(b);
- (ii) anticipation of Claims 12-17 under by CDC-PEP under 35 U.S.C. §102(b); and
- (iii) obviousness of Claims 1-17 over CDC-PEP in view of Cal-PrEP under 35 U.S.C. §103.

Petitioner submits these grounds are not redundant. The two anticipation grounds address claims with distinct requirements that are anticipated for different reasons by the disclosures of Cal-PrEP and CDC-PEP. The anticipation grounds are not redundant with the proposed obviousness ground, which rests on a different rationale for unpatentability and is presented to respond to potential arguments Patent Owner may make regarding what the prior art teaches. And because all

three grounds rely on the same two prior art references and the knowledge held by the skilled person, they are “rational, narrowly targeted, and not burdensome.”⁵

IV. KNOWLEDGE IN THE FIELD BEFORE FEBRUARY 2005

What the skilled person knew at the time of an invention is integral to the assessment of patentability. Here, the critical date is February 3, 2005—one year before the earliest priority date claimed by the ’333 Patent. The skilled person’s knowledge of HIV, antiretroviral agents, and strategies for treatment and prophylaxis of HIV by that date was extensive.

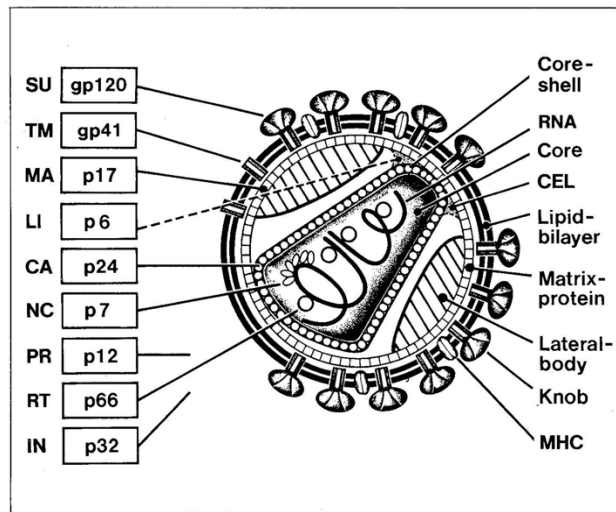
A. HIV Infections

The human immunodeficiency virus (HIV) targets and destroys the immune system’s CD4+ cells, which impedes the body’s ability to fight infections and illnesses and eventually progresses to acquired immune deficiency syndrome (“AIDS”).⁶ HIV is a retrovirus and exists outside of cells as viral particles (“virions”) (Figure)⁷:

⁵ *Great W. Cas. Co. v. Transpacific IP I Ltd.*, IPR2015-01912, Paper 10, 17-18 (P.T.A.B. Mar. 22, 2016).

⁶ *See, e.g.*, Ex. 1138 (“Janeway”), 451-57; Ex. 1147 (“Cohen-1999”), 1458-59, 1474-76.

⁷ Ex. 1148 (“Gelderblom-1991”), 620.



HIV infections can result from an HIV “exposure,” which occurs when virions are transferred via bodily fluids (e.g., semen or blood) to an individual.⁸ To create a risk of infection, HIV must encounter CD4+ cells in the body and transform them to induce those cells to produce and release new virions, which can then transform other CD4+ cells. To do that, the virion binds to the CD4+ cell, which enables the HIV viral RNA to enter the cell.⁹ Then, reverse transcriptase converts the viral RNA into viral cDNA, which enters the CD4+ cell nucleus and integrates into the host genome via the action of an integrase enzyme. The infected CD4+ cell then expresses the viral cDNA to produce viral protein precursors and additional copies of the HIV RNA. Protease enzymes then process the precursor

⁸ Ex. 1009 (“Youle-Decl.”) ¶¶43-44; Gelderblom-1991, 618-20.

⁹ Gelderblom-1991, 618, 630; Ex. 1149 (“Goldsby”), 452, Fig. 19-14.

proteins, package them together with HIV RNA and release them from the HIV-infected cell as new virions.

The CD4⁺ cells transformed by the initial exposure to HIV are called “founder” cells,¹⁰ which rapidly begin producing virions that can infect other CD4⁺ cells.¹¹ The body’s immune system targets and removes the founder and other CD4⁺ cells transformed by HIV, but at some point (approximately three days after the exposure) the volume of new virions and infected CD4⁺ cells overwhelms the host’s immune system.¹² At that point, the HIV infection was considered established.¹³

B. Antiretrovirals Target Different Phases of HIV’s Life Cycle

Antiretroviral drugs inhibit replication of HIV viral RNA in CD4⁺ cells and production of new virions, which prevents additional CD4⁺ cells from being

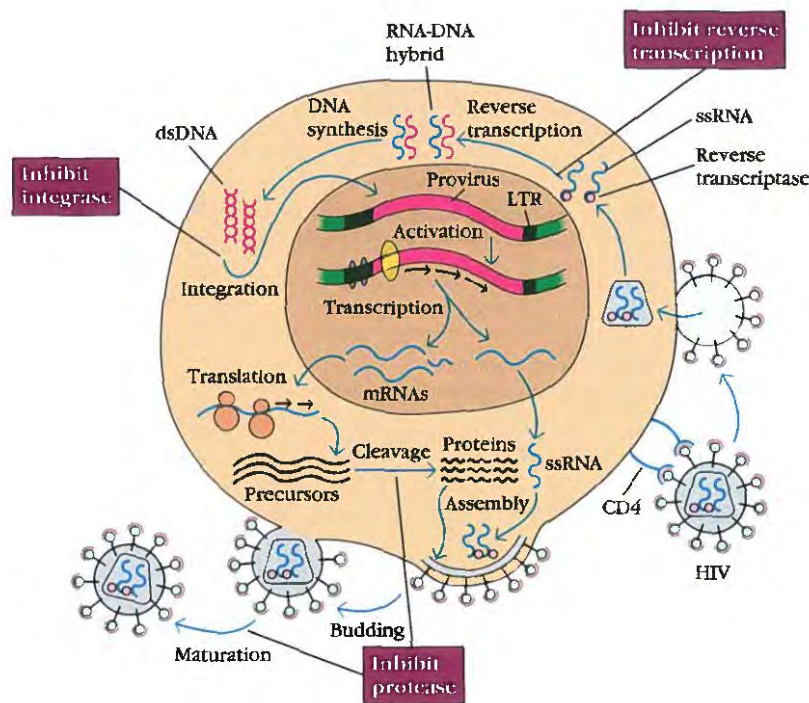
¹⁰ Ex. 1061 (“Haase-2005”), 784; Ex. 1137 (“Miller”), 9217, 9222.

¹¹ Haase-2005, 784.

¹² Youle-Decl. ¶73; Haase-2005, 784; Ex. 1156 (“Tsai-1998”), 4271 (“...short temporal window during which...treatment can block establishment of persistent infection”); Ex. 1157 (“Lifson”), 2584; Ex. 1013 (“CDC-May1998”), 5.

¹³ Youle-Decl. ¶73; Haase-2005, 784, 787; Miller, 9225-26.

transformed by HIV.¹⁴ Different classes of antiretroviral drugs were known to target different phases of HIV's life cycle (Figure).¹⁵



Agents that prevent HIV viral DNA from being created or integrated into the host cell's DNA are the most effective antiretroviral agents.¹⁶ Reverse transcriptase inhibitors ("RTIs") are particularly effective because they prevent

¹⁴ Janeway, 458-59.

¹⁵ Goldsby, 451-53; Janeway, 458-59; Lifson, 2584; Ex. 1015 ("Hu"), 6087.

¹⁶ Cal-PrEP, 11.

creation of the HIV proviral cDNA.¹⁷ Two examples of RTIs are nucleotide reverse transcriptase inhibitors (“NRTIs”) such as tenofovir and tenofovir disoproxil fumarate (TDF)¹⁸ and nucleoside reverse transcriptase inhibitors (“NRTIs”) such as emtricitabine (FTC).¹⁹

C. Combination Antiretroviral Regimens

Since the 1990s, it was known that the most effective way to “accomplish durable suppression of HIV replication” is to administer two or more different antiretroviral drugs (“combination” therapy)—one agent (“monotherapy”) does not

¹⁷ See Goldsby, 451-52; Ex. 1021 (“Barreiro”), 234; Youle-Decl. ¶95.

¹⁸ “TDF is a prodrug of tenofovir.” Cal-PrEP, 8; *see also* Youle-Decl. ¶81; Ex. 1029 (“De-Clercq-JCV”), 118-19.

¹⁹ Ex. 1025 (“Truvada®-Label”), 2-3; Ex. 1016 (“De-Clercq-IJB”), 1806-10; De-Clercq-JCV, 115-18; Ex. 1030 (“Bang”), 2413-15; *see also* Youle-Decl. ¶¶78-80, 96. A third type of RTI—non-nucleoside reverse transcriptase inhibitors (“NNRTIs”)—binds to reverse transcriptase and inhibits its functions. *See* Ex. 1067 (“Saag”), 26; De-Clercq-JCV, 118; Goldsby, 451-53; Youle-Decl. ¶83.

ensure sufficient and sustainable suppression.²⁰ Monotherapy also risks creating drug resistance if HIV mutates to overcome the inhibition of viral replication.²¹ Combination therapy minimizes that risk as it requires HIV to acquire multiple mutations to overcome the inhibitory effect of the drugs.²²

The CDC thus has recommended combinations of antiretrovirals for both treatment and prophylaxis of HIV since well before 2005, particularly two NRTIs²³ plus either a protease inhibitor (PI) or an NNRTI.²⁴ The two NRTIs are referred to

²⁰ Ex. 1014 (“CDC-ARV”), 10-11; Ex. 1017 (“Bassett”), 396; Youle-Decl. ¶¶86-87, 223.

²¹ CDC-ARV, 10; Ex. 1018 (“Coffin”), 487-88; Cal-PrEP, 11 (discussing susceptibility of TDF monotherapy to prevalent K65R mutation).

²² CDC-ARV, 10; Ex. 1019 (“Hammer”), 731; Ex. 1020 (“Gulick”), 738.

²³ NtRTIs and NRTIs are sometimes referred to generally as “NRTIs.” Youle-Decl. ¶79.

²⁴ CDC-ARV, 11 (treatment); CDC-May1998, 8-9; *see also* Ex. 1024 (“CDC-2001”), 24-27 (prophylaxis); *see also* Barreiro, 234, Youle-Decl. ¶117.

as the “backbone” of the combination regimen.²⁵ TDF+FTC is an example of a two-NRTI backbone.²⁶

D. Truvada and Its Properties

The FDA approved Truvada in August 2004 as a once-daily oral formulation of two agents, TDF+FTC, for treating HIV infection in combination with a third agent.²⁷ Truvada contains 300 mg of TDF and 200 mg of FTC, the same doses in Gilead’s single-agent formulations of FTC (Emtriva®) and TDF (Viread®).²⁸

In October 2004, zidovudine+lamivudine (Combivir®) was the prevailing backbone and when combined with efavirenz was considered “one of the most effective, thoroughly investigated, and well-tolerated regimens for the treatment of antiretroviral-naïve patients.”²⁹ Truvada’s clinical results, however, established that TDF+FTC caused fewer side-effects than Combivir (8% versus 15%) with

²⁵ Youle-Decl. ¶88.

²⁶ Ex. 1022 (“Collins”), 1, Title; Youle-Decl. ¶89.

²⁷ Truvada®-Label, 21; Ex. 1026 (“Approval-Letter”), 1, 6.

²⁸ Truvada®-Label, 1; Ex. 1027 (“Viread®-Label”), xv; Ex. 1028 (“Emtriva®-Label”), 17.

²⁹ Ex. 1034 (“DeJesus”), 1038.

comparable efficacy.³⁰ Truvada also avoided the K65R mutation seen with TDF monotherapy.³¹

Within months of its approval, skilled persons recognized Truvada's advantages over other antiretroviral combinations:

- TDF+FTC provides synergistic antiretroviral activity relative to the activity exhibited by each agent alone.³²
- TDF+FTC avoids mutual interference (when two agents compete for the same natural nucleotide/nucleoside), which decreases antiretroviral activity and increases rates of adverse events and drug-related toxicities.³³

³⁰ Ex. 1035 (“Moyer”), 3 (fewer instances of anemia, neutropenia, diarrhea, fatigue, and depression in TDF+FTC-arm patients).

³¹ *Id.* 2-3; *see also* Ex. 1039 (“Brenner”), F12; Youle-Decl. ¶101.

³² Truvada®-Label, 3; Ex. 1031 (“Vela”), Conclusions; Ex. 1032 (“Dando”), 2076; Youle-Decl. ¶¶97, 204.

³³ Barreiro, 234, 236; Youle-Decl. ¶98.

- TDF+FTC have symmetric pharmacokinetic properties³⁴—a sufficiently long half-life to be suitable for once-daily dosing and no harmful interactions, which enables Truvada to provide a prolonged exposure with less frequent dosing.³⁵

Truvada was “an important step forward”³⁶ because its once-a-day fixed-dose tablet formulation “simplif[ies] treatment regimens by reducing the number of pills and times per day patients need to take them”³⁷ “enhanc[ing] therapy adherence, and thus, the likelihood of further improvement in the success rate.”³⁸ Truvada also demonstrated superior safety,³⁹ a particularly important feature for patients using antiretrovirals for extended periods in HIV prophylaxis or who were antiretroviral-naïve.⁴⁰ Experts accurately predicted Truvada would “soon be the

³⁴ Ex. 1033 (“Back”), S3-S4; Youle-Decl. ¶104.

³⁵ Back, S2-S4; Barreiro, 235; Youle-Decl. ¶¶103-04.

³⁶ Ex. 1041 (“De-Clercq-2005”), 265.

³⁷ Ex. 1040 (“FDA-2004”), 2 (quoting Acting FDA Commissioner).

³⁸ De-Clercq-2005, 265.

³⁹ Barreiro, 238; Youle-Decl. ¶98.

⁴⁰ Cal-PrEP, 11-12; CDC-ARV, 47-48; CDC-May1998, 9.

starting treatment of choice for drug-naïve HIV patients”⁴¹ and called it “a truly recommendable drug regimen for the treatment of antiretroviral-naïve patients.”⁴²

Consequently, by 2005, a skilled person would have considered Truvada (TDF+FTC) to be a preferred option for both HIV treatment and prophylaxis.⁴³

E. HIV Chemoprophylaxis

Before February 2005, combination antiretroviral prophylaxis (including with TDF+FTC) of HIV-uninfected individuals exposed to HIV was well-established.⁴⁴ PEP was known to effectively prevent HIV infection in settings including: (i) HIV/AIDS caregivers exposed via accidental needle-sticks; (ii) uninfected infants with HIV-positive mothers exposed during childbirth or through breastfeeding; (iii) individuals engaging in unprotected sex with an infected partner; (iv) intravenous drug users; and (v) sex workers.⁴⁵

⁴¹ Moyer, 3.

⁴² De-Clercq-2005, 250.

⁴³ Youle-Decl. ¶¶103, 163, 230.

⁴⁴ CDC-PEP, 8-9; Ex. 1042 (“Youle-JIAPAC”), 103-04; Ex. 1043 (“Gayle”), 4-5; Ex. 1044 (“Chase”), 2.

⁴⁵ Youle-Decl. ¶¶111-14.

PEP regimens maintain a persistent concentration of antiretrovirals in the patient, which suppresses the CD4+ cell-mediated replication of HIV after an exposure and thereby prevents establishment of the infection.⁴⁶ Before 2005, single-agent TDF-based regimens showed protective effects in animal testing, which reinforced the viability of using TDF in HIV prophylaxis.⁴⁷ And within months of Truvada’s approval in 2004, guidelines from CDC and others endorsed it as a preferred agent for both post- and pre-exposure HIV prophylaxis.⁴⁸

V. THE ’333 PATENT

A. Person of Ordinary Skill in the Art

A person of ordinary skill in the art (“skilled person”) would have been an individual familiar with treatment and prophylaxis of HIV or similar viruses in individuals in a clinical and/or pre-clinical setting. The knowledge held by such a person would have resulted from that person’s education, training and experience,

⁴⁶ *Id.* ¶122; Janeway, 458-59.

⁴⁷ Tsai-1998, 4265, 4271 (calling TDF “PMPA,” *see* Youle-Decl. ¶81); Ex. 1045 (“Tsai-1995”), 1197, 1199 (same); Ex. 1046 (“Van Rompay-1998”), F81; Ex. 1047 (“Otten-2004”), 9772-74; Lifson, 2584, 2589.

⁴⁸ CDC-PEP, 8-10; Cal-PrEP, 11.

which would have included, for example, either an M.D. or an advanced degree in an allied field (e.g., microbiology, epidemiology, public health), along with 2-3 years of experience in those fields or in treating patients.⁴⁹

B. Summary of the Disclosure

The '333 Patent concerns methods for chemoprophylaxis of primate immune deficiency viruses by administering a “combination of antiretroviral agents.”⁵⁰ It suggests that “if the establishment of a retroviral could be blocked before the HIV burden expands into a self-propagating infection, an individual could avoid contraction of HIV.”⁵¹ The '333 Patent identifies known antiretrovirals used in highly active antiretroviral therapy (HAART) for use in its regimen, including NRTI and NtRTI formulations,⁵² and notes an “exemplary NtRTI prodrug” is

⁴⁹ Youle-Decl. ¶16.

⁵⁰ '333 Patent, 3:13.

⁵¹ *Id.* 1:47-49.

⁵² *See, e.g., id.* 5:21-25 (“With conventional NRTI and NtRTI formulations, currently approved for HAART....”); *id.* 5:60-67 (NRTIs); *id.* 6:1-9 (NtRTIs); §IV.B.

tenofovir disoproxil fumarate (TDF).”⁵³ It also indicates that subjects can be given any of a wide variety of other known antiretrovirals.⁵⁴

The ’333 Patent describes experiments in which macaques (primates) were given small doses of an engineered form of the simian immunodeficiency virus (SIV) containing components of HIV.⁵⁵ By February 2005, this was a well-known model for testing antiretroviral drugs for HIV prophylaxis.⁵⁶ The experimental results showed varying degrees of protection against infection.⁵⁷

C. Claim Construction

1. Representative Claims

Claims 1 and 12 are the independent claims; each defines a method with the same two operative steps:

- (a) selecting an uninfected primate host or an uninfected human (i.e., “a primate host not infected with the immunodeficiency retrovirus”

⁵³ ’333 Patent, 4:61-64; 1:58-62.

⁵⁴ *Id.* 6:10-24.

⁵⁵ *Id.* 7:42-8:10.

⁵⁶ *See, e.g.*, Otten-2004, 164, 166; Ex. 1048 (“Li”), 639, 642; Youle-Decl.

¶¶211, 50.

⁵⁷ ’333 Patent, 9:47-10:21.

(Claim 1) or “an uninfected human that does not have the self-replicating infection” (Claim 12)) and

- (b) administering to that subject “a combination comprising: (i) a pharmaceutically effective amount of emtricitabine [FTC]...and (ii) a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate [TDF]” (Claims 1 and 12).

Both claims specify that TDF+FTC “is administered orally, subcutaneously or vaginally.”

Despite having identical operative steps, the objective and desired results of the claimed methods are phrased differently:

<i>Claim 1</i>	<i>Claim 12</i>
A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:	A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:
[operative steps, including oral, subcutaneous, or vaginal administration]	[operative steps, including oral, subcutaneous, or vaginal administration]

wherein the combination is <u>administered prior to the exposure</u> of the primate host to the immunodeficiency retrovirus,	
thereby protecting the primate host from infection with the immunodeficiency retrovirus.	thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human.

2. Proposed Constructions

With four exceptions, the terms used in the claims require no interpretation.

- a. “[P]rotecting a primate host from a self-replicating infection” (Claims 1-11) / “[I]nhibiting establishment of a...self-replicating infection” (Claims 12-17)

The preamble of Claim 1 specifies “[a] process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus,” while that of Claim 12 specifies “[a] process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human.” Both repeat the substance of their preambles after reciting their “selecting” and “administering” steps; Claim 1 states “thereby protecting the primate host from infection with the immunodeficiency retrovirus...” while Claim 12 states “thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human...”

A preamble is not limiting if “the body of the claim sets out the complete invention, and the preamble is not necessary to give ‘life, meaning and vitality’ to the claim.”⁵⁸ Also, claim language specifying the result of performing a therapeutic method is routinely found to not require that outcome in every patient, but is only the desired result of treatment.⁵⁹ And simply reciting what inherently results from performing the steps of a known therapeutic method cannot render novel a claim specifying those same steps.⁶⁰

Here, the preambles of Claims 1 and 12 do not alter how the operative steps of each claimed method are to be performed. Instead, the “selection” and “administration” steps in each claim define the complete process. Reciting the results of performing these operative steps in “thereby” clauses likewise does not limit the scope of these claims.

The specification reinforces these conclusions. For example, it states that “‘protection’ as used in the context of a host primate response to an

⁵⁸ *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1373-74 (Fed. Cir. 2001).

⁵⁹ *See, e.g., id.* 1375-76.

⁶⁰ *See, e.g., In re Montgomery*, 677 F.3d 1375, 1381-82 (Fed. Cir. 2012).

immunodeficiency virus [HIV] challenge is defined by the host primate being serologically negative and negative in response to a polymerase chain reaction (PCR) testing for viral genome.”⁶¹ The specification, however, does not suggest these tests alter how the operative steps of the method are to be performed.

Instead, it suggests that “protection” results from administering any combination of an NRTI and an NtRTI.⁶² Moreover, the specification indicates that known FDA-approved antiretroviral agents are to be used as is—it does not suggest altering the dose of the agents or using a unique pattern of administration.⁶³ Given that the degree of viral suppression of these different agents varies widely,⁶⁴ and that the

⁶¹ ’333 Patent, 4:8-12. A host is “serologically negative” if the quantity of antiviral antibodies in a sample from the host is lower than a threshold value indicative of a “negative” result. Youle-Decl. ¶166. A negative response in PCR testing for the viral genome is when the quantity of viral DNA in a sample from the host is below a value indicative of a “negative” result. *Id.* ¶¶166-67.

⁶² ’333 Patent, 2:14-19; 4:32-64, 5:60-6:9.

⁶³ *Id.* 6:25-46.

⁶⁴ *See* Youle-Decl. ¶¶83, 85, 88, 101.

experimental examples show varying degrees of protection for even a subset of those agents,⁶⁵ “protection” must necessarily encompass a range of outcomes.

The same conclusion holds for “inhibiting establishment.” The specification nowhere defines or uses this phrase. Instead, it portrays “establishment” as the stage of progression of an HIV infection when it becomes “a self-propagating” or “self-replicating retroviral” infection.⁶⁶ None of its passages addressing “establishment” proposes altering performance of the operative steps of Claim 12, and the specification reports varying degrees of success in preventing establishment of infections.⁶⁷ “Inhibiting establishment” thus does not require success in every individual, but is simply identifying the objective of the method.

⁶⁵ See, e.g., ’333 Patent, 9:58-60 (“Treatments of Groups 1-3 are all protective to a degree with a clear dose-response relationship being observed.”) (emphasis added).

⁶⁶ *Id.* 1:47-49 (“self-propagating”), 4:65-5:2 (“self-replicating”); see also *id.* 1:20-21.

⁶⁷ See, e.g., *id.* 9:58-60; footnote 64, *supra*.

Consequently, the preamble and “thereby” clauses in Claims 1 and 12 are non-limiting—each specifies only an intended result of the process; neither requires 100% inhibition or prevention in any particular individual.

b. “[S]elf-replicating infection” (Claims 1 and 12)

All the claims use the phrase “self-replicating infection.”⁶⁸ There is no express definition of this phrase in the patent disclosure, and it does not have a uniform scientific meaning.⁶⁹

As used in the specification, “self-replicating infection” refers to a point in time after an HIV exposure when the body’s immune system alone cannot prevent progression of the HIV infection.⁷⁰ That was known to occur about three days (~72 hours) after an exposure, which corresponds to when infected CD4+ cells are

⁶⁸ If the Board determines the preambles and “thereby” clauses are not limiting, it need not construe “self-replicating infection.”

⁶⁹ HIV does not “self-replicate”—it enters cells and induces them to produce additional copies of HIV virions. *See supra* §IV.A.

⁷⁰ Youle-Decl. ¶¶187-88.

being produced faster than the immune system can destroy them.⁷¹ Consistent with this, the '333 Patent identifies the transition to a self-replicating infection as occurring “within a few days” and explains at that point HIV virions are “self-replicating into a retroviral titer detectable in host blood serum.”⁷²

A “*self-replicating infection*” thus means “*an HIV infection that can no longer be suppressed solely by the host’s immune system.*”

c. “[P]rior to the exposure” / “prior to a potential exposure” / “following potential exposure”

The claims use a variety of phrases (or none) to specify when a combination of an NRTI and an NtRTI is to be administered relative to an “exposure”:

- Independent Claim 1 specifies administration is “prior to the exposure”;
- Independent Claim 12 imposes no timing requirement;
- Claim 10 specifies that administration is “daily for several days, weeks or months both before and after an exposure”;
- Claim 13 specifies administration is “prior to a potential exposure”; and

⁷¹ See, e.g., Haase-2005, 783-84; Ex. 1065 (“Fauci-1996”), 654; CDC-PEP, 8 (recommending treatment within 72 hours of exposure); Youle-Decl. ¶¶53-54.

⁷² '333 Patent, 1:43-47.

- Claim 16 specifies administration “following potential exposure.”

The ’333 Patent uses “exposure” to refer to HIV viral particles being introduced into an individual in a manner that can result in infection.⁷³

The ’333 Patent recognizes that certain populations of individuals will experience repeated exposures to HIV, observing that prophylaxis is “particularly well suited for a human engaging in a sporadic behavior likely to bring the person into retroviral exposure.”⁷⁴ The ’333 Patent thus recognizes what was well-known in 2005—certain “high risk” populations of uninfected individuals engage in activities that cause them to be repeatedly exposed to HIV over a defined period.⁷⁵

The ’333 Patent also recognizes that the primary benefit of PrEP is to reduce the rate of new HIV infections in a community, explaining it provides an “epidemiological advantage...in controlling the outbreak and spread of a retrovirus within a population” when provided “prophylactically to high-risk persons such as sex workers....”⁷⁶ The skilled person would recognize this epidemiological goal

⁷³ *Id.* 3:16-23, 28-32.

⁷⁴ *Id.* 5:30-32 (emphasis added).

⁷⁵ Cal-PrEP, 1; Youle-Decl. ¶144.

⁷⁶ ’333 Patent, 5:48-53 (emphasis added).

may not be realized even though the regimen will prevent HIV infection in an individual who follows it.⁷⁷

The '333 Patent also distinguishes “the exposure” from the “first exposure” of the uninfected individual to HIV—only the first HIV exposure is the “initial exposure.”⁷⁸ None of the claims uses the terms “initial” or “first” or otherwise requires agents to be administered before the first/initial “exposure.” Instead, they use the words “the exposure” or “a potential exposure,” thus indicating administration of antiretroviral agents can occur after an earlier HIV exposure, as long as (i) the earlier exposure did not result in an HIV infection (i.e., the individual remains “uninfected”), and (ii) administration occurs before a future exposure.

Claim 12 makes no reference to the timing of an HIV exposure relative to administration, while Claims 13 and 16 specify administration before or after a “potential” exposure, respectively. The ordinary meaning of “potential” is that an

⁷⁷ Youle-Decl. ¶¶106-07, 253.

⁷⁸ *See, e.g.*, '333 Patent, 1:67-2:3; 3:34-37.

event may, but may not necessarily, occur.⁷⁹ Claims 12, 13 and 16, thus, do not require an HIV exposure to actually occur after administration of the antiretroviral agents, which aligns with the method being prophylactic in nature.

Consequently, each of Claims 1, 12, 13 and 16 encompasses a process whereby at least one NRTI and one NtRTI are administered after an HIV exposure of the individual that did not result in an infection. Moreover, only Claim 1 affirmatively requires an administration to precede an actual HIV exposure, with Claim 10 additionally requiring an administration after an exposure.⁸⁰

VI. PRECISE REASONS FOR RELIEF REQUESTED

A. Cal-PrEP and CDC-PEP Are Prior Art to the Claims

The '333 Patent claims priority to provisional application 60/764,811, filed February 3, 2006. The prior art used in the grounds (Cal-PrEP and CDC-PEP) was published more than a year prior to that date (i.e., before February 3, 2005).

⁷⁹ Ex. 1122 (“Random House Dictionary”), 1514 (defining “potential” as “possible, as opposed to actual”).

⁸⁰ See *SanDisk Corp. v. Kingston Tech. Co.*, 695 F.3d 1348, 1360 (Fed. Cir. 2012).

1. Cal-PrEP (Ex. 1011)

Cal-PrEP bears a publication date of November 2004.⁸¹ A December 8, 2004 archive of the website “www.aidspartnershipca.com” provides access to the Cal-PrEP document,⁸² and archived pages of that website announced Cal-PrEP’s availability as early as November 30, 2004.⁸³ Archives of another website (www.uclaisap.org) as early as December 21, 2004 likewise provide access to the Cal-PrEP document⁸⁴ and announced Cal-PrEP’s availability by November 28, 2004.⁸⁵ The Cal-PrEP authors also testified that Cal-PrEP was disseminated to the public starting in November 2004.⁸⁶

2. CDC-PEP (Ex. 1012)

CDC-PEP was published on January 21, 2005 in Volume 54, No. RR-2 of the CDC periodical Morbidity and Mortality Weekly Report Recommendations

⁸¹ Cal-PrEP, 2.

⁸² Ex. 1108 (“Wayback-Decl.”), 6-46.

⁸³ *See* Ex. 1126; *see also* Ex. 1127.

⁸⁴ Wayback-Decl., 47-87.

⁸⁵ *Id.* 170-71.

⁸⁶ Ex. 1103 (“Szekeres-Decl.”) ¶5; Ex. 1129 (“Coates-Decl.”) ¶10.

and Reports (MMWR-RR) on January 21, 2005.⁸⁷ MMWR-RR has been an official “report[] to CDC by state health departments” since prior to 1990.⁸⁸ MMWR-RR issues are published by CDC’s Coordinating Center for Health Information and Service, “officially released to the public” and “available free of charge.”⁸⁹

CDC-PEP was publicly disseminated before February 3, 2005. A CDC website archive of past issues of MMWR-RR lists the date of publication of Vol. 54(RR-2) as January 21, 2005.⁹⁰ The Internet Archives also captured the MMWR webpage announcing the availability of CDC-PEP on January 21, 2005.⁹¹ CDC-PEP also was available in libraries at least as early as January 28, 2005.⁹² MMWR-RR publication staff also represented to Petitioner’s counsel that CDC-

⁸⁷ Cal-PrEP, cover-1.

⁸⁸ *Id.* back-cover-2; Ex. 1139 (“Wayback-Decl.-II”), 6 (volumes of MMWR-RR from Volume 39, with publications dating from 1990-2003).

⁸⁹ CDC-PEP, back-cover-2.

⁹⁰ Ex. 1124 (“CDC-Archive”), 3.

⁹¹ Wayback-Decl.-II, 8.

⁹² Ex. 1128 (“UCSD-Decl.”) ¶8.

PEP was made available on their website as from January 21, 2005,⁹³ and the CDC webpage announcing CDC-PEP indicates the webpage was last reviewed and converted on January 11, 2005 (below), which matches the metadata of the CDC-PEP file sent to Petitioner's counsel by MMWR-RR publication staff.⁹⁴



B. Cal-PrEP and CDC-PEP Provide Enabling Descriptions

To anticipate, a prior art reference must provide an enabling disclosure. Well-settled law holds that a prior art reference provides an enabling disclosure of a therapeutic method if it describes administering the same agent(s) in the claim,

⁹³ Ex. 1140 (“Kushan-Decl.”) ¶¶6-11.

⁹⁴ Ex. 1125 (“CDC-2005 web”), 25; Kushan-Decl. ¶¶8-10.

even without proof that doing so provided the specified therapeutic effect⁹⁵ and even if the method was not ever performed.⁹⁶

Here, Cal-PrEP and CDC-PEP each describe a method of prophylactically administering antiretroviral drugs including Truvada to individuals who are not infected with HIV in order to prevent establishment of HIV infections in those individuals. Cal-PrEP and CDC-PEP thus each teach administering the same two agents—TDF with FTC—in their same, FDA-approved amounts (200 mg FTC and 300 mg TDF) to individuals confirmed to be HIV-negative to prevent HIV infections. Following the methods described in Cal-PrEP and CDC-PEP thus necessarily yields the results specified in the claims of the '333 Patent, as the same

⁹⁵ *Bristol-Myers*, 246 F.3d at 1378 (prior art showing performance of a claimed method need not report desired therapeutic result); *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005) (prior art need not report results inherent to process); *In re Gleave*, 560 F.3d 1331, 1335-36 (Fed. Cir. 2009) (“a prior art reference need not disclose ‘proof of efficacy’ to anticipate the claim.”) (citation omitted).

⁹⁶ *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003) (prior art anticipates if it provides enabling description of process).

two operative steps in these various claims are described in these references. Each of Cal-PrEP and CDC-PEP also provides extensive details about their methods along with citations to literature to support performing them, and thereby provide fully enabling disclosures of those methods.

C. Claims 1-18 Are Anticipated by Cal-PrEP

1. Overview of Cal-PrEP

Cal-PrEP describes a method of prophylactically administering antiretroviral drugs to “high-risk” individuals who are not infected with HIV before they have an actual or potential exposure to HIV to prevent infection:

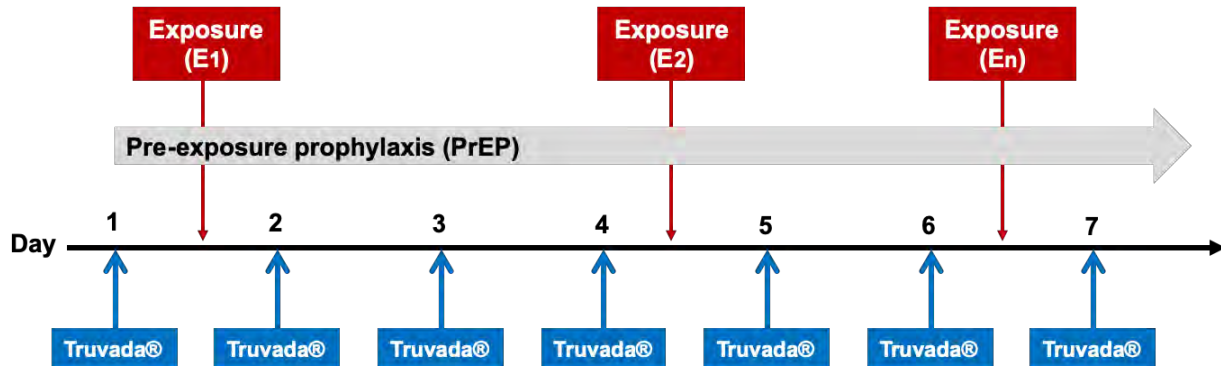
Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection. PrEP should be distinguished from postexposure prophylaxis (PEP), in which an individual takes ARVs soon after a potential HIV exposure with the goal of reducing the likelihood of infection.⁹⁷

Cal-PrEP indicates that TDF is the most suitable NRTI to use in PrEP and identifies Truvada as one of two TDF-based drug products to use in PrEP.⁹⁸

⁹⁷ Cal-PrEP, 1, 3 (same).

⁹⁸ *Id.* 11.

Cal-PrEP's regimen when followed by a high-risk individual who has multiple HIV exposures ($E_1, E_2, \dots E_n$) is illustrated below:⁹⁹



Cal-PrEP explains that its regimen was based on prior experiences with chemoprophylaxis.¹⁰⁰ It summarizes prophylactic use of antiretrovirals to prevent HIV infections following exposures in occupational (e.g., healthcare worker) as well as non-occupational (e.g., sexual and drug use) settings,¹⁰¹ and discusses experiences using antiretrovirals to prevent transmission of HIV from an infected mother to her uninfected child through birth or breastfeeding, observing the latter

⁹⁹ Youle-Decl. ¶¶164-65.

¹⁰⁰ Cal-PrEP, 4.

¹⁰¹ *Id.* 4, 8-11.

“has been shown to dramatically reduce the odds for perinatal HIV transmission.”¹⁰²

Cal-PrEP also describes initiated or planned clinical trials for evaluating PrEP regimens in different cohorts of at-risk individuals.¹⁰³ It observes that, from an epidemiological perspective, whether PrEP will be a success (i.e., whether it reduces rates of infection in a community) depends on several factors, including the risk-taking nature of individuals,¹⁰⁴ whether PrEP alters risk-taking,¹⁰⁵ whether PrEP is supported by healthcare providers and communities,¹⁰⁶ and potential barriers to access to antiretrovirals.¹⁰⁷

Importantly, a skilled person would not have understood these epidemiological questions about whether PrEP will reduce rates of infection in a

¹⁰² *Id.* 5.

¹⁰³ *Id.* 6-11.

¹⁰⁴ *Id.* 19-20.

¹⁰⁵ *Id.* 20-21.

¹⁰⁶ *Id.* 22-23.

¹⁰⁷ *Id.* 24-26.

community as casting doubt that a PrEP regimen based on Truvada (TDF+FTC) would be effective in any individual who followed it properly.¹⁰⁸

2. Independent Claims 1 and 12

Cal-PrEP anticipates Claims 1 and 12 of the '333 Patent because it describes selecting an HIV-uninfected (HIV-seronegative) individual and administering to that individual pharmaceutically effective amounts of TDF+FTC in the form of Truvada prior to an HIV exposure.

a. Preambles

Cal-PrEP describes administering antiretroviral drugs to HIV-uninfected individuals before they are exposed to HIV in order to prevent an infection: “Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection.”¹⁰⁹ While the preambles of Claims 1 and 12 are not limiting, Cal-PrEP nonetheless describes a process that meets each.

¹⁰⁸ Youle-Decl. ¶¶150, 252; Cal-PrEP, 4; Tsai-1998, 4265.

¹⁰⁹ Cal-PrEP, 1 (emphasis added); Youle-Decl. ¶¶165-67.

- b. “[S]electing” “a primate host not infected with the immunodeficiency retrovirus” [1] / “an uninfected human that does not have the self-replicating infection” [12]

Cal-PrEP teaches administering antiretroviral agents to HIV-uninfected individuals (“*primate host*”/“*human*”).¹¹⁰ It indicates that potential candidates are to be screened for eligibility for PrEP, and must be confirmed to be HIV-negative before beginning PrEP (“Planned studies of PrEP will screen for HIV infection prior to enrollment.”)¹¹¹ Cal-PrEP also indicates that being HIV-positive is a basis for excluding individuals from PrEP clinical trials conducted in the 2004/2005-time frame.¹¹² Cal-PrEP thus teaches the “selecting” step of Claims 1 and 12.

- c. “[A]dministering...a combination comprising: (i) a pharmaceutically effective amount of emtricitabine...and (ii) a pharmaceutically effective amount of tenofovir or [TDF]” “wherein the pharmaceutically effective

¹¹⁰ Cal-PrEP, 3; Youle-Decl. ¶¶165, 168.

¹¹¹ Cal-PrEP, 13.

¹¹² *Id.* (“Planned studies of PrEP will screen for HIV infection prior to enrollment....”). A “seronegative” individual is HIV-negative based on a serum antibody test. *Id.* 11; Youle-Decl. ¶166.

amount...is administered orally, subcutaneously or vaginally” “prior to the exposure” [1]

Cal-PrEP describes administering antiretroviral agents to HIV-uninfected individuals prior to an actual or potential exposure to HIV in order to prevent an HIV infection. As it states:

PrEP involves the use of antiretroviral drugs (ARVs) by an individual prior to potential HIV exposure, in order to reduce the likelihood of HIV infection.¹¹³

Cal-PrEP identifies the properties of antiretroviral agents that make them well-suited for use in PrEP, stating:

To be ideal for use as PrEP, a drug should be potent, able to be dosed once daily, have a favorable toxicity profile, and not promote development of high-level viral resistance based on a single mutation. In addition, drugs whose mechanisms of action focus on pre-integration phases of the viral life cycle (prior to completion of effective viral

¹¹³ Cal-PrEP, 3 (emphasis added); *see also id.* 1 (“Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection.”).

integration into host cell DNA) are, at least in theory, likely to be more effective than those that focus on post-integration.¹¹⁴

Cal-PrEP then explains that FTC and TDF have these features. Regarding FTC, it explains:

Of the NRTIs, several drugs have characteristics that may limit their potential as PrEP candidates. Lamivudine (3TC) and emtricitabine (FTC) cause few toxicities and may be taken once daily, but both are susceptible to a single-point mutation at codon 184 that confers resistance, especially when taken alone.¹¹⁵

Cal-PrEP's observation that FTC monotherapy can lead to resistance would have been understood by the skilled person as indicating FTC should be co-administered with another antiretroviral.¹¹⁶

Cal-PrEP then states that TDF is the “most suitable” NRTI for use in PrEP regimens, explaining that it provides the best combination of features for use in

¹¹⁴ *Id.*, 11.

¹¹⁵ *Id.* (emphasis added).

¹¹⁶ Youle-Decl. ¶¶163, 227; Saag, 29.

PrEP regimens and stating, *inter alia*, that it is “a relatively safe agent with few adverse side-effects and interactions with other drugs.”¹¹⁷

Cal-PrEP specifically identifies Truvada as one of two TDF-based drug products that can be used in PrEP, stating:

Tenofovir disoproxil fumarate (TDF) is the NRTI that is currently most suitable for use as PrEP. TDF is potent, can be dosed once daily, and has a relatively favorable toxicity profile....TDF was approved by FDA in 2001 to treat HIV infection and is formulated as a once-daily, 300 mg oral tablet (Viread®); a once-daily, fixed-dose combination tablet of TDF and emtricitabine (Truvada™) was approved in August 2004 (both Gilead Sciences, Inc., Foster City, CA).¹¹⁸

Cal-PrEP also recommends use of FDA-approved antiretroviral products,¹¹⁹ which a skilled person would understand to mean that such drugs should be used in their FDA-approved doses.¹²⁰ Truvada contains FDA-approved doses of 200 mg

¹¹⁷ Cal-PrEP, 11-12.

¹¹⁸ *Id.* 11 (emphasis added).

¹¹⁹ *Id.* 10-11.

¹²⁰ Youle-Decl. ¶237.

FTC and 300 mg TDF,¹²¹ the same doses in the FDA-approved single-agent formulations of TDF (Viread) and FTC (Emtriva). When Truvada is administered to a human, it will suppress HIV viral replication and exhibit potent antiviral activity against HIV.¹²² By doing so, Truvada (as well as each of its constituent agents) not only effectively treats an HIV infection but prevents establishment of an HIV infection.¹²³

The '333 Patent does not identify what amounts of TDF and FTC constitute a “pharmaceutically effective amount” of either agent, stating instead that doses should be selected to “create a therapeutic concentration of the active composition at the situs of retrovirus initial founder cell population infection prior to viral exposure.”¹²⁴ Clinical evidence demonstrates that occurs when Truvada, with its FDA-approved doses of 300 mg of TDF and 200 mg of FTC, is administered.¹²⁵ The '333 Patent also observes that “[p]referably, NRTI and NtRTI prophylactic

¹²¹ Truvada®-Label, 21; Youle-Decl. ¶¶92.

¹²² See §IV.D; CDC-PEP, 8; Truvada®-Label, 2-3; Youle-Decl. ¶¶95.

¹²³ See Youle-Decl. ¶¶92, 237, 242; Dumond-PRN, 14-15.

¹²⁴ '333 Patent, 6:26-29.

¹²⁵ Truvada®-Label, 1; Viread®-Label, i; Emtriva®-Label, 5.

dosing according to the present invention uses as a starting point the maximal recommended tolerated dosing levels for the given active agent combination associated with HAART treatment protocols.”¹²⁶

Cal-PrEP also teaches “*orally*” administering TDF+FTC, given that Truvada is a tablet designed for oral ingestion.¹²⁷

Cal-PrEP thus teaches orally administering Truvada to an uninfected individual before an HIV exposure, which results in that individual being given pharmaceutically effective amounts of TDF and FTC as Claims 1 and 12 specify.

d. “Thereby” Clauses

While the “thereby” clauses of Claims 1 and 12 are not limiting (see §V.C.2.a), Cal-PrEP necessarily satisfies each. Cal-PrEP teaches administering Truvada to an HIV-uninfected individual before an HIV exposure, which results in oral administration to that individual of the same “pharmaceutically effective” amounts of TDF and FTC that the claims and ’333 patent disclosure say will protect the host from an HIV infection or will inhibit establishment of infection.

¹²⁶ ’333 Patent, 6:41-46.

¹²⁷ Cal-PrEP, 11; Truvada®-Label, 1 (“TRUVADA Tablets are for oral administration.”).

Consequently, administering Truvada as Cal-PrEP teaches will both “*protect*” the individual from an HIV infection (“*a self-replicating infection...*”) and will “*inhibit establishment*” of an HIV infection as Claims 1 and 12 specify.

As Cal-PrEP describes every element of Claims 1 and 12, it anticipates both claims.

3. Claims 13 and 16

Claims 13 and 16 depend from Claim 12. Claim 13 specifies “*the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus*” while Claim 16 specifies administration “*following potential exposure of the primate host to the human immunodeficiency retrovirus.*”

As noted in §V.C.2.c, a “potential exposure” does not require an actual HIV exposure to occur. Regardless, the PrEP regimen described in Cal-PrEP teaches providing antiretroviral therapy to uninfected individuals before and after an actual or potential HIV exposure. First, Cal-PrEP explains that “PrEP involves the use of antiretroviral drugs (ARVs) by an individual prior to potential HIV exposure, in order to reduce the likelihood of HIV infection.”¹²⁸ Second, Cal-PrEP teaches that

¹²⁸ Cal-PrEP, 3 (emphasis added).

its PrEP regimen is to be followed for an extended period of time (e.g., 9 to 24 months)¹²⁹ by uninfected human subjects who, over that period, will engage in activities that cause multiple actual or potential HIV exposures (e.g., sex workers, men who have sex with men (“MSM”), intravenous drug users).¹³⁰

Cal-PrEP thus teaches that HIV-uninfected high risk individuals on its regimen will be given doses of recommended TDF-based drugs (e.g., Truvada) on days that precede and follow days on which that individual is actually or potentially exposed to HIV, as Claims 13 and 16 specify, respectively.

4. Claims 2-3

Claim 2 specifies the primate host is an “*adult human*,” while Claim 3 specifies the primate host is a “*male adult primate host*.” Cal-PrEP indicates that candidates for prophylaxis include, *inter alia*, MSM, i.e., adult human males.¹³¹

¹²⁹ Cal-PrEP describes clinical trials in which individuals are to be given a daily administration of a TDF-based drug for periods between 9 to 24 months. Cal-PrEP, 7-9; Youle-Decl. ¶203.

¹³⁰ Cal-PrEP, 1; *see also infra* Figures in §VI.E.1.

¹³¹ Cal-PrEP, 4, 7, Table 1.

5. Claims 4 and 14

Claims 4 and 14 specify, respectively, that TDF+FTC are administered “*directly to a human in a combined single dosage formulation*” or “*into a single combination formulation.*” Truvada is a tablet containing both TDF+FTC that is administered orally to humans. Cal-PrEP thus teaches administration of a single combination of TDF+FTC as Claims 4 and 14 specify.¹³²

6. Claim 5

Claim 5 requires the “*immunodeficiency retrovirus*” to be a “*human immunodeficiency virus.*” Cal-PrEP proposes the use of PrEP for HIV.¹³³

7. Claim 6

Claim 6 specifies the “*human immunodeficiency virus (HIV) is HIV-1.*” The most prevalent strain of HIV in the U.S. in 2005 and today is HIV-1, with 99.9% of cases involving HIV-1.¹³⁴ Cal-PrEP focuses on Californians, and thus would be understood as teaching use of chemoprophylaxis of HIV-1 infections.¹³⁵

¹³² See *id.* 11.

¹³³ *Id.* 1.

¹³⁴ Ex. 1056 (“Torian”), 1334; Ex. 1057 (“CDC-Surveillance”), 986.

¹³⁵ Cal-PrEP, 2, 7 (Table 1); see Youle-Decl. ¶¶91, 141.

8. Claims 7 and 17

Claim 7 specifies a “*rectal and/or vaginal exposure of the primate host to the immunodeficiency retrovirus,*” while Claim 17 specifies the exposure “*comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.*”

Cal-PrEP explains that PrEP is “targeted to MSM, [and] female partners of MSM...”¹³⁶ It also describes use of PrEP in “high-risk, HIV-negative MSM” and “[f]emale commercial sex workers.”¹³⁷ Men within the MSM category are exposed to HIV rectally, orally, and through the reproductive organs, while women who are partners of MSM and female sex workers are exposed to HIV vaginally, orally, and rectally.¹³⁸ Thus, Cal-PrEP teaches use of HIV chemoprophylaxis to prevent HIV infection in one or more of the manners of exposure in Claims 7 and 17.

¹³⁶ Cal-PrEP, 1.

¹³⁷ *Id.* 8-9; *see also id.* 7 (Table 1).

¹³⁸ *See Youle-Decl.* ¶143.

9. Claim 8

Claim 8 specifies “*administering 200 milligrams (mg) of emtricitabine and 300 mg of tenofovir disoproxil fumarate to a human host.*” Cal-PrEP teaches use of Truvada in PrEP, which results in administration of 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate to the individual.¹³⁹

10. Claim 9

Claim 9 specifies that TDF+FTC is to be “*administered daily for several days, weeks or months.*” Because the claim is written with the disjunctive “or,” it encompasses administrations that last as few as “*several days.*”¹⁴⁰

Cal-PrEP describes PrEP regimens being tested in clinical studies in which TDF is administered to subjects for a period of 9 to 24 months.¹⁴¹ A skilled person would understand from Cal-PrEP’s description of these clinical trials that study participants will take the TDF drug (e.g., Truvada) daily for the specified period

¹³⁹ Truvada®-Label, 21.

¹⁴⁰ *SkinMedica, Inc. v. Histogen Inc.*, 727 F.3d 1187, 1199 (Fed. Cir. 2013).

¹⁴¹ Cal-PrEP, 8-9, 12 (“The PrEP studies described in Section II are providing participants with 300 mg TDF tablets (or placebo) to be taken once daily during the study period.”); Youle-Decl. ¶203.

(e.g., 9, 12 or 24 months).¹⁴² Cal-PrEP also explains that “individuals take PrEP throughout their sexual lifetimes.”¹⁴³

Cal-PrEP also indicates that FDA-approved antiretroviral products are to be used, and identifies two such products: Viread (TDF) and Truvada (TDF+FTC).¹⁴⁴ A skilled person would understand from Cal-PrEP that these products should be used in their FDA-approved forms.¹⁴⁵

Cal-PrEP thus anticipates Claim 9.

11. Claim 10

Claim 10 specifies the combination is “*administered daily for several days, weeks or months both before and after an exposure of the primate host to the immunodeficiency retrovirus,*” and, like Claim 9, encompasses administrations that last “*several days*” before and after an exposure.

¹⁴² Youle-Decl. ¶203.

¹⁴³ Cal-PrEP, 22; Youle-Decl. ¶145.

¹⁴⁴ Cal-PrEP, 11.

¹⁴⁵ *Id.*; Truvada®-Label, 20; Youle-Decl. ¶¶159, 201.

Cal-PrEP describes clinical trials in which antiretroviral agents are administered for extended periods (i.e., 9 to 24 months) to high-risk individuals.¹⁴⁶ Cal-PrEP justifies its PrEP regimen by reasoning that high-risk individuals are likely to engage in conduct that repeatedly exposes them to HIV during any particular period of time, and that if such individuals are on PrEP when those exposures occur, that will decrease the likelihood of infection.¹⁴⁷ When HIV exposures might occur after any individual's commencement of PrEP, and how frequently they may occur while that individual is on PrEP, will depend on that individual's conduct. Consistent with this, Cal-PrEP instructs that while patients are on the PrEP regimen, they are to be continuously counseled on ways to decrease high-risk activity, are to be repeatedly tested for HIV infection,¹⁴⁸ and are not to suspend taking antiretrovirals after an initial exposure.¹⁴⁹

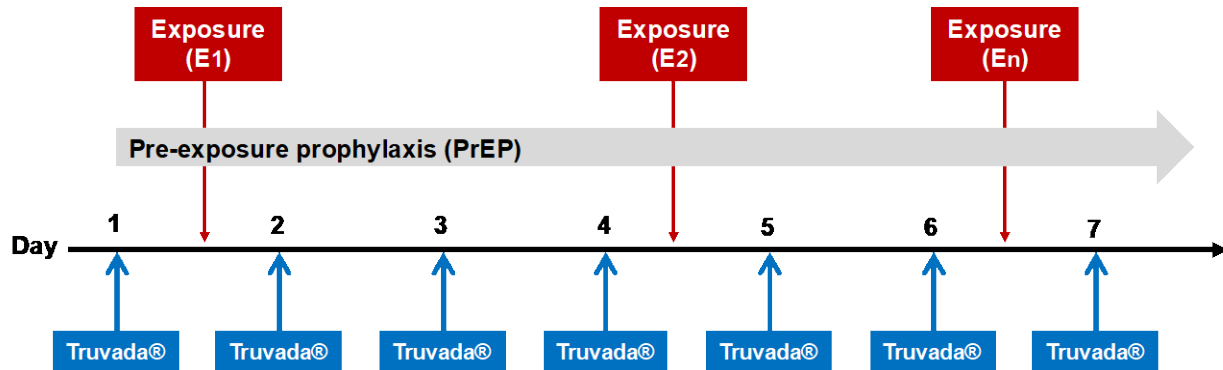
¹⁴⁶ Cal-PrEP, 8-9, 12.

¹⁴⁷ *Id.* 6-10; Youle-Decl. ¶149.

¹⁴⁸ Cal-PrEP, 9, 13-14; Youle-Decl. ¶260.

¹⁴⁹ Cal-PrEP, 8-9, 12 (“[T]ablets (or placebo) [are]to be taken once daily during the study period.”) (emphasis added); Youle-Decl. ¶¶149, 201, 203.

Cal-PrEP thus describes a regimen in which, relative to any of the daily administrations of antiretrovirals, some HIV exposures will occur in a high-risk individual several days before and several days after that HIV exposure (as illustrated below).¹⁵⁰



Cal-PrEP also cites Tsai-1995, a study in which antiretrovirals were administered for multiple days, both before and after exposure to the virus.¹⁵¹

Cal-PrEP thus teaches administration of Truvada (TDF+FTC) to high-risk individuals that will occur several days before and several days after any individual HIV exposure, as Claim 10 specifies.

¹⁵⁰ Youle-Decl. ¶164.

¹⁵¹ Tsai-1995, 1197.

12. Claims 11 and 15

Claims 11 and 15 each specify that the administration of TDF+FTC results in “*an absence of persistent viremia and seroconversion.*”

The PrEP regimen described in Cal-PrEP is designed to prevent HIV infection after exposure in an uninfected human subject.¹⁵² Before February 2005, physicians considered the absence of viremia and seroconversion to demonstrate an absence of HIV infection.¹⁵³ Viremia was conventionally determined by evaluating the presence or absence of HIV in the patient (i.e., “viral load”), while seroconversion was determined by detection of a minimum quantity of anti-HIV antibodies in the patient’s blood.¹⁵⁴

Cal-PrEP teaches testing for viremia and seroconversion to determine if a subject has become infected with HIV under PrEP. For example, it points to the absence of viremia and seroconversion in animals exposed to SIV as evidence that PrEP was effective to prevent infection.¹⁵⁵ A skilled person would understand

¹⁵² See *supra* §VI.C.1.

¹⁵³ Youle-Decl. ¶¶183, 166-67.

¹⁵⁴ *Id.*; see also Ex. 1110 (“Fearon”), 26-29.

¹⁵⁵ Cal-PrEP, 8, n.32-33 (citing Tsai-1995, Van-Rompay-1998).

from Cal-PrEP that negative test results for persistent viremia and seroconversion indicates successful prophylaxis.¹⁵⁶

D. Claims 12-17 Are Anticipated by CDC-PEP

1. Overview of CDC-PEP

CDC-PEP describes a regimen of daily administrations of combinations of antiretroviral agents for an extended period following an HIV exposure to prevent an HIV infection:

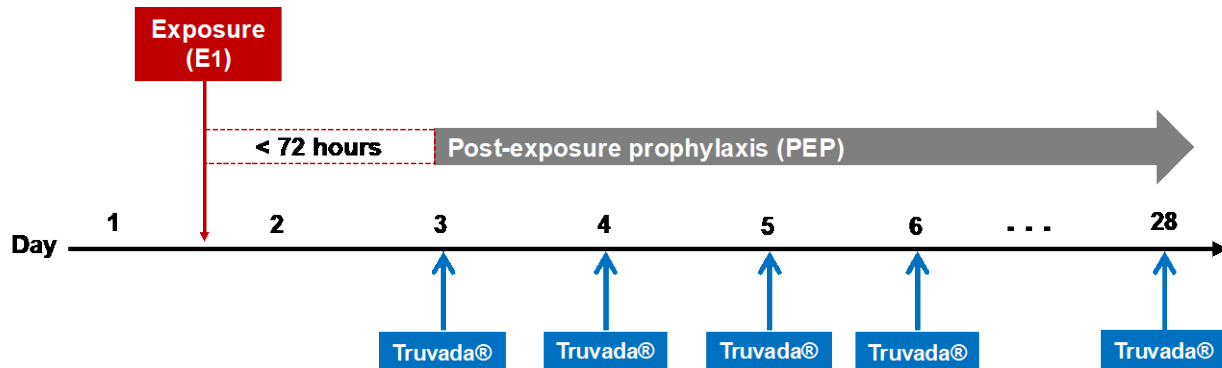
A 28-day course of HAART¹⁵⁷ is recommended for persons who have had nonoccupational exposure to blood, genital secretions, or other potentially infected body fluids of a person[] known to be HIV infected.¹⁵⁸

¹⁵⁶ Youle-Decl. ¶¶166-67.

¹⁵⁷ Highly active antiretroviral therapy (HAART) involves daily administrations of two or more antiretroviral agents. See CDC-PEP, 8; '333 Patent, 5:17-25.

¹⁵⁸ CDC-PEP, 8.

CDC-PEP identifies TDF+FTC as one of two “preferred” backbone combinations to use in PEP, and notes that Truvada is an oral formulation containing 300 mg of TDF and 200 mg of FTC.¹⁵⁹ PEP is illustrated below:¹⁶⁰



CDC-PEP indicates the PEP regimen is based on “[e]vidence from animal studies and human observational studies [which] demonstrate that [PEP] administered within 48-72 hours and continued for 28 days might reduce the risk for acquiring HIV infection after mucosal and other nonoccupational exposures.”¹⁶¹ CDC-PEP also identifies non-clinical and clinical evidence supporting the efficacy of PEP in HIV prophylaxis:

¹⁵⁹ *Id.* 9-10.

¹⁶⁰ Youle-Decl. ¶174.

¹⁶¹ CDC-PEP, 8.

[D]ata are available from animal transmission models, perinatal clinical trials, studies of health-care workers receiving prophylaxis after occupational exposures, and from observational studies.¹⁶²

CDC-PEP notes that PEP in an occupational setting “was associated with an 81% decrease in the risk for acquiring HIV.”¹⁶³

CDC-PEP encourages use of PEP “as soon as possible” after exposure, and no later than 72 hours after exposure, because “[t]he sooner []PEP is administered after exposure, the more likely it is to interrupt transmission.”¹⁶⁴ CDC-PEP also explains PEP is warranted despite side-effects of antiretrovirals, explaining:

Because HIV is an incurable transmissible infection that affects the quality and duration of life, HAART should be used to maximally

¹⁶² *Id.* 2.

¹⁶³ *Id.* 3.

¹⁶⁴ *Id.* 8 (“A 28-day course of HAART is recommended for persons who have had nonoccupational exposure...when the person seeks care within 72 hours of exposure.”); *see also id.* 9, 15 (“Accumulated data from animal and human clinical and observational studies demonstrate that antiretroviral therapy initiated as soon as possible within 48-72 hours ... and continued for 28 days might reduce the likelihood of transmission.”).

suppress local viral replication that otherwise might occur in the days after exposure and potentially lead to a disseminated, established infection.¹⁶⁵

CDC-PEP likewise observes that “[i]nitial concerns about severe side effects and toxicities have been ameliorated by experience with health-care workers who have taken PEP after occupational exposures.”¹⁶⁶

The use of combinations of antiretrovirals also was known to mitigate the risk of viral resistance.¹⁶⁷ In addition, physicians prefer backbones based on a single pill because they facilitate compliance, which is critically important in preventing HIV.¹⁶⁸

2. Claim 12

a. Preamble

As described in §V.C.2.a, the preamble of Claim 12 is not limiting. Regardless, CDC-PEP teaches that the purpose of commencing a PEP regimen is

¹⁶⁵ *Id.* 8.

¹⁶⁶ *Id.* 4.

¹⁶⁷ *Id.* 5; Youle-Decl. ¶¶222, 224, 116; Gerberding, 828.

¹⁶⁸ Youle-Decl. ¶103.

to prevent the HIV infection from being established in an individual exposed to HIV, and emphasizes its effectiveness depends on how rapidly after the exposure it is commenced.¹⁶⁹ That is consistent with the understanding that HIV infections become established in an individual approximately three days after the HIV exposure. CDC-PEP thus teaches the same objective as the preamble of Claim 12.

b. “[S]electing an uninfected human that does not have the self-replicating infection”

CDC-PEP teaches selecting individuals that are HIV-negative for receiving PEP, explaining that PEP is to be used in humans who have an “exposure [that] represents a substantial risk for HIV transmission (Figure 1) and when the person seeks care within 72 hours of exposure.”¹⁷⁰ A patient who is “at risk” does not yet have an established infection but may have been exposed to HIV.¹⁷¹ CDC-PEP

¹⁶⁹ CDC-PEP, 8 (“[P]EP administered within 48-72 hours and continued for 28 days might reduce the risk for acquiring HIV infection after mucosal and other nonoccupational exposures. The sooner [P]EP is administered after exposure, the more likely it is to interrupt transmission.”).

¹⁷⁰ *Id.*, 6, 8.

¹⁷¹ Youle-Decl. ¶43.

also teaches use of a “baseline” test to ensure the at-risk patient is not infected, followed by recurring testing to ensure that the prophylaxis is effective.¹⁷²

- c. “[A]dministering...a combination comprising: (i) a pharmaceutically effective amount of emtricitabine...and (ii) a pharmaceutically effective amount of tenofovir or [TDF]” “wherein the pharmaceutically effective amount...is administered orally, subcutaneously or vaginally”

CDC-PEP teaches that “[a] 28-day course of HAART is recommended for persons who have had nonoccupational exposure.”¹⁷³ CDC-PEP notes “no evidence indicates that any specific antiretroviral medication...is optimal,” but indicates certain regimens are “preferred.”¹⁷⁴ CDC-PEP then recommends two “NNRTI-based” backbone regimens: efavirenz plus either (i) lamivudine plus zidovudine or (ii) emtricitabine plus tenofovir.¹⁷⁵

¹⁷² CDC-PEP, 7, 12; Youle-Decl. ¶¶182-83.

¹⁷³ CDC-PEP, 8.

¹⁷⁴ *Id.* 8.

¹⁷⁵ *Id.* 9, Table 2.

TABLE 2. Antiretroviral regimens for nonoccupational postexposure prophylaxis of HIV infection

Preferred regimens

NNRTI*-based	Efavirenz [†] plus (lamivudine or emtricitabine) plus (zidovudine or tenofovir)
Protease inhibitor (PI)-based	Lopinavir/ritonavir (co-formulated as Kaletra) plus (lamivudine or emtricitabine) plus zidovudine

The word “plus” after efavirenz (an NNRTI) in Table 2 indicates this agent is to be combined with one of the two backbone regimens: either two NRTIs (lamivudine plus zidovudine) or one NRTI (emtricitabine) and one NtRTI (tenofovir).¹⁷⁶

Table 3 of CDC-PEP indicates that both backbones can be provided through administration of a single combination formulation, either: (i) “Combivir®” for the lamivudine plus zidovudine backbone or (ii) Truvada for emtricitabine plus tenofovir (in the form of TDF) backbone. CDC-PEP labels Truvada (TDF+FTC) one of two “preferred regimens” for prophylaxis,¹⁷⁷ specifying use of “1 tablet once daily 200 mg emtricitabine/300 mg tenofovir” in the form of Truvada.¹⁷⁸

¹⁷⁶ Youle-Decl. ¶176.

¹⁷⁷ CDC-PEP, 9, Table 2.

¹⁷⁸ *Id.* 10, Table 3; Youle-Decl. ¶¶171, 176.

TABLE 3. Highly active antiretroviral therapy medications, adult dosage, cost, and side effects

Medication	Adult dosage*	Cost (in dollars) for 4 weeks*	Side effects and toxicities
Combination tablets			
Lopinavir/ritonavir (Kaletra [®]) ⁵	3 tablets twice daily 400 mg lopinavir/100 mg ritonavir	650	Diarrhea, nausea, vomiting; asthenia; elevated transaminases; hyperglycemia; fat redistribution; lipid abnormalities; possible increased bleeding in persons with hemophilia; and pancreatitis
→ Zidovudine/lamivudine (Combivir [®])	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine	640	See following individual medications
Zidovudine/lamivudine/abacavir (Trizivir [®])	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine/ 300 mg abacavir	1,020	See following individual medications
Lamivudine/abacavir (Epzicom [®])	1 tablet once daily 300 mg lamivudine/600 mg abacavir	760	See following individual medications
→ Emtricitabine/tenofovir (Truvada [®])	1 tablet once daily 200 mg emtricitabine/300 mg tenofovir	800	See following individual medications

While CDC-PEP proposes use of a third ARV, it elsewhere explains that “[n]o evidence indicates that a three-drug HAART regimen is more likely to be effective than a two-drug regimen” in prophylaxis.¹⁷⁹ CDC-PEP also recommends use of only two agents—one NRTI and one NtRTI—in situations where the clinician or patient has concerns over the individual taking three antiretroviral agents.¹⁸⁰ Claim 12 encompasses administration of a third agent in addition to TDF and FTC by its use of “comprising” language.

A skilled person who follows CDC-PEP will administer Truvada *orally* to an HIV uninfected individual as required by the claims. Doing that orally administers to the individual the FDA-approved doses of 200 mg TDF and 300 mg

¹⁷⁹ CDC-PEP, 8.

¹⁸⁰ *Id.*, 8; Youle-Decl. ¶177.

FTC, which are pharmaceutically effective amounts of each agent.¹⁸¹ The '333 Patent acknowledges these amounts are effective in preventing HIV infection.¹⁸² CDC-PEP thus discloses the “administering” step of Claim 12.

CDC-PEP also teaches that commencing PEP using the recommended regimens as soon as possible after an exposure can prevent an HIV infection.¹⁸³ It credits animal studies and human clinical evidence as supporting this conclusion.¹⁸⁴ For example, it notes that prophylactic use of a less potent single-agent ARV (i.e., zidovudine) in a health-worker prophylaxis study “was associated with an 81% decrease in the risk for acquiring HIV.”¹⁸⁵

d. “Thereby” Clause

As explained in §V.C.2.a, Claim 12’s “thereby” clause is not limiting. Nevertheless, CDC-PEP discloses methods that meet this requirement. Most notably, because CDC-PEP teaches administering a daily oral dose of the same,

¹⁸¹ CDC-PEP, 10, Table 3; Youle-Decl. ¶¶174-75.

¹⁸² '333 Patent, 6:56-58, 7:44-60.

¹⁸³ CDC-PEP, 2, 8.

¹⁸⁴ *Id.* 8-9.

¹⁸⁵ *Id.* 3.

FDA-approved and pharmaceutically effective amounts of TDF+FTC as the claims, it must yield the same result specified in the claims.¹⁸⁶ CDC-PEP also repeatedly states that PEP regimens are effective in preventing HIV infection if commenced early enough after an exposure. CDC-PEP thus discloses the “thereby” clause of Claim 12.

3. Claims 13 and 16

Claims 13 and 16 specify that administration is to occur “*prior to*” or “*following*” a “*potential*” exposure, respectively. As explained in §V.C.2.c, a “potential” exposure does not have to actually occur. Both claims are anticipated for the same reason that Claim 12 is anticipated.

CDC-PEP also expressly teaches administration of TDF+FTC following potential non-occupational HIV exposure, such as unprotected sex, and thus anticipates Claim 16.¹⁸⁷

CDC-PEP further indicates that in a non-occupational setting, PEP is to be followed for at least a 28-day period.¹⁸⁸ CDC-PEP also explains that certain

¹⁸⁶ *Id.* 10, Table 3; Youle-Decl. ¶175.

¹⁸⁷ CDC-PEP, 8.

¹⁸⁸ *Id.*

categories of individuals engage in activity that may repeatedly expose them to HIV, and teaches that these “high-risk” individuals are to be counseled to refrain from such activities during the 28-day PEP regimen.¹⁸⁹ Such individuals, however, are likely to nonetheless engage in activities that may expose them to HIV during the 28-day PEP period.¹⁹⁰ Such individuals who have remained HIV-negative after a prior exposure will be administered TDF+FTC prior to the next (i.e., “a”) potential exposure as Claim 13 specifies.

4. Claim 14

CDC-PEP teaches use of “Emtricitabine/tenofovir (Truvada)” as one of its two preferred PEP backbone regimens.¹⁹¹ Truvada is formulated as a single dosage oral tablet.¹⁹² CDC-PEP thus describes use of TDF+FTC that “*is compounded into a single combination formulation.*”

¹⁸⁹ *Id.* 8-9, 12; Youle-Decl. ¶180.

¹⁹⁰ Youle-Decl. ¶135.

¹⁹¹ CDC-PEP, 10, Table 3.

¹⁹² Truvada®-Label, 1; Youle-Decl. ¶92.

5. Claim 15

CDC-PEP teaches use of HIV antibody tests (which assess seroconversion) and viral load tests (which assess persistent viremia) after the conclusion of prophylaxis to confirm that an infection has not occurred.¹⁹³ “HIV viral load” testing and “HIV antibody testing” are accepted ways of confirming a lack of persistent viremia and an absence of seroconversion.¹⁹⁴ Table 4 of CDC-PEP provides guidance on using these tests to confirm that prophylaxis was successful in a subject.¹⁹⁵ CDC-PEP thus teaches determining “*an inhibition of infection in the host*” “*by an absence of persistent viremia and seroconversion in the human following the exposure to the immunodeficiency retrovirus.*”

6. Claim 17

CDC-PEP recommends a 28-day course of ARVs in the case of “[e]xposure of vagina, rectum...[w]ith...semen, vaginal secretions....”¹⁹⁶ These are all forms of exposure via sexual intercourse recited in Claim 17, which lists those exposures as alternatives. CDC-PEP thus teaches that “*the potential exposure to the human*

¹⁹³ CDC-PEP, 13, Table 4.

¹⁹⁴ Youle-Decl. ¶183, 166-67; Fearon, 26.

¹⁹⁵ CDC-PEP, 13, Table 4.

¹⁹⁶ *Id.* 8, Fig. 1.

immunodeficiency retrovirus comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.”

E. Claims 1 to 17 Would Have Been Obvious

Patent Owner may contend that Cal-PrEP does not describe the method of Claims 1 to 17, pointing to Cal-PrEP’s observation that clinical trials to test its effectiveness were underway but not completed. But Cal-PrEP describes administering the same agents in the same doses to the same subjects for the same purpose as the contested claims, and thus necessarily describes the same process.¹⁹⁷

Regardless, a skilled person would have found Cal-PrEP to provide a specific motivation (i.e., the need to decrease rates of HIV infections in high-risk individuals and within their communities) to modify the PEP regimen described in CDC-PEP by administering Truvada (TDF+FTC) to high-risk individuals before (rather than after) an actual HIV exposure. A skilled person thus would have found it obvious to administer Truvada to an uninfected individual before an HIV exposure to prevent an HIV infection and would have reasonably expected doing so to be effective based on, *inter alia*, experiences with PEP. Consequently, each

¹⁹⁷ See, e.g., *Bristol-Myers*, 246 F.3d at 1378; *Rasmussen*, 413 F.3d at 1326.

of the claimed methods would have been obvious based on CDC-PEP in view of Cal-PrEP in February 2005.

1. A Skilled Person Would Have Been Motivated to Commence Prophylaxis Before an Exposure Based on Cal-PrEP

By February 2005, a skilled person would have known from CDC-PEP and their own experiences using the PEP regimen that starting administration of TDF+FTC within 72 hours after an HIV exposure can prevent establishment of an HIV infection.¹⁹⁸ As CDC-PEP teaches, commencing ARV administration as soon as possible after the HIV exposure is a key factor influencing success of that regimen.¹⁹⁹ Indeed, CDC-PEP emphasizes that “[t]he sooner []PEP is administered after exposure, the more likely it is to interrupt transmission.”²⁰⁰

The skilled person also would have known that antiretrovirals “interrupt transmission” of HIV by actively suppressing HIV viral replication at the initial

¹⁹⁸ CDC-PEP at 8-12; Youle-Decl. ¶¶174, 179.

¹⁹⁹ CDC-PEP, 8.

²⁰⁰ *Id.* 8, 15 (“Accumulated data from animal and human clinical and observational studies demonstrate that antiretroviral therapy initiated as soon as possible within 48-72 hours....”); Youle-Decl. ¶¶246, 129-30; CDC-2001, 26.

site of HIV exposure in the body.²⁰¹ That person likewise knew that antiretrovirals require time after ingestion to transit to the sites of an HIV exposure (e.g., the mucosa) and create drug concentrations at those sites sufficient to suppress HIV replication—at least two hours for TDF and FTC.²⁰² The skilled person thus would have recognized that the theoretically optimal time to administer TDF+FTC to prevent HIV infection under the PEP regimen would be several hours before an HIV exposure. Doing that would create the maximally suppressive effect of antiretrovirals at the site of the exposure starting at the exact moment of the HIV exposure, and, if maintained without interruption, would maximally inhibit HIV replication within the founder cell population.²⁰³ The skilled person, thus, would have been motivated to administer antiretrovirals even before an HIV exposure to maximize the effectiveness of antiretroviral prophylaxis.

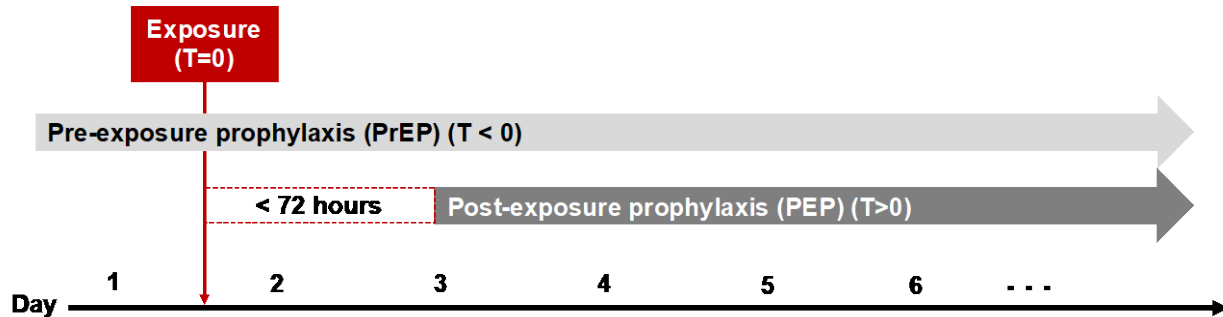
The skilled person further would have recognized that the PrEP regimen in Cal-PrEP differs from the PEP regimen described in CDC-PEP solely with respect to timing: the PrEP regimen effectively shifts the start of a PEP regimen from a

²⁰¹ CDC-PEP, 8; Youle-Decl. ¶¶247-48.

²⁰² Ex. 1079 (“Dumond-PRN”), 15; Youle-Decl. ¶¶244, 131.

²⁰³ Youle-Decl. ¶¶131-33; Saag, 28.

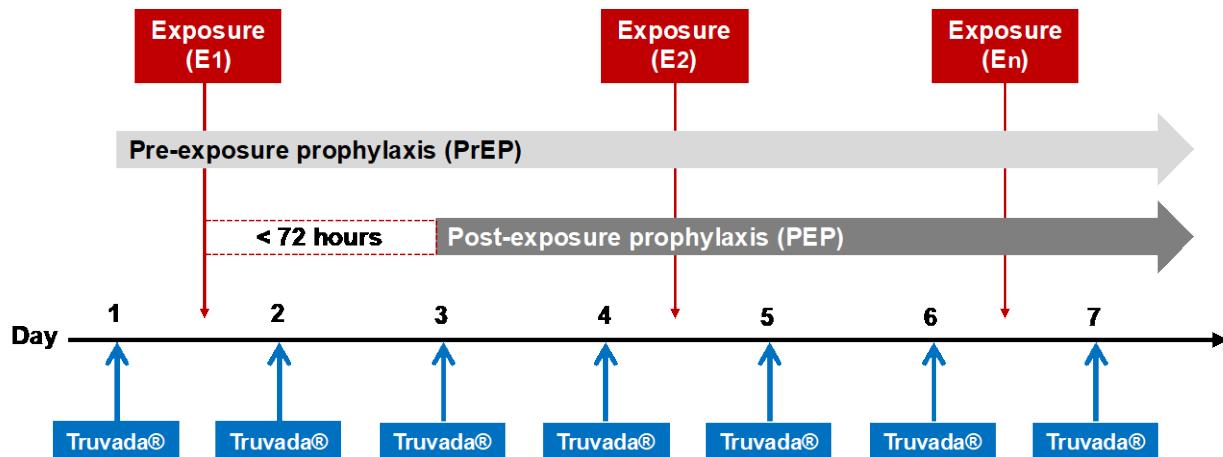
time immediately after ($T > 0$) an HIV exposure to a time prior to that exposure ($T < 0$).²⁰⁴



Indeed, the skilled person would have recognized that a “high risk” individual, such as a sex worker, placed on a 28-day PEP regimen after a first exposure to HIV cannot be meaningfully differentiated from the same individual on a PrEP regimen—in both, the high-risk individual during that 28-day period will have “an exposure” to HIV multiple times ($E_2, \dots E_n$), both before and after taking daily doses of the antiretroviral agents, as illustrated below.²⁰⁵

²⁰⁴ Youle-Decl. ¶¶245, 134.

²⁰⁵ *See id.*



Before 2005, the guidance in Cal-PrEP provided a specific motivation to the skilled person to alter the PEP regimen in CDC-PEP by administering, *inter alia*, Truvada to “high-risk,” HIV-uninfected individuals before an exposure to HIV (rather than after).²⁰⁶ As Cal-PrEP explains, high-risk individuals (e.g., commercial sex workers, intravenous drug users, MSM) engage in conduct that repeatedly exposes them to HIV, and such exposures significantly increase the risks of HIV infection to not only those individuals but to others in their community with whom they interact.²⁰⁷ Cal-PrEP thus proposes to administer combinations of antiretrovirals (including Truvada) to such high-risk individuals for periods that will span when those individuals are likely to have multiple

²⁰⁶ *Id.* ¶136.

²⁰⁷ Cal-PrEP, 3; Youle-Decl. ¶146; Youle-JIAPAC, 104.

exposures to HIV due to their conduct. Certainly, Cal-PrEP recognizes that antiretrovirals can cause side-effects, and that continued use of them presents risks for individuals who take them for extended periods.²⁰⁸ But the skilled person would have understood that by nonetheless recommending chemoprophylaxis for these high-risk individuals for extended periods (e.g., 9 to 24 months), Cal-PrEP teaches that the individual and community benefits of preventing HIV infections (i.e., a lifelong, incurable disease) outweigh those risks of potential side-effects.²⁰⁹

Cal-PrEP justifies its regimen as being part of a broader strategy for reducing the rate of HIV infection in communities—it proposes administering antiretrovirals to uninfected high-risk individuals to not only prevent those individuals from contracting HIV, but to prevent those individuals from infecting others in their community. For example, Cal-PrEP advocates antiretroviral prophylaxis as a supplement to “intensive risk-reduction interventions” proposed in CDC-PEP to prevent HIV infections in high-risk uninfected individuals.²¹⁰ Cal-PrEP also observes that behavioral interventions alone have not meaningfully

²⁰⁸ Cal-PrEP, 10-11.

²⁰⁹ Youle-Decl. ¶146; Cal-PrEP, 6-10.

²¹⁰ CDC-PEP, 6; see Youle-Decl. ¶¶145, 147.

reduced HIV infection rates in communities with high-risk individuals in them, and observes that effective epidemiological strategies were urgently needed in such communities.²¹¹

Cal-PrEP thus justifies its recommendation to alter the known PEP strategy by administering Truvada to uninfected high-risk individuals to advance its community-focused goal of reducing the spread of HIV via these individuals in communities where they are active.²¹² Indeed, whether PrEP could reduce HIV infection rates in communities was one of the objectives of the clinical trials referenced in Cal-PrEP.²¹³

2. CDC-PEP and Cal-PrEP Both Recommended Truvada for Prophylaxis of HIV-Uninfected Individuals

CDC-PEP and Cal-PrEP each specifically identify Truvada as a “preferred”²¹⁴ or “optimal”²¹⁵ product to use in their respective chemoprophylaxis

²¹¹ CDC-PEP, 3; Cal-PrEP, 3; Youle-Decl. ¶250.

²¹² Youle-Decl. ¶¶147, 149, 250.

²¹³ *Id.* ¶261.

²¹⁴ CDC-PEP, 8-9, Table 2; 10, Table 3; *see also supra* §VI.D.2.c.

²¹⁵ Cal-PrEP, 11; *see also supra* §VI.C.2.c.

regimens for HIV-uninfected individuals. By February 2005, a skilled person also would have been motivated to use Truvada given its favorable side-effects profile relative to Combivir and other antiretrovirals,²¹⁶ and to minimize risks of viral resistance that can arise from TDF or FTC monotherapy.²¹⁷

For example, Cal-PrEP notes the “possible emergence of resistance due to selection of the K65R mutation” for TDF monotherapy and that FTC is “susceptible to a single-point mutation at codon 184 that confers resistance, especially when taken alone.”²¹⁸ Truvada’s clinical trial results showed no instances of viral resistance.²¹⁹ The skilled person thus would have understood that monotherapy-linked risks could be minimized by using Truvada, which combines TDF with FTC.²²⁰

²¹⁶ Moyer, 1; Youle-Decl. ¶237.

²¹⁷ *See, e.g., Cal-PrEP*, 11 (“To be ideal for use as PrEP, a drug should...not promote development of high-level viral resistance based on a single mutation.”); Youle-Decl. ¶¶87, 163.

²¹⁸ Cal-PrEP, 11 (emphasis added).

²¹⁹ Moyer, 1.

²²⁰ Youle-Decl. ¶¶163, 222, 224.

Thus, before February 2005, CDC-PEP taught that Truvada was a “preferred” agent to use in the PEP regimen and Cal-PrEP taught that Truvada met every feature of the “ideal” PrEP agent.²²¹ Consequently, a skilled person would have found it obvious to use Truvada in the PrEP regimen suggested by CDC-PEP and Cal-PrEP.

3. A Skilled Person Would Reasonably Expect PrEP Using Truvada to be Effective in Preventing HIV Infection

During examination, Patent Owner represented to the Patent Office that a skilled person in February 2005 would have doubted that a pre-exposure HIV chemoprophylaxis regimen based on TDF+FTC would have been effective in preventing HIV infection.²²² That assertion has no basis in fact. It also ignores that the claims do not require any particular degree of success, given that the preamble and “thereby” clauses of Claims 1 and 12 are non-limiting.²²³ And the

²²¹ CDC-PEP, 9, Table 2; Cal-PrEP, 11; Youle-Decl. ¶¶241, 96, 161.

²²² Ex. 1004 (“’333 File History”), 105-07.

²²³ *See supra* §V.C.2.a.

law only requires a reasonable expectation of success, not certainty, a standard more than met by the scientific evidence known before February 2005.²²⁴

a. Extensive Experiences with PEP Established a Reasonable Expectation of Success

More than 15 years of experience before February 2005 established that combinations of antiretroviral agents can prevent HIV infections in uninfected individuals after they have been exposed to HIV. Indeed, the CDC's own guidelines (CDC-PEP) rest on the principle that aggressively suppressing HIV viral replication by administering combinations of antiretroviral agents shortly after an HIV exposure will prevent establishment of an HIV infection.²²⁵

CDC-PEP identifies timing, not viral inhibition by ARVs, as the most critical factor in successful prophylaxis, explaining that delays in starting administration of ARVs makes the chemoprophylactic regimen less effective.²²⁶ That observation also makes it clear that administering antiviral agents before an

²²⁴ *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367-68 (Fed. Cir. 2016).

²²⁵ CDC-PEP, 2-4; Youle-Decl. ¶¶130-31.

²²⁶ CDC-PEP, 2.

HIV exposure yields the maximum prophylactic effectiveness, as it will create effective concentrations of the antiretroviral agents at the site of exposure the moment an HIV exposure occurs.²²⁷ PrEP, in essence, is the most optimal form of the PEP regimen.

CDC-PEP also catalogs the extensive scientific evidence known before 2005 that supports the effectiveness of antiretroviral-based prophylaxis in preventing HIV infection in uninfected individuals. That evidence includes animal studies, experiences with mother-to-child prophylaxis, observational studies of PEP, and case reports.²²⁸ CDC-PEP, for example, refers to data showing an 81% reduction in infections in needle-stick settings using antiretroviral therapy with zidovudine.²²⁹ CDC's own reliance on this evidence to support its PEP guidelines directly refutes Patent Owner's assertions during examination that a skilled person would not have expected administration of Truvada before an HIV exposure to effectively prevent establishment of an HIV infection in an uninfected

²²⁷ Youle-Decl. ¶133; Saag, 28.

²²⁸ CDC-PEP, 2-4.

²²⁹ *Id.* 3.

individual.²³⁰ And expectations of success could only increase with the advances of the early 2000s, particularly clinical experiences with TDF+FTC, which showed effective suppression of viral replication with fewer side-effects than Combivir.²³¹

b. PrEP and PEP Regimens Have the Same Pharmacological Mechanism and Cause the Same Result

A skilled person familiar with how antiretroviral agents such as TDF and FTC work in treatment and in post-exposure prophylaxis would have expected the same pharmacological effect to be observed if the agents are administered before an HIV exposure. That is because the same agents when administered to a human subject at the same doses will cause the same effects—they will create a drug concentration at the site of the exposure that maximally suppresses HIV replication.²³² The skilled person thus would have recognized that the way Truvada prevents HIV infection in the human body in the PEP regimen is identical

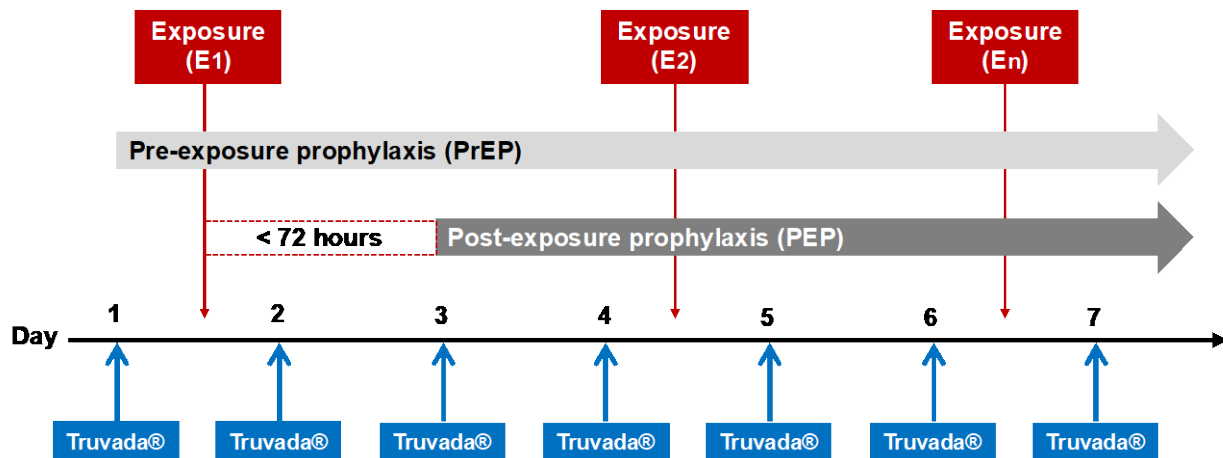
²³⁰ See, e.g., '333 File History, 105 (“The art teaches that use of an anti-HIV agent to treat HIV infection does not reasonably predict the ability of that agent to protect against HIV infection.”).

²³¹ Moyer, 1.

²³² Youle-Decl. ¶¶242-43, 248.

to the way it does so in a PrEP regimen, and the reasons why PEP is effective in preventing HIV infection are the reasons it is effective in PrEP.

CDC-PEP and Cal-PrEP also describe performing the same operative steps—orally administering once a day at least 300 mg of TDF and 200 mg of FTC (i.e., Truvada) to an uninfected individual—with the only difference being when those steps are performed. Indeed, a high-risk uninfected individual placed on a Truvada-based PEP regimen who does not become infected and who experiences an additional HIV exposure during the 28-day or longer PEP regimen will meet all the requirements of the contested claims. That is because the HIV-uninfected individual will be given pharmaceutically effective amounts of TDF and FTC before an HIV exposure (i.e., at exposures E_2 or later).²³³



²³³ *Id.* ¶¶135-36.

A skilled person thus would have reasonably expected pre-exposure administration of Truvada to prevent establishment of an HIV infection in an uninfected individual (i.e., PrEP with Truvada), given that post-exposure administration of the same dose of the same two agents (i.e., PEP with Truvada) does.²³⁴

c. Cal-PrEP Described Clinical Trials Focused on Decreasing Community Rates of HIV Infection

Patent Owner may contend that Cal-PrEP's indication that clinical trials were needed to prove the effectiveness of PrEP, coupled with its identification of factors that could limit the effectiveness of PrEP, would have led a skilled person to doubt that Truvada, when administered to an HIV uninfected individual before an HIV exposure, would “protect[]” a host from a HIV infection or “inhibit[] establishment” of an infection per Claims 1 and 12. Such contentions have no merit.

Initially, the claims do not require the successful prevention of HIV in every individual—they only require performing the steps of administering pharmaceutically effective amounts of TDF and of FTC to one uninfected

²³⁴ *Id.* ¶¶245, 248.

individual before an HIV exposure. That is precisely what is taught or suggested by both Cal-PrEP and CDC-PEP.

Moreover, nothing in the '333 Patent answers the questions supposedly raised in Cal-PrEP about the feasibility of PrEP. Most notably, the macaque studies reported in the '333 Patent do not address any of the human behavioral factors that Cal-PrEP identifies as potentially limiting the effectiveness of PrEP in slowing the rate of infection. Those factors include, *inter alia*, compliance (i.e., whether patients take the pills each day at the right time), access to drugs, and a variety of societal and behavioral factors.²³⁵ A skilled person reading Cal-PrEP would have instead recognized that in its ideal implementation (i.e., an individual with a steady supply of Truvada who takes it every day as prescribed), PrEP would be effective in preventing HIV infection in that individual.²³⁶

More generally, both Cal-PrEP and CDC-PEP recognize that reducing the rate of HIV infections within a community can be best achieved by a combination of interventions. For example, CDC-PEP instructs caregivers to counsel

²³⁵ *Id.* ¶¶262, 258.

²³⁶ *Id.* ¶¶251-52.

individuals to avoid high-risk activities while on the PEP regimen.²³⁷ Cal-PrEP likewise explains that to “reduce the occurrence of future HIV exposures,” individuals on PrEP should be continuously counseled on ways to decrease high-risk activity (e.g., abstinence, protective behaviors, and being repeatedly tested for HIV infection).²³⁸ Cal-PrEP, however, recognized that some patients will not follow advice to reduce high-risk activities, be exposed to HIV, and create risks for the broader community. Cal-PrEP thus portrayed the risk-benefit assessment as tilting in favor of administering antiretroviral agents to HIV-uninfected individuals to span periods of their “high-risk” activities.²³⁹

Ultimately, the relevant question for obviousness is whether a skilled person would reasonably believe that administering TDF+FTC to one uninfected individual will prevent establishment of an HIV infection in that individual.²⁴⁰ More than substantial evidence shows that to be true.

²³⁷ CDC-PEP, 5.

²³⁸ Cal-PrEP, 27.

²³⁹ *Id.* 3.

²⁴⁰ Youle-Decl. ¶¶251, 253, 259.

d. HIV Chemoprophylaxis Was Not “Highly Unpredictable”

During examination of this and a related patent, Patent Owner claimed HIV chemoprophylaxis was “highly unpredictable” for various reasons.²⁴¹ Patent Owner’s assertions are contradicted by the literature and/or are legally irrelevant.

First, Patent Owner cited results from a PrEP trial using a CCR5 inhibitor.²⁴² Besides involving an agent with a different mechanism of action than TDF+FTC, those results could not have influenced expectations of a skilled person in February 2005 because they were not published until 2013.²⁴³

Second, Patent Owner portrayed Subbarao-2006 as showing that prophylaxis using TDF monotherapy in animal studies was unsuccessful, and, relying on a declaration from two of the inventors, claimed that “protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus,” was significant and unexpected.²⁴⁴ But skilled persons—including the CDC and the authors of

²⁴¹ Ex. 1002 (“’509 File History”), 82, 116-17; ’333 File History, 105.

²⁴² *Id.*; Youle-Decl. ¶¶83, 207.

²⁴³ ’333 File History, 105.

²⁴⁴ *Id.* 106, 49-52.

Subbarao-2006—portrayed these same TDF monotherapy animal studies as being positive clinical results supporting PrEP.²⁴⁵

Notably, Subbarao-2006 reported that even after 14 weekly exposures, “[o]ne macaque (RQ4180) in the daily-TDF group remained uninfected,” and credited that to TDF’s effectiveness, stating “oral TDF must have played a role in preventing infection in this macaque.”²⁴⁶ Subbarao-2006 also stated “that oral TDF prophylaxis of macaques in our study resulted in a 60% decrease in the per-exposure probability of infection,” thereby providing at least “partial protection” when administered prior to exposure.²⁴⁷ And Subbarao-2006 not only reported that “tenofovir prophylaxis may be of benefit” in a pre-exposure setting (noting it delayed median times to infection), but stated this in the paper’s title.²⁴⁸ Moreover, a commentary published in the same issue of *Science* cited Subbarao-2006’s experimental results as supporting the viability of TDF-based PrEP *combination* therapy, stating “combinations of agents may be more suited for PrEP” than TDF

²⁴⁵ Youle-Decl. ¶¶216-19, 233-36.

²⁴⁶ Ex. 1050 (“Subbarao-2006”), 907, 909; Youle-Decl. ¶217.

²⁴⁷ Subbarao-2006, 907; Youle-Decl. ¶216.

²⁴⁸ See Subbarao-2006, 910; see also *id.* 907.

alone, and specifically recommended use of Truvada in PrEP.²⁴⁹ And other contemporaneous publications cited other TDF-based PrEP animal studies as supporting the viability of TDF PrEP monotherapy in humans.²⁵⁰ Thus, by February of 2005, it was expected (not unexpected) that TDF+FTC would be more effective than TDF monotherapy in PrEP.

Post-filing publications from the CDC also directly contradict Patent Owner's assertions. Most notably, in its 2014 PrEP guidelines, the CDC cited Subbarao-2006 as *supporting* the efficacy of TDF in PrEP, stating:

Evidence from these human studies of blood-borne and perinatal transmission as well as studies of vaginal and rectal exposure among animals [FN17-19] *suggested that PrEP (using antiretroviral drugs)*

²⁴⁹ Grant-2006, 875; *see also* Ex. 1053 (“Grant-2005”), 2170; Youle-Decl.

¶¶220-21; *supra* §IV.D.

²⁵⁰ *E.g.*, Ex. 1051 (“Grant-2006”), 874 (observing that Subbarao’s results “advance[]...the use of antiretroviral drugs in...PrEP...for HIV disease); Ex. 1052 (“Subbarao-2007”), 241 (follow-up publication stating “oral TDF can be initially effective for a while”); Youle-Decl. ¶209.

*could reduce the risk of acquiring HIV infection from sexual and drug-use exposures.*²⁵¹

The last assertion made by Patent Owner was that Cambodian TDF PrEP clinical trials were cancelled due to concerns over therapeutic efficacy.²⁵² That too is incorrect: one report identified concerns over trial participants being unfairly exploited as the reason, and that same report observed that tenofovir “has a better safety profile than any anti-HIV drug on the market” and “already has proven to be extremely effective as an HIV preventative in monkey experiments.”²⁵³

And while Patent Owner asserted during examination that “the references, when considered in combination, do not disclose or suggest that a tenofovir/TDC [sic] can be combined with FTC” for PEP or PrEP,²⁵⁴ that statement is demonstrably incorrect. As shown in §§VI.B-VI.D, CDC-PEP and Cal-PrEP each are based on the proposition that HIV prophylaxis with Truvada is effective. Critically, neither of those publications was provided to the Examiner during

²⁵¹ Ex. 1123 (“CDC-2014”), 14 (emphasis added) (FN17 is Subbarao-2006).

²⁵² ’333 File History, 105-06.

²⁵³ Ex. 1054 (“Cohen-2004”), 1092.

²⁵⁴ ’333 File History, 104.

examination of the '333 Patent and each is far more relevant to patentability than the references that were actually considered.

F. There Are No Secondary Indicia of Non-Obviousness

Patent Owner may contend that evidence of secondary considerations, such as unexpected results or commercial success, warrant finding the claims non-obvious.²⁵⁵ But to be pertinent to obviousness, the secondary considerations evidence must have a nexus to *the invention*. “[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent.”²⁵⁶

Here, the evidence shows that any unexpected results or commercial success of using TDF+FTC in PrEP regimens are attributable to the prior art, not the '333 Patent. That prior art clearly identifies not only the process of administering Truvada to HIV-uninfected individuals before an HIV exposure to prevent HIV infections but also identifies the characteristics of drugs “ideal for use as PrEP” and explains that “drugs [like NRTIs] whose mechanisms of action focus on pre-

²⁵⁵ Secondary considerations are irrelevant to anticipation.

²⁵⁶ *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006).

integration” are likely to be effective.²⁵⁷ Indeed, at best, the ’333 Patent provided simply a confirmation of what scientists knew and expected from the prior art.

Likewise, if “market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak.”²⁵⁸ Gilead holds patents claiming once-daily oral formulations of TDF, FTC, and their combination, which cover all uses of the compounds.²⁵⁹ Because market entry for third parties was blocked by Gilead’s patents on the Truvada product, any inference of non-obviousness for commercial success of the claimed methods (which concern a use of Truvada) is weak at best.

Other secondary considerations are absent. For example, by February 2005, there was no failure of others or skepticism in the field with respect to Truvada’s use in PrEP. Instead, by then, the CDC had recommended its use in both treatment

²⁵⁷ See, e.g., Cal-PrEP, 10-11.

²⁵⁸ *Merck & Co. v. Teva Pharmaceuticals USA*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

²⁵⁹ E.g., U.S. Patent Nos. 5,922,695 (TDF); 6,703,396 (FTC); 8,592,397 (TDF+FTC).

and prophylaxis²⁶⁰ and skilled persons proposed using it in large-scale PrEP trials.²⁶¹ Physicians also had begun recommending Truvada for PrEP to high-risk patients and such individuals began obtaining Truvada from friends to take in prophylaxis before and after high-risk behavior.²⁶² And Truvada’s more recent success in PrEP is not due to anything disclosed in the ’333 Patent, but to the efforts of the CDC and Gilead to promote its use.

Thus, no secondary indicia have a nexus to the claimed methods, and none supports the non-obviousness of the contested claims. Petitioner also submits any evidence of secondary indicia advanced by Patent Owner in its response should be addressed after institution, where that evidence and its relevance can be contested.

VII. THE BOARD SHOULD NOT EXERCISE ITS DISCRETION UNDER 35 U.S.C. §325(D)

Under the relevant factors identified in *Becton Dickinson & Co. v. B. Braun Melsungen AG* and in the Board’s July 2019 Trial Practice Guide Update, the

²⁶⁰ Ex. 1075 (“DHHS-2004”), 14; CDC-PEP, 9 (Table 2).

²⁶¹ Youle-Decl. ¶¶230-32; *see also* Ex. 1135 (“Grant-Proposal”), 3-4.

²⁶² Youle-Decl. ¶241.

Board should not exercise its discretion under §325(d).²⁶³ Neither Cal-PrEP nor CDC-PEP was cited during examination of the '333 Patent, and neither is cumulative or equivalent to the prior art used during its examination. Both references also are far more relevant than the art considered during examination.²⁶⁴ This petition also proposes different grounds (including anticipation), and presents new evidence not considered by the Office—a declaration from Dr. Michael Youle (Ex. 1009), a noted expert in the field of HIV therapy and prevention.²⁶⁵ This Petition therefore does not present the “same or substantially the same prior art or arguments” raised or considered during examination of the '333 Patent.

²⁶³ Trial Practice Guide, 84 Fed. Reg. 33,925 (July 2019 Update) (“Trial Practice Guide”), 29-30 (factors 1 to 4) (citing *Becton Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (P.T.A.B. Dec. 15, 2017) (precedential)).

²⁶⁴ *Microsoft Corp. v. Parallel Networks Licensing, LLC*, IPR2015-00486, Paper 10, 14-15 (P.T.A.B. July 15, 2015); *Becton Dickinson*, IPR2017-01586, Paper 8, 17-18; Trial Practice Guide, 29-30.

²⁶⁵ *Apotex Inc. v. Novartis AG*, IPR2017-00854, Paper 11, 13-14 (P.T.A.B. July 18, 2017).

Patent Owner may nonetheless contend the Board should not institute trial because Cal-PrEP and CDC-PEP were considered during examination of a subsequently filed application, U.S. Application No. 15/406,344, which issued as U.S. Patent No. 9,937,191 (Ex. 1005) (“’191 Patent”). The issuance of the ’191 Patent was in turn based on events that occurred during examination of U.S. Patent No. 9,044,509 (Ex. 1001) (“’509 Patent”). But the examination record of the ’191 Patent reveals that “the Office erred in evaluating the asserted prior art” during its examination, which, if anything, justifies the Board not exercising its discretion under §325(d) here.²⁶⁶

What the ’191 Patent file wrapper shows is that the Examiner rejected claims similar to those in the ’509 Patent as being obvious over seven prior art references, two of which were Cal-PrEP and CDC-PEP. The Examiner correctly observed that Cal-PrEP (also referred to as “Szekeres”) identified (1) the need for biomedical approaches to HIV prevention including PrEP and that (2) TDF was

²⁶⁶ Trial Practice Guide, 30 (factor 5).

well-suited for PrEP.²⁶⁷ The Examiner also correctly observed that CDC-PEP disclosed Truvada for use in PEP and that it would have been obvious to treat uninfected individuals who are exposed to or at risk of exposure to HIV with Truvada.²⁶⁸

Rather than address the merits of this rejection, Patent Owner secured an interview with the Examiner, proposed an amendment to add a “tablet” limitation to the ’509 Patent claims, and appeared to convince the Examiner this amended claim would be patentable for the same reasons the Examiner had found the ’509 Patent claims patentable. As the Examiner’s interview summary states:

Applicants’ attorney indicates that applicants will pursue subject matter within the scope of allowed claim in parent application (now US 9,044,509).... Particularly, claims 1 herein will be amended to the same as claim 1 in ’509, but with a further limitation of the oral

²⁶⁷ Ex. 1006 (“’191 File History”), 60. The Examiner consequently did not observe that Cal-PrEP also identified Truvada as one of two TDF options to use in PrEP.

²⁶⁸ *Id.*, 60-61.

dosage form: a tablet. The examiner indicates that such a claim would be allowable for reasons as set forth in the parent application.²⁶⁹

Then, when Patent Owner presented this amended “tablet” claim, it stated the Examiner had “confirmed that it was not necessary to address the rejection under 35 U.S.C. §103 if the proposed claim amendments were made in the response.”²⁷⁰

But neither Cal-PrEP nor CDC-PEP was ever cited during examination of the ’509 Patent, much less were the basis of rejections that were imposed and overcome during its examination.²⁷¹ Thus, the statement in the Examiner’s interview summary form (reinforced by Patent Owner’s response) that the ’191 Patent claims were patentable *for the same reasons the Examiner had found the ’509 Patent claims patentable* was and is demonstrably false—the ’509 Patent claims were never even considered in connection with Cal-PrEP or CDC-PEP because Patent Owner did not provide those references to the Office until years after the ’509 Patent granted.

²⁶⁹ *Id.*, 53 (emphasis added).

²⁷⁰ *Id.* 40 (emphasis added).

²⁷¹ The same Examiner examined all four patents that issued from this family of applications.

The examination record of the '191 Patent thus shows that Patent Owner never addressed, much less overcame, any rejection that relied on the substantive teachings of Cal-PrEP and CDC-PEP. What it shows instead is that the Examiner mistakenly equated the basis of the rejections of the '191 Patent claims with a rejection imposed over different and much less relevant prior art (i.e., not Cal-PrEP or CDC-PEP) during examination of the '509 Patent claims—and relied on that mistake to find the '191 Patent claims patentable. That mistake would warrant the Board not exercising its discretion in proceedings against the '191 Patent. And, if the examination record of the '191 Patent were somehow relevant to the earlier-examined '333 Patent at issue in this petition, the Office's later error there would (if anything) support the Board not exercising its §325(d) discretion here.

Consequently, because the patentability issues presented in this petition were never considered during examination of the '333 Patent, the Board should not exercise its discretion under §325(d).

VIII. CONCLUSION

Petitioner respectfully requests that trial be instituted and that the claims be held unpatentable for the reasons set forth above.

Dated: August 21, 2019

Respectfully Submitted,

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CERTIFICATE OF COMPLIANCE

I hereby certify that this Petition complies with the type-volume limitations of 37 C.F.R. §42.24, because it contains 13,918 words (as determined by the Microsoft Word word-processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §42.6(e), I hereby certify that on this 21st day of August, 2019, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by Federal Express on the following counsel:

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 9,044,509 (“509 Patent”)
1002	File History of U.S. Patent No. 9,044,509 (“509 File History”)
1003	U.S. Patent No. 9,579,333 (“333 Patent”)
1004	File History of U.S. Patent No. 9,579,333 (“333 File History”)
1005	U.S. Patent No. 9,937,191 (“191 Patent”)
1006	File History of U.S. Patent No. 9,937,191 (“191 File History”)
1007	U.S. Patent No. 10,335,423 (“423 Patent”)
1008	File History of U.S. Patent No. 10,335,423 (“423 File History”)
1009	Declaration of Michael Youle, MB, ChB (“Youle-Decl.”)
1010	Curriculum Vitae of Michael Youle, MB, ChB
1011	Szekeres et al., “Anticipating the Efficacy of HIV Pre-Exposure Prophylaxis (PrEP) and the Needs of At-Risk Californians,” Center for HIV Identification, Prevention and Treatment Services (2004) (“Cal-PrEP”)
1012	Centers for Disease Control and Prevention, “Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States,” Recommendations from the U.S. Department of Health and Human Services, Morbidity and Mortality Weekly Report 54(2) (Jan. 21, 2005) (“CDC-PEP”)
1013	Centers for Disease Control and Prevention, “Public Health Service Guidelines for the Management of Health-Care Worker Exposures to HIV and Recommendations for Postexposure Prophylaxis,” Morbidity and Mortality Weekly Report 47(7) (1998) (“CDC-May1998”)
1014	Centers for Disease Control and Prevention, “Report of the NIH Panel to Define Principles of Therapy of HIV Infection and Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and

	Adolescents,” Morbidity and Mortality Weekly Report 47(5) (1998) (“CDC-ARV”)
1015	Hu et al., “Simian Immunodeficiency Virus Rapidly Penetrates the Cervicovaginal Mucosa after Vaginal Inoculation and Infects Intraepithelial Dendritic Cells,” J. Virol. 74(13): 6087–95 (2000) (“Hu”)
1016	De Clercq, “HIV-chemotherapy and -prophylaxis: new drugs, leads and approaches,” Int’l J. Biochem. Cell Bio. 36(9): 1800–22 (2004) (“De Clercq-IJB”)
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1018	Coffin, “HIV Population Dynamics in Vivo: Implications for Genetic Variation, Pathogenesis, and Therapy,” Science 267(5197): 483–9 (1995) (“Coffin”)
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1021	Barreiro et al., “Combinations of Nucleoside/Nucleotide Analogues for HIV Therapy,” AIDS Rev. 6(4): 234–43 (2004) (“Barreiro”)
1022	Collins, “Tenofovir/FTC Backbone Outperforms AZT/3TC (Combivir) with Efavirenz in Treatment Naive Patients; Reduced Toxicity Drives ITT Viral Efficacy,” HIV i-Base (Jan. 29, 2005), http://i-base.info/htb/7665 (“Collins”)
1023	Gerberding, “Occupational Exposure to HIV in Health Care Settings,” N. Engl. J. Med. 348(9): 826–33 (2003) (“Gerberding”)

1024	Centers for Disease Control and Prevention, “Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis,” Morbidity and Mortality Weekly Report 50(11) (2001) (“CDC-2001”)
1025	Truvada® Label, FDA.gov (Aug. 2004), https://web.archive.org/web/20041014005516/http://www.truvada.com:80/fpi.pdf (“Truvada®-Label”)
1026	Truvada® Approval Letter, FDA.gov (Aug. 2, 2004), http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2004/21752ltr.pdf (“Approval-Letter”)
1027	Viread®-Label, FDA.gov (Oct. 2001), https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21356lbl.pdf (“Viread®-Label”)
1028	Emtriva®-Label, FDA.gov (July 2003), https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21500_emtriva_lbl.pdf (“Emtriva®-Label”)
1029	De Clercq, “Antiviral Drugs in Current Clinical Use,” J. Clin. Virol. 30(2): 115–33 (2004) (“De-Clercq-JCV”)
1030	Bang & Scott, “Emtricitabine: An Antiretroviral Agent for HIV Infection,” Drugs 63(22): 2413–24 (2003) (“Bang”)
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1032	Dando & Wagstaff, “Emtricitabine/Tenofovir Disoproxil Fumarate,” Drugs 64(18): 2075–82 (2004) (“Dando”)
1033	Back et al., “The Pharmacology of Antiretroviral Nucleoside and Nucleotide Reverse Transcriptase Inhibitors: Implications for Once-Daily Dosing,” J. Acquir. Immune Defic. Syndr. 39(1): S1–23 (Aug. 1, 2005) (“Back”)

1034	DeJesus et al., “Abacavir versus Zidovudine Combined with Lamivudine and Efavirenz, for the Treatment of Antiretroviral-Naive HIV-Infected Adults,” Clin. Infect. Dis. 39(7): 1038–46 (2004) (“DeJesus”)
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1036	Feinberg, “Tenofovir + Emtricitabine vs. AZT + 3TC,” AIDS Clin. Care 17(1): 7 (Jan. 1, 2005) (“Feinberg”)
1037	Mascolini, “Truvada Goes Toe-to-Toe with Combivir,” ICAAC Report: Evolving Antiretroviral Strategies, Conference Report for the National AIDS Treatment Advocacy Project (2004) (“Mascolini”)
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1039	Brenner et al., “HIV-1 Subtype C Viruses Rapidly Develop K65R Resistance to Tenofovir in Cell Culture,” AIDS 20(9): F9–F13 (Jun. 12, 2006) (“Brenner”)
1040	Food and Drug Administration, “Treatment Options for HIV, AIDS,” FDA Consumer Magazine, Nov.–Dec. 2004 (“FDA-2004”)
1041	De Clercq, “Emerging Anti-HIV Drugs,” Expert Opin. Emerg. Drugs 10(2): 241–73 (May 10, 2005) (“De-Clercq-2005”)
1042	Youle & Wainberg, “Pre-Exposure Chemoprophylaxis (PREP) as an HIV Prevention Strategy,” J. Int’l Assoc. Physicians AIDS Care 2(3): 102–5 (2003) (“Youle-JIAPAC”)
1043	Helene Gayle, Prepared Remarks, “Prevention Now! A Vision for the Future,” Bill & Melinda Gates Foundation (July 9, 2002), https://www.gatesfoundation.org/Media-Center/Speeches/2002/07/Helene-Gayle-2002-Prevention-Now (“Gayle”)

1044	Marilyn Chase, “Trials Will Test Whether AIDS Drug Can Also Prevent HIV,” Wall St. J., Dec. 4, 2003 (“Chase”)
1045	Tsai et al., “Prevention of SIV Infection in Macaques by (R)-9-(2-Phosphonylrr-ethoxypropyl)adenine,” Science 270(5239): 1197–9 (1995) (“Tsai-1995”)
1046	Van Rompay et al., “Two Doses of PMPA Protect Newborn Macaques Against Oral Simian Immunodeficiency Virus Infection,” AIDS 12(9): F79–83 (1998) (“Van-Rompay-1998”)
1047	Otten et al., “Multiple Vaginal Exposures to Low Doses of R5 Simian-Human Immunodeficiency Virus: Strategy to Study HIV Preclinical Interventions in Nonhuman Primates,” J. Inf. Dis. 191(2): 164–73 (Dec. 9, 2004) (“Otten-2004”)
1048	Li et al., “Infection of Cynomolgus Monkeys with a Chimeric HIV-1/SIVmac Virus that Expresses the HIV-1 Envelope Glycoproteins,” J. Acquir. Immune Defic. Syndr. 5(7): 639–46 (1992) (“Li”)
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1051	Grant & Wainberg, “Chemoprophylaxis of HIV Infection: Moving Forward with Caution,” J. Infect. Dis. 194(7): 874–876 (Oct. 1, 2006) (“Grant-2006”)
1052	Subbarao et al., “Direct Stringency Comparison of Two Macaque Models (Single-high vs. Repeat-low) for Mucosal HIV Transmission

	Using an Identical Anti-HIV Chemoprophylaxis Intervention,” J. Med. Primatol. 36(4–5): 238–43 (2007) (“Subbarao-2007”)
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1061	Haase, “Perils at Mucosal Front Lines for HIV and SIV and Their Hosts,” Nature Rev. Immunol. 5(10):783–92 (Oct. 2005) (“Haase-2005”)
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1063	Chakraborty, “Viral Burden in Genital Secretions Determines Male-to-Female Sexual Transmission of HIV-1: A Probabilistic Empiric Model,” <i>AIDS</i> 15(5): 621–7 (2001) (“Chakraborty”)
1064	Cohen & Pilcher, “Amplified HIV Transmission and New Approaches to HIV Prevention,” <i>J. Infect. Dis.</i> 191(9): 1391–3 (May 1, 2005) (“Cohen-Pilcher”)
1065	Fauci et al., “Immunopathogenic Mechanisms of HIV Infection,” <i>Ann Intern Med.</i> 124:654-663 (1996) (“Fauci-1996”)
1066	Rubbert & Ostrowski, “Pathogenesis of HIV-1 Infection,” in <i>HIV Medicine 2003</i> (Hoffmann & Kamps eds. 2003), 15–46 (“Rubbert”)
1067	Saag, “Candidate Antiviral Agents for Use in Postexposure Prophylaxis,” <i>Am. J. Med.</i> 102(5B): 25–31 (1997) (“Saag”)
1068	Angarano et al., “Transmission of Zidovudine-Resistant HIV-1 Through Heterosexual Contacts,” <i>AIDS</i> 8(7): 1013–4 (1994) (“Angarano”)
1069	Conlon et al., “Heterosexual Transmission of Human Immunodeficiency Virus Type-1 Variants Associated with Zidovudine Resistance,” <i>J. Infect. Dis.</i> 169(2): 411–5 (1994) (“Conlon”)
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1071	Little et al., “Antiretroviral-Drug Resistance Among Patients Recently Infected With HIV,” <i>N. Eng. J. Med.</i> 347(6): 385–394 (2002) (“Little”)
1072	Pozniak et al., “British HIV Association (BHIVA) Guidelines for the Treatment of HIV-Infected Adults with Antiretroviral Therapy,” British HIV Association Writing Committee (July 2003) (“BHIVA”)
1073	Carpenter et al., “Antiretroviral Therapy for HIV Infection in 1998, Updated Recommendations of the International AIDS Society—USA Panel,” <i>JAMA</i> 280(1): 78–86 (1998) (“Carpenter”)

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1077	Arribas et al., “The Combination of Tenofovir DF (TDF), Emtricitabine (FTC) and Efavirenz (EFV) Has Significantly Greater Response vs Fixed Dose Zidovudine/Lamivudine (CBV) And EFV in Antiretroviral Naïve Patients: A 24-Week Preliminary Analysis,” Abstract PL14.27th, Int’l Congress on Drug Therapy in HIV Infection, Glasgow (Nov. 14–18, 2004) (“Arribas”)
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1079	Dumond et al., “Non-Occupational Post-Exposure Prophylaxis and Antiretroviral Pharmacokinetics in the Male and Female Genital Tracts,” PRN 11(2): 10–16 (Oct. 2006) (“Dumond-PRN”)
1080	Rey et al., “Post-Exposure Prophylaxis After Occupational and Non-Occupational Exposures to HIV: An Overview of the Policies Implemented in 27 European Countries,” AIDS Care 12(6): 695–701 (2000) (“Rey”)
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1082	Guay et al., “Intrapartum and Neonatal Single-Dose Nevirapine Compared with Zidovudine for Prevention of Mother-to-Child Transmission of HIV-1 in Kampala, Uganda: HIVNET 012 Randomised Trial,” <i>Lancet</i> 354(9387): 795–802 (1999) (“Guay”)
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EXHIBIT J



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Recommendations and Reports

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Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States

**Recommendations from the U.S. Department
of Health and Human Services**

INSIDE: Continuing Education Examination

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION**

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Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States

Recommendations from the U.S. Department of Health and Human Services

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Summary

The most effective means of preventing human immunodeficiency virus (HIV) infection is preventing exposure. The provision of antiretroviral drugs to prevent HIV infection after unanticipated sexual or injection-drug-use exposure might be beneficial. The U.S. Department of Health and Human Services (DHHS) Working Group on Nonoccupational Postexposure Prophylaxis (nPEP) made the following recommendations for the United States. For persons seeking care ≤ 72 hours after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person known to be HIV infected, when that exposure represents a substantial risk for transmission, a 28-day course of highly active antiretroviral therapy (HAART) is recommended. Antiretroviral medications should be initiated as soon as possible after exposure. For persons seeking care ≤ 72 hours after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person of unknown HIV status, when such exposure would represent a substantial risk for transmission if the source were HIV infected, no recommendations are made for the use of nPEP. Clinicians should evaluate risks and benefits of nPEP on a case-by-case basis. For persons with exposure histories that represent no substantial risk for HIV transmission or who seek care > 72 hours after exposure, DHHS does not recommend the use of nPEP. Clinicians might consider prescribing nPEP for exposures conferring a serious risk for transmission, even if the person seeks care > 72 hours after exposure if, in their judgment, the diminished potential benefit of nPEP outweighs the risks for transmission and adverse events. For all exposures, other health risks resulting from the exposure should be considered and prophylaxis administered when indicated. Risk-reduction counseling and indicated intervention services should be provided to reduce the risk for recurrent exposures.

Introduction

The most effective methods for preventing human immunodeficiency virus (HIV) infection are those that protect against exposure to HIV. Antiretroviral therapy cannot replace behaviors that help avoid HIV exposure (e.g., sexual abstinence, sex only in a mutually monogamous relationship with a noninfected partner, consistent and correct condom use, abstinence from injection-drug use, and consistent use of sterile equipment by those unable to cease injection-drug use). Medi-

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cal treatment after sexual, injection-drug-use, or other non-occupational HIV exposure* is less effective than preventing HIV infection by avoiding exposure.

In July 1997, CDC sponsored the External Consultants Meeting on Antiretroviral Therapy for Potential Nonoccupational Exposures to HIV. This panel of scientists, public health specialists, clinicians, ethicists, members of affected communities, and representatives from professional associations and industry evaluated the available evidence related to use of antiretroviral medications after nonoccupational HIV exposure. In 1998, DHHS issued a statement that outlined the available information and concluded that evidence was insufficient about the efficacy of nonoccupational postexposure prophylaxis (nPEP) to recommend either for or against its use (1).

Since 1998, additional data about the potential efficacy of nPEP have accumulated from human, animal, and laboratory studies. Clinicians and organizations have begun providing nPEP to patients they believe might benefit. In certain instances, health departments have issued advisories or recommendations or otherwise supported the establishment of nPEP treatment programs in their jurisdictions (2–6). In May 2001, CDC convened the second external consultants meeting on nonoccupational post-exposure prophylaxis to review and discuss the available data. This report summarizes knowledge about the use and potential efficacy of nPEP and details guidelines for its use in the United States.† The recommendations are intended for nonoccupational exposures and are not applicable for occupational exposures.

Evidence of Possible Benefits from nPEP

For ethical and logistical reasons, a randomized, placebo-controlled clinical trial of nPEP probably will not be performed. However, data are available from animal transmission models, perinatal clinical trials, studies of health-care workers receiving prophylaxis after occupational exposures, and from observational studies. These data indicate that nPEP might sometimes reduce the risk for HIV infection after nonoccupational exposures.

* In this report, a nonoccupational exposure is any direct mucosal, percutaneous, or intravenous contact with potentially infectious body fluids that occurs outside perinatal or occupational situations (e.g., health-care, sanitation, public safety, or laboratory employment). Potentially infectious body fluids are blood, semen, vaginal secretions, rectal secretions, breast milk or other body fluid that is contaminated with visible blood.

† Information included in these recommendations might not represent Food and Drug Administration (FDA) approval or approved labeling for the particular products or indications in question. Specifically, the terms safe and effective might not be synonymous with the FDA-defined legal standards for product approval.

Animal Studies

Animal studies have demonstrated mixed results (1,7). In macaques, PMPA (tenofovir) blocked simian immunodeficiency virus (SIV) infection after intravenous challenge if administered within 24 hours of exposure and continued for 28 days. PMPA was not as effective if initiated 48 or 72 hours postexposure or if continued for only 3 or 10 days (8). Two macaque studies of combination antiretroviral therapy (zidovudine, lamivudine, and indinavir) initiated 4 hours after simian/human immunodeficiency virus (SHIV) challenge and continued for 28 days did not protect against infection but did result in reduced viral load among the animals infected (9). In a macaque study designed to model nPEP for mucosal HIV exposure, all animals administered PMPA for 28 days, beginning 12 hours (four animals) or 36 hours (four animals) after vaginal HIV-2 exposure, were protected. Three of four animals treated 72 hours after exposure were also protected; the fourth animal had delayed seroconversion and maintained a low viral load after treatment (10).

These findings are consistent with those of macaque studies of the biology of vaginal SIV transmission. After atraumatic vaginal inoculation, lamina propria cells of the cervicovaginal subepithelium were infected first, virus was present in draining lymph nodes within 2 days, and virus was disseminated to the blood stream by 5 days (11). Similarly, in another study, SIV-RNA was detected in dendritic cells from the vaginal epithelium within 1 hour of intravaginal viral exposure, and SIV-infected cells were detected in the lymph nodes within 18 hours (12). These data indicate a small window of opportunity during which it might be possible to interrupt either the initial infection of cells in the cervicovaginal mucosa or the dissemination of local infection by the prompt administration of antiretroviral medications.

Postnatal Prophylaxis

Abbreviated regimens for reducing mother-to-child HIV transmission have been studied extensively. Certain regimens have included a postexposure component (antiretroviral medications given to the neonate). Although reduction in maternal viral load during late pregnancy, labor, and delivery seems to be a major factor in the effectiveness of these regimens, an additional effect is believed to occur because the neonate receives prophylaxis, which protects against infection from exposure to maternal HIV during labor and delivery (13,14). In a Ugandan perinatal trial, the rate of transmission at 14–16 weeks postpartum was substantially lower for women who received a single dose of nevirapine at the beginning of labor followed by a single dose of nevirapine to the neonate within

72 hours of birth (transmission rate: 13.1%) than for the women who received intrapartum zidovudine followed by 1 week of zidovudine to the neonate (transmission rate: 25.1%) (15). Similarly low transmission rates were noted in a study in South Africa in which intrapartum and postpartum antiretroviral medications were used. At 8 weeks postpartum, the transmission rate was 9.3% after intrapartum zidovudine and lamivudine followed by 1 week of zidovudine and lamivudine to mother and neonate, and the transmission rate was 12.3% after a single dose of nevirapine administered to the mother during labor and then to the neonate within 72 hours of birth (16). Although these studies lacked control groups, these dosing schedules could not have substantially reduced HIV exposure of the neonate through reducing maternal viral load, demonstrating that a combination of pre-exposure and postexposure prophylaxis for the neonate reduces HIV transmission. A study in Malawi among women who did not receive intrapartum antiretrovirals compared postnatal prophylaxis with single-dose nevirapine with and without zidovudine for 1 week. The transmission rate at 6–8 weeks was 7.7% among infants who received zidovudine plus nevirapine compared with 12.1% among those who received nevirapine alone (17). Although this study did not have a placebo or no-prophylaxis arm, the transmission rate for the zidovudine-nevirapine arm compares favorably with the rate of 21% at 4 weeks, noted in the placebo arm of a study of zidovudine prophylaxis conducted in Cote d'Ivoire (18).

Two observational studies with relatively limited numbers documented a potential effect of postnatal zidovudine prophylaxis alone (without intrapartum medication). A review of medical records in New York indicated that zidovudine monotherapy administered to the mother intrapartum or to the infant within 72 hours of birth reduced perinatal transmission >50%; initiating monotherapy for the infant >72 hours after birth was less effective (19). Similarly, an analysis of births in the PACTS study demonstrated that zidovudine administered to infants within 24 hours of birth, when mothers had not been treated either antepartum or intrapartum, compared with no treatment for mothers or infants, reduced perinatal transmission by 48% (20).

Observational Studies of nPEP

The most direct evidence supporting the efficacy of postexposure prophylaxis is a case-control study of needlestick injuries to health-care workers. In this study, the prompt initiation of zidovudine was associated with an 81% decrease in the risk for acquiring HIV (21). Although analogous clinical studies of nPEP have not been conducted, data are available from observational studies and registries.

In a high-risk HIV incidence cohort in Brazil, nPEP instruction and 4-day starter packs of zidovudine and lamivudine were administered to 200 homosexual and bisexual men. Men who began taking nPEP after a self-identified high-risk exposure were evaluated within 96 hours; 92% met the event eligibility criteria (clinician-defined high-risk exposure). Seroincidence was 0.7 per 100 person-years (one seroconversion) among men who took nPEP and 4.1 per 100 person-years among men who did not take nPEP (11 seroconversions) (22,23). Subsequent analysis of data from patients who took nPEP and had been followed for a median of 24.2 months indicated 11 seroconversions and a sero-incidence of 2.9 per 100 person-years, compared with an expected sero-incidence of 3.1 per 100 person years, $p>0.97$) (24). In a study of sexual assault survivors in Sao Paulo, Brazil, women who sought care within 72 hours after exposure were treated for 28 days with either zidovudine and lamivudine (for those without mucosal trauma) or zidovudine, lamivudine, and indinavir (for those with mucosal trauma or those subjected to unprotected anal sex) for 28 days. Women were not treated if they sought care >72 hours after assault, if the assailant was HIV-negative, or if a condom was used and no mucosal trauma was seen. Of 180 women treated, none seroconverted. Of 145 women not treated, four (2.7%) seroconverted (25). Although these studies demonstrate that nPEP might reduce the risk for infection after sexual HIV exposures, participants were not randomly assigned, and sample sizes were too small for statistically significant conclusions.

In a study of rape survivors in South Africa, of 480 initially seronegative survivors begun on zidovudine and lamivudine and followed up for at least 6 weeks, one woman seroconverted. She had started taking medications 96 hours after the assault. An additional woman, who sought treatment 12 days after assault, was seronegative at that time but not offered nPEP. At retesting 6 weeks after the assault, she had seroconverted and had a positive polymerase chain reaction result (Personal communication, A. Wulfsohn, MD, Sunninghill Hospital, Gauteng, South Africa).

In a feasibility trial of nPEP conducted in San Francisco, 401 persons with eligible sexual and injection-drug-use exposures were enrolled. No seroconversions were observed among those who completed treatment, those who interrupted treatment, or those who did not receive nPEP (26). In a study in British Columbia of 590 persons who completed a course of nPEP, no seroconversions were observed (27). In registries from four countries (Australia, France, Switzerland, and the United States), including approximately 2,000 nonoccupational exposure case reports, no confirmed seroconversions

have been attributed to a failure of nPEP in approximately 350 nPEP-treated persons reported to have been exposed to HIV-infected sources. However, the absence of seroconversions might not be attributed to receipt of nPEP but rather to the low per-act risk for infection and incomplete follow-up in the registries.

Case Reports

In addition to these studies, two case reports are of note. In one, a patient who received a transfusion of red blood cells from a person subsequently determined to have early HIV infection began taking combination PEP 1 week after transfusion and continued for 9 months. The patient did not become infected despite the high risk associated with the transfusion of HIV-infected blood (28). In the other case, nPEP was initiated 10 days after self-insemination with semen from a homosexual man later determined to have early HIV infection. The woman did not become infected but did become pregnant and gave birth to a healthy infant (29).

Although data from the studies and case reports do not provide definitive evidence of the efficacy of nPEP after sexual, injection-drug-use, and other nonoccupational exposures to HIV, the cumulative data demonstrate that antiretroviral therapy initiated soon after exposure and continued for 28 days might reduce the risk for acquiring HIV.

Evidence of Possible Risks from nPEP

Concerns about the potential risks from nPEP as a public health intervention include possible decrease in risk-reduction behaviors resulting from a perception that postexposure treatment is available, the occurrence of serious adverse effects from antiretroviral treatment in otherwise healthy persons, and potential selection for resistant virus (particularly if adherence is poor during the nPEP course). Evidence indicates that these theoretical risks might not be major problems.

Effects on Risk-Reduction Behaviors

The availability or use of nPEP might not lead to increases in risk behavior. Of participants in the nPEP feasibility study in San Francisco, 72% reported a decrease in risk behavior over the next 12 months relative to baseline reported risk behavior, 14% reported no change, and 14% reported an increase (30). However, 17% of participants requested a second course of nPEP during the year after the first course, indicating that although participants did not increase risk

behaviors, a substantial proportion of the participants did not eliminate risk behaviors. A similar proportion of participants (14%) requested a second course of nPEP at the Fenway Clinic in Boston (31). In the Brazil nPEP study of homosexual and bisexual men followed up for a median of 24 months, all groups, including those who elected to take nPEP, reported decreases in risk behavior (24,32). Among highly educated (75% with ≥ 4 years of college), predominantly white (74%) homosexual men who completed a street-outreach interviewer-administered survey in San Francisco, those who reported that they were aware of the availability of nPEP did not report more risk behavior than those who were not aware (33). In a study of discordant heterosexual couples, none reported decreased condom use because of the availability of nPEP (34).

Antiretroviral Side Effects and Toxicity

Initial concerns about severe side effects and toxicities have been ameliorated by experience with health-care workers who have taken PEP after occupational exposures. Of 492 health-care workers reported to the occupational PEP registry, 63% took at least three medications. Overall, 76% of workers who received PEP and had 6 weeks of follow-up reported certain symptoms (i.e., nausea [57%] and fatigue or malaise [38%]). Only 8% of these workers had laboratory abnormalities, few of which were serious and all of which resolved promptly at the end of antiretroviral treatment (35). Six (1.3%) reported severe adverse events, and four stopped taking PEP because of them. Of 68 workers who stopped taking PEP despite exposure to a source person known to be HIV-positive, 29 (43%) stopped because of side effects. According to the U.S. nPEP surveillance registry, among 107 exposures for which nPEP was taken, the regimen initially prescribed was stopped or modified in 22%; modifications or stops were reported because of side effects in half of these instances (36). In addition to reports in these registries, serious side effects have been reported (e.g., nephrolithiasis and hepatitis) in the literature.

During 1997–2000, a total of 22 severe adverse events in persons who had taken nevirapine-containing regimens for occupational or nonoccupational postexposure prophylaxis were reported to FDA (37–38). Severe hepatotoxicity occurred in 12 (one requiring liver transplantation), severe skin reactions in 14, and both hepatic and cutaneous manifestations occurred in four. Because the majority of occupational exposures do not lead to HIV infection, the risk for using a nevirapine-containing regimen for occupational PEP outweighs the potential benefits. The same rationale indicates that nevirapine should not be used for nPEP.

Selection of Resistant Virus

Antiretroviral PEP does not prevent all infections in occupational and perinatal settings. Similarly, PEP is not expected to have complete efficacy after nonoccupational exposures. In instances where nPEP fails to prevent infection, selection of resistant virus by the antiretroviral drugs is theoretically possible. However, because of the relative paucity of documented nPEP failures for which resistance testing was performed, the likelihood of this occurring is unknown.

PEP failures have been documented after at least one sexual (39) and 21 occupational (38,40) exposures. Three fourths of these patients were treated with zidovudine monotherapy. Only three received three or more antiretroviral medications for PEP. Among the patients tested, several were infected with strains that were resistant to antiretroviral medications. In a study in Brazil (24), virus obtained on day 28 of therapy from the only treated person who seroconverted (whose regimen included 3TC) had a 3TC-resistance mutation. However, the source-person could not be tested. Therefore, whether the mutation was present when the virus was transmitted or whether it developed during nPEP could not be determined.

Selection of resistant virus might occasionally result from the use of nPEP. However, because the majority of nonoccupational exposures do not lead to HIV infection and because the use of combination antiretroviral therapy might reduce further the transmission rate, such occurrences are probably rare. For patients who seroconvert despite nPEP, resistance testing should be considered to guide early and subsequent treatment decisions.

Cost-Effectiveness of nPEP

Although the potential benefits of nPEP to persons are measured by balancing its anticipated efficacy after a given exposure against individual health risks, the value of nPEP as a public health intervention is best addressed at the population level by using techniques such as cost-benefit analysis. Such analyses have been published. One cost-effectiveness evaluation of nPEP in different potential exposure scenarios in the United States reported it to be cost-effective only in situations in which the sex partner source was known to be HIV-infected or after unprotected receptive anal intercourse with a homosexual or bisexual man of unknown serostatus (41,42). A similar analysis in France reported that nPEP was cost-saving for unprotected receptive anal intercourse with a partner known to be HIV-infected and cost-effective for receptive anal intercourse with a homosexual or bisexual partner of unknown serostatus. It was not cost-effective for penile-

vaginal sex, insertive anal intercourse, or other exposures considered (43).

Another study and anecdotal reports indicate difficulty limiting nPEP to the exposures most likely to benefit from it. In British Columbia, where guidelines for nPEP use have been implemented (5), an analysis indicated that >50% of those receiving nPEP should not, according to the guidelines, have been treated (e.g., for exposure to intact skin). The use of nPEP in these circumstances doubled the estimated cost per HIV infection prevented (\$530,000 versus \$230,000) (44).

Even if nPEP is cost-effective for the highest risk exposures, behavioral interventions are more cost-effective (41,45). This emphasizes the importance, when considering nPEP, of providing risk-avoidance and risk-reduction counseling to reduce the occurrence of future HIV exposures.

Evidence of Current Practice

Although 40,000 new HIV infections occur in the United States each year, relatively few exposed persons seek care after nonoccupational exposure. Certain exposures are unrecognized. Certain patients have frequently recurring exposures and would not benefit from nPEP because 4 weeks of potential protection cannot substantially reduce their overall risk for acquiring HIV infection. In addition, certain clinicians and exposed patients are unaware of the availability of nPEP or unconvinced of its efficacy and safety. Finally, access to knowledgeable clinicians or a means of paying for nPEP might constrain its use.

Certain populations in the United States remain at high risk for exposure. In a cohort study of homosexual and bisexual men, 17% reported at least one condom failure during the 6 months preceding study enrollment (46). Other studies indicate that increasing use of highly active antiretroviral therapy (HAART) by HIV-infected persons might be leading some persons to have unprotected sex more frequently, in part because of the belief that lowered viral load substantially reduces infectivity (47–50). This finding is supported by increased rates of sexually transmitted infections among HIV-infected patients (51). In a California study, 69% of discordant heterosexual couples reported having had unprotected sex during the preceding 6 months (34).

Since 1998, certain clinicians have recommended wider availability and use of nPEP (52–58), and others have been more cautious about implementing it in the absence of definitive evidence of efficacy (59,60). Multiple public health jurisdictions, including the New York State AIDS Institute, the San Francisco County Health Department, the Massachusetts Department of Public Health, the Rhode Island

Department of Health, and the California State Office of AIDS, have issued policies or advisories for nPEP use. Some of these recommendations have focused on sexual assault survivors, who constitute few of the estimated 40,000 new HIV infections annually in the United States.

Surveys of clinicians and facilities indicate a need for more widespread implementation of guidelines and protocols for nPEP use (61). In a survey of Massachusetts emergency department directors, 52% of facilities had received nPEP requests during the preceding year, but only 15% had written nPEP protocols (62). Similarly, in a survey of Massachusetts clinicians, approximately 20% had a written nPEP protocol (63). Among pediatric emergency medicine specialists surveyed throughout the United States and Canada, approximately 20% had a written policy about nPEP use, but 33% had prescribed it for children and adolescents; different prescribing practices were reported (64). In a survey of 27 European Union countries, 23 had guidelines for occupational PEP use, but only six had guidelines for nPEP use (65).

Evidence indicates considerable awareness of nPEP and interest in its use among potential patients. In a cohort study of homosexual and bisexual men, 60% were willing to participate in a study of nPEP if it involved a single daily dose of medication; 30% were willing to take 3 doses daily (66). Among men surveyed at a "gay pride" festival in Atlanta, although only 3% had used nPEP, 26% planned to if exposed in the future (67). When nPEP studies were established in San Francisco, approximately 400 persons sought treatment in 2½ years (24). At a clinic primarily serving homosexual and bisexual men in Boston, 71 requests for nPEP were evaluated in 1½ years (30). In a California study of heterosexual discordant couples, 28% had heard of nPEP, 55% of seronegative partners believed that it was effective, and 78% reported they would take it if exposed (34).

No nationally representative data exists on nPEP use in the United States. In 1998, CDC established a national nPEP surveillance registry that accepts voluntary reports by clinicians. Although approximately 800 reports have been received, the majority of clinicians prescribing nPEP do not report to the registry. Similarly, low reporting rates were obtained in attempts to establish voluntary registries to monitor occupational PEP and antiretroviral use during pregnancy. No national surveys of clinicians have been reported. However, one multisite HIV vaccine trial largely conducted in the United States has assessed nPEP use by 5,418 participants, who included men who have sex with men (94%) and heterosexual women at high risk (6%). Two percent of trial participants from 27 study sites reported having taken nPEP during the trial. Supplementary data from six U.S. sites indicated that 46% of participants had heard of nPEP. Enrollment at one of

seven California sites (odds ratio [OR] = 3.2), having a known positive partner (OR = 2.0), higher educational level (OR = 1.4), and greater recreational drug use (OR = 1.2) were significant predictors of having used nPEP ($p < 0.05$) (68).

Evaluation of Persons Seeking Care After Potential Nonoccupational Exposure to HIV

The effective delivery of nPEP after exposures that have a substantial risk for HIV infection requires prompt evaluation of patients and consideration of biomedical and behavioral interventions to address current and ongoing health risks. This evaluation should include determination of the HIV status of the potentially exposed person, the timing and characteristics of the most recent exposure, the frequency of exposures to HIV, the HIV status of the source, and the likelihood of concomitant infection with other pathogens or negative health consequences of the exposure event.

HIV Status of the Potentially Exposed Person

Because persons who are infected with HIV might not be aware they are infected, baseline HIV testing should be performed on all persons seeking evaluation for potential nonoccupational HIV exposure. If possible, this should be done with an FDA-approved rapid test kit (with results available within an hour). If rapid tests are not available, an initial treatment decision should be made based on the assumption that the potentially exposed patient is not infected, pending HIV test results.

Timing and Frequency of Exposure

Available data indicate that nPEP is less likely to be effective if initiated >72 hours after HIV exposure. If initiation of nPEP is delayed, the likelihood of benefit might not outweigh the risks inherent in taking antiretroviral medications.

Because nPEP is not 100% effective in preventing transmission and because antiretroviral medications carry a certain risk for adverse effects and serious toxicities, nPEP should be used only for infrequent exposures. Persons who engage in behaviors that result in frequent, recurrent exposures that would require sequential or near-continuous courses of antiretroviral medications (e.g., discordant sex partners who rarely use condoms or injection-drug users who often share injection equipment) should not take nPEP. In these instances, exposed persons should instead be provided with intensive risk-reduction interventions.

HIV Status of Source

Patients who have had sexual, injection-drug-use, or other nonoccupational exposures to potentially infectious fluids of persons known to be HIV infected are at risk for acquiring HIV infection and should be considered for nPEP if they seek treatment within 72 hours of exposure. If possible, source persons should be interviewed to determine his or her history of antiretroviral use and most recent viral load because this information might provide information for the choice of nPEP medications.

Persons with exposures to potentially infectious fluids of persons of unknown HIV status might or might not be at risk for acquiring HIV infection. When the source is known to be from a group with a high prevalence of HIV infection (e.g., a homosexual or bisexual man, an injection-drug user, or a commercial sex worker), the risk for transmission might be increased. The risk for transmission might be especially great if the source person has been infected recently, when viral burden in blood and semen might be particularly high (69,70). However, ascertaining this in the short time available for nPEP evaluation is rarely possible. When the HIV status of the source is unknown, it should be determined whether the source is available for HIV testing. If the risk associated with the exposure is considered substantial, nPEP can be started pending determination of the HIV status of the source and then stopped if the source is determined to be noninfected.

Transmission Risk from the Exposure

Although the estimated per-act transmission risk from unprotected exposure to a partner known to be HIV infected is relatively low for different types of exposure (Table 1), different nonoccupational exposures are associated with different levels of risk (71–79). The highest levels of estimated per-act risk for HIV transmission are associated with blood transfusion, needle sharing by injection-drug users, receptive anal

intercourse, and percutaneous needlestick injuries. Insertive anal intercourse, penile-vaginal exposures, and oral sex represent substantially less per-act risk.

A history should be taken of the specific sexual, injection-drug-use, or other behaviors that might have led to, or modified, a risk for acquiring HIV infection. Eliciting a complete description of the exposure and information about the HIV status of the partner(s) can substantially lower (e.g., if the patient was the insertive partner or a condom was used) or increase (e.g., if the partner is known to be HIV-positive) the estimate of risk for HIV transmission resulting from a specific exposure.

In addition to sexual and injection-drug-use exposures, percutaneous injuries from needles discarded in public settings (e.g., parks and buses) result in requests for nPEP with a certain frequency. Although no HIV infections from such injuries have been documented, concern exists that syringes discarded by injection-drug users (e.g., for whom the HIV infection rate is higher than that for diabetics) might pose a substantial risk. However, these injuries typically involve small-bore needles that contain only limited amounts of blood, and the viability of any virus present is limited. In a study of syringes used to administer medications to HIV-infected persons, only 3.8% had detectable HIV RNA (72). In a study of the viability of virus in needles, viable virus was recovered from 8% at 21 days when the needles had been stored at room temperature; <1% had viable virus after 1 week of storage at higher temperatures (73).

Bite injuries represent another potential means of transmitting HIV. However, HIV transmission by this route has been reported rarely (80–82). Transmission might theoretically occur either through biting or receiving a bite from an HIV-infected person. Biting an HIV-infected person, resulting in a break in the skin, exposes the oral mucous membranes to infected blood; being bitten by an HIV-infected person exposes nonintact skin to saliva. Saliva that is contaminated with infected blood poses a substantial exposure risk. Saliva that is not contaminated with blood contains HIV in much lower titers and constitutes a negligible exposure risk (83).

TABLE 1. Estimated per-act risk for acquisition of HIV, by exposure route*

Exposure route	Risk per 10,000 exposures to an infected source	Reference
Blood transfusion	9,000	74
Needle-sharing injection-drug use	67	75
Receptive anal intercourse	50	76, 77
Percutaneous needle stick	30	78
Receptive penile-vaginal intercourse	10	76, 77, 79
Insertive anal intercourse	6.5	76, 77
Insertive penile-vaginal intercourse	5	76, 77
Receptive oral intercourse	1	77 [†]
Insertive oral intercourse	0.5	77 [†]

*Estimates of risk for transmission from sexual exposures assume no condom use.

[†]Source refers to oral intercourse performed on a man.

Evaluation for Sexually Transmitted Infections, Hepatitis, and Emergency Contraception

Evaluation for sexually transmitted infections is important because these infections might increase the risk for acquiring HIV infection from a sexual exposure. In 1996, an estimated 5,042 new HIV infections were attributable to sexually transmitted infection at the time of HIV exposure (84). In addition,

tion, any sexual exposure that presents a risk for HIV infection might also place a patient at risk for acquiring other sexually transmitted infections, including hepatitis B. Prophylaxis for sexually transmitted disease, testing for hepatitis, and vaccination for hepatitis B (for those not immune) should be considered (85).

For women of reproductive capacity who have had genital exposure to semen, the risk for pregnancy also exists. In these instances, emergency contraception should be discussed with the potentially exposed patient.

Recommendations for Use of Antiretroviral nPEP

A 28-day course of HAART is recommended for persons who have had nonoccupational exposure to blood, genital secretions, or other potentially infected body fluids of a persons known to be HIV infected when that exposure represents a substantial risk for HIV transmission (Figure 1) and when the person seeks care within 72 hours of exposure. When indicated, antiretroviral nPEP should be initiated promptly for the best chance of success.

Evidence from animal studies and human observational studies demonstrate that nPEP administered within 48–72 hours

and continued for 28 days might reduce the risk for acquiring HIV infection after mucosal and other nonoccupational exposures. The sooner nPEP is administered after exposure, the more likely it is to interrupt transmission. Because HIV is an incurable transmissible infection that affects the quality and duration of life, HAART should be used to maximally suppress local viral replication that otherwise might occur in the days after exposure and potentially lead to a disseminated, established infection (11,86). One of the HAART combinations recommended for the treatment of persons with established HIV infection should be selected on the basis of adherence, toxicity, and cost considerations (Tables 2 and 3) (87,88).

No evidence indicates that any specific antiretroviral medication or combination of medications is optimal for use as nPEP. However, on the basis of the degree of experience with individual agents in the treatment of HIV-infected persons, certain agents and combinations are preferred. Preferred regimens include efavirenz and lamivudine or emtricitabine with zidovudine or tenofovir (as a nonnucleoside-based regimen) and lopinavir/ritonavir (coformulated in one tablet as Kaletra®) and zidovudine with either lamivudine or emtricitabine. Different alternative regimens are possible (Table 2).

No evidence indicates that a three-drug HAART regimen is more likely to be effective than a two-drug regimen. The recommendation for a three-drug HAART regimen is based on the assumption that the maximal suppression of viral replication afforded by HAART (the goal in treating HIV-infected persons) will provide the best chance of preventing infection in a person who has been exposed. Clinicians and patients who are concerned about potential adherence and toxicity issues associated with a three-drug HAART regimen might consider the use of a two-drug regimen (i.e., a combination of two reverse transcriptase inhibitors). Regardless of the regimen chosen, the exposed person should be counseled about the potential associated side effects and adverse events that require immediate medical attention. The use of medications to treat symptoms (e.g., antiemetics or antimotility agents) might improve adherence in certain instances.

Although certain preliminary studies have evaluated the penetration of antiretroviral medications into genital tract secretions and tissues (89,90), evidence is insufficient to recommend a specific antiretroviral medication as most effective for nPEP. In addition, new antiretroviral medications might become available. As new medications and new information become available, these recommendations will be amended and updated.

When the source-person is available for interview, his or her history of antiretroviral medication use and most recent

FIGURE 1. Algorithm for evaluation and treatment of possible nonoccupational HIV exposures

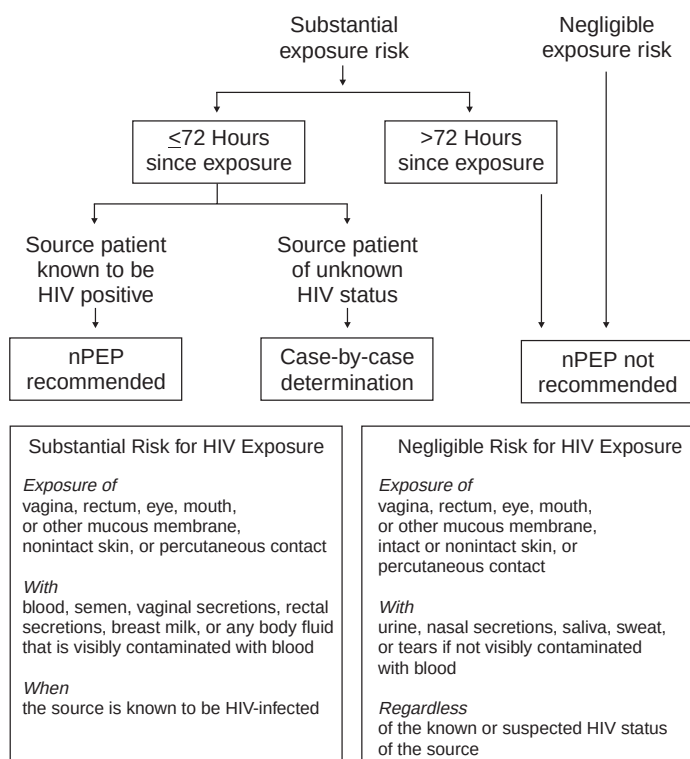


TABLE 2. Antiretroviral regimens for nonoccupational postexposure prophylaxis of HIV infection

Preferred regimens	
NNRTI*-based	Efavirenz [†] plus (lamivudine or emtricitabine) plus (zidovudine or tenofovir)
Protease inhibitor (PI)-based	Lopinavir/ritonavir (co-formulated as Kaletra) plus (lamivudine or emtricitabine) plus zidovudine
Alternative regimens	
NNRTI-based	Efavirenz plus (lamivudine or emtricitabine) plus abacavir or didanosine or stavudine [§]
PI-based	Atazanavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or didanosine) or (tenofovir plus ritonavir [100 mg/day])
	Fosamprenavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine) or (abacavir or tenofovir or didanosine)
	Fosamprenavir/ritonavir [¶] plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Indinavir/ritonavir ^{**} plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Lopinavir/ritonavir (co-formulated as Kaletra) plus (lamivudine or emtricitabine) plus (stavudine or abacavir or tenofovir or idanosine)
	Nelfinavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
Triple NRTI*	Saquinavir (hgc* or sgc*)/ritonavir [†] plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Abacavir plus lamivudine plus zidovudine (only when an NNRTI- or PI-based regimen cannot or should not be used)

* NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; sgc = soft-gel saquinavir capsule (Fortovase); hgc = hard-gel saquinavir capsule (Invirase).

[†] Efavirenz should be avoided in pregnant women and women of child-bearing potential.

[§] Higher incidence of lipoatrophy, hyperlipidemia, and mitochondrial toxicities associated with stavudine than with other NRTIs.

[¶] Low-dose (100–400 mg) ritonavir. See Table 4 for doses used with specific PIs.

^{**} Use of ritonavir with indinavir might increase risk for renal adverse events.

Source: U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, October 29, 2004 revision. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=50. This document is updated periodically; refer to website for updated versions.

viral load measurement should be considered when selecting antiretroviral medications for nPEP. This information might help avoid prescribing antiretroviral medications to which the source-virus is likely to be resistant. If the source-person is willing, the clinician might consider drawing blood for viral load and resistance testing, the results of which might be use-

ful in modifying the initial nPEP medications if the results can be obtained promptly (91).

For persons who have had nonoccupational exposure to potentially infected body fluids of a person of unknown HIV infection status, when that exposure represents a substantial risk for HIV transmission (Figure 1) and when care is sought within 72 hours of exposure, no recommendations are made either for or against the use of antiretroviral nPEP. Clinicians should evaluate the risk for and benefits of this intervention on a case-by-case basis.

When a source-person is not known to be infected with HIV, the risk for exposure (and therefore the potential benefit of nPEP) is unknown. Prescribing antiretroviral medication in these cases might subject patients to risks that are not balanced with the potential benefit of preventing the acquisition of HIV infection. Judging whether the balance is appropriate depends entirely on the circumstances of the possible exposure (i.e., the risk that the source is HIV infected and the risk for transmission if the source is HIV infected) and is best determined through discussion between the clinician and the patient.

If the source-person is available for interview, additional information about risk history can be obtained and permission for an HIV test requested to assist in determining the likelihood of HIV exposure. When available, FDA-approved rapid HIV tests are preferable for obtaining this information as quickly as possible. These additional factors might assist in the decision whether to start or complete a course of nPEP. If data to clearly determine risk are not immediately available, clinicians might consider initiating nPEP while further assessments are being made and then stopping it when other information is available (e.g., the source-person is determined to be noninfected).

For persons whose exposure histories represent no substantial risk for HIV transmission (Figure 1) or who seek care >72 hours after potential nonoccupational HIV exposure, the use of antiretroviral nPEP is not recommended. When the risk for HIV transmission is negligible, limited benefit is anticipated from the use of nPEP. In addition, animal and human study data demonstrate that nPEP is less likely to prevent HIV transmission when initiated >72 hours after exposure. Because the risks associated with antiretroviral medications are likely to outweigh the potential benefit of nPEP in these circumstances, nPEP is not recommended for such exposures, regardless of the HIV status of the source. However, it cannot be concluded on the basis of the available data that nPEP will be completely ineffective when initiated >72 hours after exposure. Moreover, data do not indicate an absolute time after exposure beyond which nPEP will not be effective. When

TABLE 3. Highly active antiretroviral therapy medications, adult dosage, cost, and side effects

Medication	Adult dosage*	Cost (in dollars) for 4 weeks†	Side effects and toxicities
Combination tablets			
Lopinavir/ritonavir (Kaletra®) §	3 tablets twice daily 400 mg lopinavir/100 mg ritonavir	650	Diarrhea, nausea, vomiting; asthenia; elevated transaminases; hyperglycemia; fat redistribution; lipid abnormalities; possible increased bleeding in persons with hemophilia; and pancreatitis
Zidovudine/lamivudine (Combivir®)	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine	640	See following individual medications
Zidovudine/lamivudine/abacavir (Trizivir®)	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine/ 300 mg abacavir	1,020	See following individual medications
Lamivudine/abacavir (Epzicom®)	1 tablet once daily 300 mg lamivudine/600 mg abacavir	760	See following individual medications
Emtricitabine/tenofovir (Truvada®)	1 tablet once daily 200 mg emtricitabine/300 mg tenofovir	800	See following individual medications
Single agents			
Nucleoside and nucleotide reverse transcriptase inhibitors (Side effects as a class: lactic acidosis, severe hepatomegaly with steatosis, including some fatal cases)			
Abacavir (Ziagen®, ABC)§	300 mg twice daily or 600 mg once daily	400	Severe hypersensitivity reaction (can be fatal); nausea; and vomiting
Didanosine (Videx®, ddl)§	>60 kg (132 lb) body weight: 200 mg twice daily or 400 mg daily; if with tenofovir, 250 mg/daily <60 kg (132 lb): 125 mg twice daily or 250 mg daily; if with tenofovir, dose not established Do not use with stavudine (d4T, Zerit) during pregnancy; avoid ddl/d4T combination in general because of increased risk for adverse events (e.g., neuropathy, pancreatitis, and hyperlactatemia)	260	Pancreatitis; nausea, diarrhea; and peripheral neuropathy
Emtricitabine (Emtriva®, FTC)	200 mg once daily	280	Minimal toxicity; lactic acidosis and hepatic steatosis a rare but possibly life-threatening event
Lamivudine (Epivir®, 3TC)§	150 mg twice daily or 300 mg once daily	300	Minimal toxicity; lactic acidosis and hepatic steatosis a rare but possibly life-threatening event
Stavudine (Zerit®, d4T)§	>60 kg (132 lb) body weight: 40 mg twice daily <60 kg (132 lb) body weight: 30 mg twice daily Do not use with didanosine (ddl, Videx) during pregnancy; avoid ddl/d4T combination in general because of increased risk for adverse events (e.g., neuropathy, pancreatitis, and hyperlactatemia)	320	Pancreatitis; peripheral neuropathy; rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir (Viread®)	300 mg daily	400	Nausea, vomiting, diarrhea; headache; asthenia; flatulence; and renal impairment
Zidovudine (Retrovir®, AZT)§	200 mg three times daily or 300 mg twice daily	350	Bone marrow suppression (anemia, neutropenia); gastrointestinal intolerance; headache; insomnia; asthenia; and myopathy

TABLE 3. (Continued) Highly active antiretroviral therapy medications, adult dosage, cost, and side effects

Medication	Adult dosage*	Cost (in dollars) for 4 weeks†	Side effects and toxicities
Single agents			
Non-nucleoside reverse transcriptase inhibitors (Side effects as a class: Stevens-Johnson syndrome)			
Efavirenz (Sustiva®)	600 mg daily at bedtime Do not use during known or possible pregnancy	420	Rash; central nervous system symptoms (e.g., dizziness, impaired concentration, insomnia, and abnormal dreams); transaminase elevation; and false-positive cannabinoid test
Protease inhibitors (Side effects as a class: gastrointestinal intolerance, hyperlipidemia, hyperglycemia, diabetes, fat redistribution, and possible increased bleeding in hemophiliacs)			
Atazanavir (Reyataz®)	400 mg once daily; if administered with tenofovir plus ritonavir, 300 mg once daily	760	Indirect hyperbilirubinemia; prolonged PR interval (use caution in patients with underlying cardiac conduction defects or on concomitant medications that can cause PR prolongation)
Fosamprenavir (Lexiva®)§	1,400 mg twice daily	1,260	Gastrointestinal intolerance, nausea, vomiting, diarrhea; rash; elevated transaminases; and headache
Indinavir (Crixivan®)	800 mg every 8 hours With ritonavir (might increase risk for renal adverse events): 800 mg indinavir and 100 mg ritonavir every 12 hours or 800 mg indinavir and 200 mg ritonavir every 12 hours	500	Gastrointestinal intolerance, nausea; nephrolithiasis; headache; asthenia; blurred vision; metallic taste; thrombocytopenia; hemolytic anemia; and indirect hyperbilirubinemia (inconsequential)
Nelfinavir (Viracept®)§	750 mg three times daily or 1,250 mg twice daily	600	Diarrhea; and elevated transaminases
Ritonavir (Norvir®)§	See doses used in combination with other specific protease inhibitors	700–2,800	Gastrointestinal intolerance; nausea, vomiting, diarrhea; paresthesias; hepatitis; pancreatitis; asthenia; and taste perversion; many drug interactions
Saquinavir (hard-gel capsule) (Invirase®)	With ritonavir: 400 mg saquinavir and 400 mg ritonavir twice daily or 1,000 mg saquinavir and 100 mg ritonavir twice daily	270	Gastrointestinal intolerance; nausea, diarrhea; headache; and elevated transaminases
Saquinavir (soft-gel capsule) (Fortavase®)	With Ritonavir: 400 mg saquinavir and 400 mg ritonavir twice daily or 1,000 mg saquinavir and 100 mg ritonavir twice daily	460	Gastrointestinal intolerance; nausea, diarrhea; abdominal pain; dyspepsia; headache; and elevated transaminases

* For pediatric dosing information, see *Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection* (available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=51)

† Available at <http://www.cvs.com/CVSApp/cvs/gateway/rxpriceqrequest>

§ Pediatric formulation available.

Sources: U.S. Department of Health and Human Services and the Henry J. Kaiser Family Foundation. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=50 (refer to website for updated versions). Bartlett JG, Finkbeiner AK. HIV drugs: the guide to living with HIV infection. 2001. 11-13-2001. Available at <http://www.thebody.com/jh/bartlett/drugs.html>.

safer and more tolerable drugs are used, the risk-benefit ratio of providing nPEP >72 hours postexposure is more favorable. Therefore, clinicians might consider prescribing nPEP after exposures that confer a serious risk for transmission, even if the exposed person seeks care >72 hours postexposure if, in the clinician's judgment, the diminished potential benefit of nPEP outweighs the potential risk for adverse events from antiretroviral drugs.

Considerations for All Patients Treated with Antiretroviral nPEP

Use of Starter Packs

Patients might be under considerable emotional stress when seeking care after a potential HIV exposure and might not attend to, or retain, all the information relevant to making a decision about nPEP. Clinicians should give an initial prescription for 3–5 days of medication and schedule a follow-up visit to review the results of baseline HIV testing (if rapid tests are not used), provide additional counseling and support, assess medication side effects and adherence, and provide additional medication if appropriate (with an altered regimen if indicated by side effects or laboratory test results).

Scientific Consultation

When clinicians are not experienced with using HAART or when information from source-persons indicates the possibility of antiretroviral resistance, consultation with infectious disease or other HIV-care specialists, if it is available immediately, might be warranted before prescribing nPEP. Similarly, when considering prescribing nPEP to pregnant women or children, consultation with obstetricians or pediatricians might be advisable. However, if such consultation is not immediately available, initiation of nPEP should not be delayed. An initial nPEP regimen should be started and, if necessary, revised after consultation is obtained. Patients who seek nPEP might benefit from referral for psychological counseling that helps ease the anxiety about possible HIV exposure, strengthens risk-reduction behaviors, and promotes adherence to nPEP regimens if prescribed.

Facilitating Adherence

Adherence to antiretroviral medications can be challenging, even for 28 days. In addition to common side effects such as nausea and fatigue, each dose reminds the patient of his or her risk for acquiring HIV infection. Adherence has been reported to be especially poor among sexual assault survivors

(92–96). Steps to maximize medication adherence include prescribing medications with fewer doses and fewer pills per dose, educating patients about the importance of adherence and about potential side effects, offering ancillary medications for side effects (e.g., anti-emetics) if they occur, and providing access to ongoing encouragement and consultation by phone or office visit.

Follow-up Testing and Care

All patients seeking care after HIV exposure should be tested for the presence of HIV antibodies at baseline and at 4–6 weeks, 3 months, and 6 months after exposure to determine whether HIV infection has occurred. In addition, testing for sexually transmitted diseases, hepatitis B and C, and pregnancy should be offered (Table 4).

Patients should be instructed about the signs and symptoms associated with acute retroviral infection (Table 5), especially fever and rash (97), and asked to return for evaluation if these occur during or after nPEP. Acute HIV infection is associated with high viral loads. However, clinicians should be aware that available assays might yield low viral-load results (e.g., <3,000) in noninfected persons. Such false-positive results can lead to misdiagnosis of HIV infection (98).

Transient, low-grade viremia has been observed both in macaques exposed to SIV (99) and humans exposed to HIV who were administered antiretroviral PEP (100) and did not become infected. In certain cases, this outcome might represent aborted infection rather than false-positive test results, but this can be determined only through further study. For patients with clinical or laboratory evidence of acute HIV infection, continuing antiretroviral therapy for >28 days might be prudent because such early treatment (no longer prophylaxis) might slow the progression of HIV disease (101). Patients with acute HIV infection should be transferred to the care of HIV treatment specialists.

In addition, clinicians who provide nPEP should monitor liver function, renal function, and hematologic parameters as indicated by the prescribing information found in antiretroviral treatment guidelines (87,102,103), package inserts, and the *Physician's Desk Reference* (Table 3). Unusual or severe toxicities from antiretroviral drugs should be reported to the manufacturer or FDA.

HIV Prevention Counseling

The majority of persons who seek care after a possible HIV exposure do so because of failure to initiate or maintain effective risk-reduction behaviors. Notable exceptions are sexual assault survivors and children with community-acquired needlestick injuries.

TABLE 4. Recommended laboratory evaluation for nonoccupational postexposure prophylaxis (nPEP) of HIV infection

Test	Baseline	During nPEP*	4–6 Weeks after exposure	3 Months after exposure	6 Months after exposure
HIV antibody testing	E [†] , S [§]		E	E	E
Complete blood count with differential	E	E			
Serum liver enzymes	E	E			
Blood urea nitrogen/creatinine	E	E			
Sexually transmitted diseases screen (gonorrhea, chlamydia, syphilis)	E, S	E [¶]	E [¶]		
Hepatitis B serology	E, S		E [¶]	E [¶]	
Hepatitis C serology	E, S			E	E
Pregnancy test (for women of reproductive age)	E	E [¶]	E [¶]		
HIV viral load	S		E ^{**}	E ^{**}	E ^{**}
HIV resistance testing	S		E ^{**}	E ^{**}	E ^{**}
CD4 ⁺ T lymphocyte count	S		E ^{**}	E ^{**}	E ^{**}

* Other specific tests might be indicated dependent on the antiretrovirals prescribed. Literature pertaining to individual agents should be consulted.

† E = exposed patient, S = source.

§ HIV antibody testing of the source patient is indicated for sources of unknown serostatus.

¶ Additional testing for pregnancy, sexually transmitted diseases, and hepatitis B should be performed as clinically indicated.

** If determined to be HIV infected on follow-up testing; perform as clinically indicated once diagnosed.

TABLE 5. Expected frequency of associated signs and symptoms among persons with signs and symptoms of acute retroviral syndrome

Symptom/sign	%
Fever	96
Lymphadenopathy	74
Pharyngitis	70
Rash	70
Erythematous maculopapular with lesions on face, trunk and sometimes extremities, including palms and soles; mucocutaneous ulceration involving mouth, esophagus or genitals	
Myalgia or arthralgia	54
Diarrhea	32
Headache	32
Nausea and vomiting	27
Hepatosplenomegaly	14
Weight loss	13
Thrush	12
Neurologic symptoms	12
Meningoencephalitis or aseptic meningitis; peripheral neuropathy or radiculopathy; facial palsy; Guillain-Barré syndrome; brachial neuritis; or cognitive impairment or psychosis	

Although nPEP might reduce the risk for HIV infection, it is not believed to be 100% effective. Therefore, patients should practice protective behaviors with sex partners (e.g., abstinence or consistent use of male condoms) or drug-use partners (e.g., avoidance of shared injection equipment) throughout the course

of nPEP to avoid transmission to others if they become infected, and after nPEP to avoid future HIV exposures.

At follow-up visits, clinicians should assess their patients' needs for behavioral intervention, education, and services. This assessment should include frank, nonjudgmental questions about sexual behaviors, alcohol use, and illicit drug use. Clinicians should help patients identify ongoing risk issues and develop plans for improving their use of protective behaviors (104).

To help patients obtain indicated interventions and services, clinicians should be aware of local resources for high-quality HIV education and ongoing behavioral risk reduction, counseling and support, inpatient and outpatient alcohol and drug-treatment services, substance/drug abuse treatment programs, family and mental health counseling services, and support programs for HIV-infected persons. Information about publicly funded HIV prevention programs can be obtained from state or local health departments.

Management of Source Persons

When source-persons are seen during the course of evaluating a patient for potential HIV exposure, clinicians should also assess the source-person's access to relevant medical care, behavioral intervention, and social support services. If needed care cannot be provided directly, clinicians should help source-persons obtain care in the community.

If a new diagnosis of HIV infection is made or evidence of other sexually transmitted infection is identified, the patient

should be assisted in notifying their sexual and drug-use contacts. Assistance with confidential partner notification (without revealing the patient's identity) is available through local health departments.

Reporting and Confidentiality

Because of the emotional, social, and potential financial consequences of possible HIV infection, clinicians should handle nPEP evaluations with the highest level of confidentiality. Confidential reporting of sexually transmitted infections and newly diagnosed HIV infections to health departments should take place as dictated by local law and regulations.

For cases of sexual assault, clinicians should document their findings and assist patients with notifying local authorities. HIV test results should be recorded separately from the findings of the sexual assault examination to protect patients' confidentiality in the event that medical records are later released for legal proceedings. Certain states and localities have special programs to provide reimbursement for medical therapy, including antiretroviral medication after sexual assault, and these areas might have specific reporting requirements. When the sexual abuse of a child is suspected or documented, the clinician should report it in compliance with state and local law and regulations.

Considerations for Vulnerable Populations

Pregnant Women and Women of Childbearing Potential

Considerable experience has been gained in recent years in the safe and appropriate use of antiretroviral medications during pregnancy, either for the benefit of the HIV-infected woman's health or to prevent transmission to newborns. To facilitate the selection of antiretroviral medications likely to be both effective and safe for the developing fetus, clinicians should consult DHHS guidelines (102) before prescribing nPEP for a woman who is or might be pregnant.

Because of potential teratogenicity, efavirenz should not be used in any nPEP regimen during pregnancy or among women of childbearing age at risk for becoming pregnant during the course of antiretroviral prophylaxis (Table 3). A protease inhibitor- or nucleoside reverse transcriptase inhibitor-based regimen should be considered in these circumstances. When efavirenz is prescribed to women of childbearing potential, they should be instructed about the need to avoid pregnancy. Because the effect of efavirenz on hormonal contraception is unknown, women using such contraception should be

informed of the need to use an additional method (e.g., barrier contraception). In addition, because of reports of maternal and fetal mortality attributed to lactic acidosis associated with prolonged use of d4T in combination with ddI in HIV-infected pregnant women, this combination is not recommended for use in an nPEP regimen (105).

Children

Potential HIV exposures in children occur most often by accident (e.g., needlesticks in the community, fights, or playground incidents resulting in bleeding by an HIV-infected child) or by sexual abuse or assaults (106). In a review of charts from 1 year in the pediatric emergency department of one hospital, 10 children considered for nPEP were identified (six because of sexual assault and four because of needlestick injury). Eight began taking nPEP, but only two completed the 4-week course (63,107). An analysis of 9,136 reported acquired immunodeficiency syndrome cases in children identified 26 who were sexually abused with confirmed or suspected exposure to HIV infection (108).

The American Academy of Pediatrics has issued nPEP guidelines for pediatric patients (109). In addition, DHHS pediatric antiretroviral treatment guidelines (103) provide information about the use of antiretroviral agents in children. For young children who cannot swallow capsules or tablets and to ensure appropriate dosing for drugs that do not have capsule/tablet formulations that allow pediatric dosing, drugs for which pediatric formulations are available might need to be prescribed (Table 3). Adherence to the prescribed medications will depend on the involvement of, and support provided to, parents or guardians.

Sexual Assault Survivors

Use of nPEP for sexual assault survivors has been widely encouraged both in the United States and elsewhere (56, 94,110,111). Sexual assault is relatively common among women: 13% of a national sample of adult women reported having ever been raped (60% before age 18), and 5% reported having been raped more than once (112). Sexual assault is not uncommon among men. In one series from an emergency department, 5% of reported rapes involved men sexually assaulted by men (113). Males accounted for 11.6 % of rapes reported among persons aged ≥ 12 years who responded to the National Crime Victimization Survey in 1999 (114). However, only three documented cases of HIV infection resulting from sexual assault have been published (94,115,116). In observational studies, HIV infections have been temporally associated with sexual assault (Personal communication,

A. Wulfsohn, MD, Sunninghill Hospital, Gauteng, South Africa).

Studies have examined HIV infection rates for sexual assailants (117,118). The largest of these, an evaluation of men incarcerated in Rhode Island, determined that 1% of those convicted of sexual assault were HIV infected when they entered prison, compared with 3% of all prisoners and 0.3% of the general male population (119).

Sexual assault typically has multiple characteristics that increase the risk for HIV transmission if the assailant is infected. In one prospective study of 1,076 sexual assault cases, 20% were attacked by multiple assailants, 39% were assaulted by strangers, 83% of females were vaginally penetrated, and 17% overall were sodomized. Genital trauma was documented in 53% of those assaulted, and sperm or semen was detected in 48% (120). In another study, in which toluidine blue dye was used as an adjunct to naked-eye examination, 40% of assaulted women (70% of nulliparas) had detectable vaginal lacerations, compared with 5% of women examined after consensual sex (121).

Despite these risks and the establishment of multidisciplinary support services, sexual assault survivors often decline nPEP, and many who do take it do not complete the 28-day course. This pattern has been reported in several countries and several programs in North America. In Vancouver, 71 of 258 assault survivors accepted the 5-day starter pack of nPEP, 29 returned for additional doses, and eight completed 4 weeks of therapy (96). Those with the highest risk for HIV exposure (i.e., source known to be HIV infected, a homosexual or bisexual man, or an injection-drug user) were more likely to begin and complete nPEP.

Patients who have been sexually assaulted will benefit from supportive services to improve adherence to nPEP if it is prescribed, and from psychological and other support provided by sexual assault crisis centers. All sexually assaulted patients should be tested and administered prophylaxis for sexually transmitted infections (85), and women who might become pregnant should be offered emergency contraception (122).

Inmates

Certain illegal behaviors that result in imprisonment (e.g., prostitution and injection-drug use) also might be associated with a higher prevalence of HIV infection among prison inmates than among the general population (119). However, studies indicate that the risk for becoming infected in prison is probably less than the risk outside prison (122–125). However, when exposure does occur, because sexual contact and injection-drug use are prohibited in jails and prisons, prison-

ers who have experienced such exposures might be unable or unwilling to report the behaviors to health-care providers.

Administrators and health-care providers working in correctional settings should develop and implement systems to make HIV education and risk-reduction counseling, nPEP, voluntary HIV testing, and HIV care confidentially available to inmates. Such programs will allow inmates to benefit from nPEP when indicated, facilitate treatment services for those with drug addiction, and assist in the identification and treatment of sexual assault survivors.

Injection-Drug Users

A history of injection-drug use should not deter clinicians from prescribing nPEP if the exposure provides an opportunity to reduce the risk for consequent HIV infection. A survey of clinicians serving injection-drug users determined a high degree of willingness to provide nPEP after different types of potential HIV exposure (126).

In judging whether exposures are isolated, episodic, or ongoing, clinicians should consider that persons who continue to engage in risk behaviors (e.g., commercial sex workers or users of illicit drugs) might be practicing risk reduction (e.g., using condoms with every client, not sharing syringes, and using a new sterile syringe for each injection). Therefore, a high-risk exposure might represent an exceptional occurrence for such persons despite their ongoing risk behavior.

Injection-drug users should be assessed for their interest in substance abuse treatment and their knowledge and use of safe injection and sex practices. Patients desiring substance abuse treatment should be referred for such treatment. Persons who continue to inject or who are at risk for relapse to injection-drug use should be instructed in the use of a new sterile syringe for each injection and the importance of avoiding the sharing of injection equipment. In areas where programs are available, health-care providers should refer such patients to appropriate sources of sterile injection equipment.

Conclusion

Accumulated data from animal and human clinical and observational studies demonstrate that antiretroviral therapy initiated as soon as possible within 48–72 hours of sexual, injection-drug-use, and other substantial nonoccupational HIV exposure and continued for 28 days might reduce the likelihood of transmission. Because of these findings, DHHS recommends the prompt initiation of nPEP with HAART when persons seek care within 72 hours after exposure, the source is known to be HIV infected, and the exposure event presents a substantial risk for transmission. When the HIV

status of the source is not known and the patient seeks care within 72 hours after exposure, DHHS does not recommend for or against nPEP but encourages clinicians and patients to weigh the risks and benefits on a case-by-case basis. When the transmission risk is negligible or when patients seek care >72 hours after a substantial exposure, nPEP is not recommended; however, clinicians might consider prescribing nPEP for patients who seek care >72 hours after a substantial exposure if, in their judgment, the diminished potential benefit of nPEP outweighs the potential risk for adverse events from antiretroviral medications. These recommendations are intended for the United States and might not apply in other countries.

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MMWRTM

Morbidity and Mortality Weekly Report

Recommendations and Reports

January 21, 2005 / Vol. 54 / No. RR-2

Continuing Education Activity Sponsored by CDC Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States Recommendations from the U.S. Department of Health and Human Services

EXPIRATION — January 21, 2008

You must complete and return the response form electronically or by mail by **January 21, 2008**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 2.0 hours Continuing Medical Education (CME) credit; 0.15 Continuing Education Units (CEUs);

or 2.2 contact hours Continuing Nursing Education (CNE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

By Internet

1. Read this *MMWR* (Vol. 54, RR-2), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at <http://www.cdc.gov/mmwr/cme/conted.html>.
3. Select which exam you want to take and select whether you want to register for CME, CEU, or CNE credit.
4. Fill out and submit the registration form.
5. Select exam questions. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
6. Submit your answers no later than **January 21, 2008**.
7. Immediately print your Certificate of Completion for your records.

By Mail or Fax

1. Read this *MMWR* (Vol. 54, RR-2), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for CME, CEU, or CNE credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
5. Sign and date the response form or a photocopy of the form and send no later than **January 21, 2008**, to
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6. Your Certificate of Completion will be mailed to you within 30 days.

ACCREDITATION

Continuing Medical Education (CME). CDC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 2.0 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Continuing Education Unit (CEU). CDC has been approved as an authorized provider of continuing education and training programs by the International Association for Continuing Education and Training and awards 0.15 Continuing Education Units (CEUs).

Continuing Nursing Education (CNE). This activity for 2.2 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION**

Goal and Objectives

This *MMWR* describes the potential risks and benefits of antiretroviral postexposure prophylaxis after nonoccupational exposures to human immunodeficiency virus (HIV). These recommendations were developed by CDC staff in collaboration with scientists, public health officials, clinicians, ethicists, members of affected communities, and representatives from professional associations and industry. The goal of this report is to provide information on which to base decisions regarding postexposure prophylaxis after a nonoccupational exposure to HIV. After completing this educational activity, the reader should be able to 1) describe the characteristics of a potential HIV exposure; 2) describe situations in which postexposure prophylaxis is most likely to be beneficial; 3) describe sources for obtaining information on antiretroviral regimens; and 4) describe appropriate follow-up schedules for persons who are prescribed antiretroviral postexposure prophylaxis.

To receive continuing education credit, please answer all of the following questions.

1. Evidence from controlled studies among humans indicates that the administration of antiretroviral postexposure prophylaxis after nonoccupational exposures to HIV is an effective means of preventing HIV infection.
 - A. True.
 - B. False.
2. On the basis of available evidence from animal studies, antiretroviral postexposure prophylaxis is most likely to be beneficial when initiated as soon as possible after exposure, and in the majority of cases, should not be initiated if > ____ hours have elapsed since exposure.
 - A. 72.
 - B. 24.
 - C. 36.
 - D. None of the above.
3. Contact of which of the following body sites with HIV-infected bodily fluids constitutes a substantial HIV exposure?
 - A. Vagina.
 - B. Eye.
 - C. Intact skin.
 - D. Rectum.
 - E. A and D are correct.
 - F. A, B, and D are correct.
4. In a person with HIV infection, potentially infectious fluids include all of the following, except . . .
 - A. blood.
 - B. saliva visibly contaminated with blood.
 - C. urine not visibly contaminated with blood.
 - D. genital secretions.
 - E. none of the above; all are potentially infectious.
5. Which of the following lists of exposure types are correctly ordered from greatest risk of infection to least risk of infection?
 - A. Insertive anal is greater than insertive oral, which is greater than insertive vaginal.
 - B. Receptive anal is greater than receptive vaginal, which is greater than receptive oral.
 - C. Insertive anal is greater than receptive anal, which is greater than receptive oral.
 - D. None of the above.
6. The recommended duration of antiretroviral postexposure prophylaxis is . . .
 - A. 10 days.
 - B. 14 days.
 - C. 28 days.
 - D. none of the above.
7. Antiretroviral medications that should be avoided for pregnant women and women of childbearing potential include . . .
 - A. efavirenz.
 - B. nevirapine.
 - C. zidovudine (AZT).
 - D. stavudine (D4T) in combination with didanosine (ddI).
 - E. A, B, and D.
8. Patients who are prescribed antiretroviral postexposure prophylaxis should be instructed about the symptoms of acute retroviral infection, which can include . . .
 - A. thrush.
 - B. fever.
 - C. rash.
 - D. all of the above.
 - E. B and C only.
9. Follow-up visits and testing of persons who are prescribed antiretroviral postexposure prophylaxis should be performed at approximately . . .
 - A. 4–6 weeks.
 - B. 3 months.
 - C. 6 months.
 - D. all of the above.
10. In addition to HIV antibody testing, follow-up laboratory testing of persons who are prescribed antiretroviral postexposure prophylaxis should include . . .
 - A. hepatitis A serology.
 - B. hepatitis B serology.
 - C. hepatitis C serology.
 - D. complete blood count, blood urea nitrogen/creatinine, and hepatic enzymes.
 - E. all of the above.
 - F. B, C, and D.
11. Which best describes your professional activities?
 - A. Physician.
 - B. Nurse.
 - C. Health educator.
 - D. Office staff.
 - E. Other.
12. I plan to use these recommendations as the basis for . . . (Indicate all that apply.)
 - A. health education materials.
 - B. insurance reimbursement policies.
 - C. local practice guidelines.
 - D. public policy.
 - E. other.

13. Each month, approximately how many patients with a potential HIV exposure do you treat?

- A. None.
- B. 1–5.
- C. 6–20.
- D. 21–50.
- E. 51–100.
- F. >100.

14. How much time did you spend reading this report and completing the exam?

- A. <2.0 hours.
- B. >2.0 hours but <3.0 hours.
- C. >3.0 hours but <4.0.
- D. >4.0 hours.

15. After reading this report, I am confident I can describe the characteristics of a potential HIV exposure.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

16. After reading this report, I am confident I can describe situations in which postexposure prophylaxis is most likely to be beneficial.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

17. After reading this report, I am confident I can describe sources for obtaining information on antiretroviral regimens.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

18. After reading this report, I am confident I can describe appropriate follow-up schedules for persons who are prescribed antiretroviral postexposure prophylaxis.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

(Continued on pg CE-4)

MMWR Response Form for Continuing Education Credit January 21, 2005/Vol. 54/No. RR-2

Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States
Recommendations from the U.S. Department of Health and Human Services

To receive continuing education credit, you must

1. provide your contact information;
 2. indicate your choice of CME, CME for nonphysicians, CEU, or CNE credit;
 3. answer all of the test questions;
 4. sign and date this form or a photocopy;
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- Failure to complete these items can result in a delay or rejection of your application for continuing education credit.

Check One

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1. [] A [] B	14. [] A [] B [] C [] D
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4. [] A [] B [] C [] D [] E	17. [] A [] B [] C [] D [] E
5. [] A [] B [] C [] D	18. [] A [] B [] C [] D [] E
6. [] A [] B [] C [] D	19. [] A [] B [] C [] D [] E
7. [] A [] B [] C [] D [] E	20. [] A [] B [] C [] D [] E
8. [] A [] B [] C [] D [] E	21. [] A [] B [] C [] D [] E
9. [] A [] B [] C [] D	22. [] A [] B [] C [] D [] E
10. [] A [] B [] C [] D [] E [] F	23. [] A [] B [] C [] D [] E
11. [] A [] B [] C [] D [] E	24. [] A [] B [] C [] D [] E
12. [] A [] B [] C [] D [] E [] F	25. [] A [] B [] C [] D [] E [] F
13. [] A [] B [] C [] D [] E [] F	

Signature

Date / Completed Exam

19. The objectives are relevant to the goal of this report.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

20. The teaching strategies used in this report (text, figure, and tables) were useful.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

21. Overall, the presentation of the report enhanced my ability to understand the material.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

22. These recommendations will affect my practice.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

23. The content of this activity was appropriate for my educational needs.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

24. The availability of continuing education credit influenced my decision to read this report.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

25. How did you learn about this continuing education activity?

- A. Internet.
- B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
- C. Coworker/supervisor.
- D. Conference presentation.
- E. *MMWR* subscription.
- F. Other.

Correct answers for questions 1–10.
1. B, 2. A, 3. F, 4. C, 5. B, 6. C, 7. E, 8. D, 9. D, 10. F.

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Federal Consultants: Deborah von Zinkernagel, Office of the Secretary, U.S. Department of Health and Human Services; Andrea Washington, Division of Applied Public Health Training, Epidemiology Program Office, CDC; John Miles, Ron Valdiserri, Office of the Director, National Center for HIV, STD, and TB Prevention, CDC; Marc Bulterys, Ken Dominguez, Donatus Ekwueme, Kathleen Gallagher, Richard Garfein, Robert Janssen, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, CDC; Elise Beltrami, Adelisa Panlilio, Division of Healthcare Quality Promotion, National Center for Infectious Diseases, CDC; Kim Workowski, Division of STD Prevention, National Center for HIV, STD, and TB Prevention, CDC; Sara Critchley, Bruce Evatt, Ron Otten, Division of AIDS, STD, and TB Laboratory Research, National Center for Infectious Diseases, CDC; Eben Ingram, Division of Violence Prevention, National Center for Injury Prevention and Control, CDC; Kevin Ryan, National Institute of Allergy and Infectious Diseases, NIH; Cedric Dumont, Athena Moundalexis, U. S. Department of State; Newton Kendig, Mike Nelson, Federal Bureau of Prisons.

External Consultants: Bruce Agins, *New York State AIDS Institute*; James Aldridge, *National Alliance of State and Territorial AIDS Directors*; Beth Barnhill, *National Alliance of Sexual Assault Coalitions*; Carol Berkowitz, *University of California, Los Angeles Medical Center*; Barry Bernstein, *Abbot Pharmaceuticals*; Ricky Blumenthal, *RAND Corporation*; Stephen Boswell, *Fenway Community Health Center*; Helena Brett-Smith, *Bristol-Myers Squibb*; Jordi Casabona, *Centre d'Estudis Epidemiològics de la SIDA a Catalunya*; David Cochetto, *GlaxoSmithKline*; Myron Cohen, *University of North Carolina, Chapel Hill*; Roxanne Cox-Hamu, *Whitman -Walker Clinic*; Tim Cuniff, *Agouron-Pfizer*; Brian Edlin, *University of California, San Francisco*; Richard Ellison, *University of Massachusetts Medical Center*; Janet Endress Squires, *Children's Medical Center of Dallas*; Bruce Ewenstein, *Boston Hemophilia Center*; Susan Forlenza, *New York City Department of Health*; David Gootnick, *Peace Corps*; Peter L. Havens, *American Academy of Pediatrics, Pediatric AIDS Committee*; Barbara Herbert, *Lawrence General Hospital*; David Holtgrave, *Rollins School of Public Health, Emory University*; Michael Imperiale, *Boeringer-Ingelheim*; Asim Jani, *Florida Department of Health*; Mitchell Katz, *San Francisco Department of Public Health*; Laureen Kunches, *John Snow, Incorporated*; Jean Maguire, *Massachusetts Department of Health*; Laurent Mandelbrot, *Groupe Hospitalier Cochin*; Ken Mayer, *Fenway Community Health Center*; Michael Meit, *National Association of County and City Health Officials*; Diego Miralles, *Trimeris, Inc.*; Patrick O'Connor, *Yale University*; Amrita Paul, *Canadian Non-Occupational Post-exposure Prophylaxis Working Group*; Bea Pearce, *National Hemophilia Foundation*; Steve Pinkerton, *University of Wisconsin*; Josiah Rich, *The Miriam Hospital*; Laurie Robert, *John Snow, Incorporated*; Pierre Robillard, *Canadian Non-Occupational Post-exposure Prophylaxis Working Group*; Michelle Roland, *University of California, San Francisco*; Jim Rooney, *Gilead Sciences*; Richard Rothman, *Johns Hopkins University*; Elise Roy, *Canadian Non-Occupational Post-exposure Prophylaxis Working Group*; Miklos Salgo, *Roche Laboratories*; Brian Saltzman, *Harvard Medical School*; Susie Sargent, *Roche*; Timothy Schacker, *University of Minnesota*; Mauro Schechter, *Hospital Universitario Clementino Fraga Filho*; Gerry Schochetman, *Abbot Diagnostics*; Michael Tapper, *Lenox Hill Hospital*; Mark Waters, *New York AIDS Institute*.

trust•wor•thy: *adj*

('trəst-"wər-thē) 1 : worthy of belief

2 : capable of being depended upon;

see also *MMWR*.



know what matters.



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EXHIBIT K

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DISCLAIMER IN PATENT UNDER 37 CFR 1.321(a)

Name of Patentee The United States of America, as represented by the Secretary Department of Health and Human Services	Docket Number (Optional) 4239-92970-02

Patent Number 9,044,509	Date Patent Issued June 2, 2015

Title of Invention

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

I hereby disclaim the following complete claims in the above identified patent: _____

12 and 14-18The extent of my interest in said patent is (if assignee of record, state liber and page, or reel and frame, where assignment is recorded): **100% (Assignments recorded at Reel 017372, Frames 0494-0503 and Reel****035315, Frames 0651-0668)**

The fee for this disclaimer is set forth in 37 CFR 1.20(d).

- ☐ Patentee claims small entity status. See 37 CFR 1.27.
- ☐ Small entity status has already been established in this case, and is still proper.
- ☐ A check in the amount of the fee is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized to charge any fees which may be required or credit any overpayment to Deposit Account No. **02-4550**.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.Signed at **Portland**, State of **OR**, this **2** day of **December** 20**19**.

/Susan Alpert Siegel/

Signature

43,121Registration Number, if
applicable**Susan Alpert Siegel****503-595-5300**

Typed or printed name of patentee/ attorney or agent of record

Telephone Number

Klarquist Sparkman, LLP, 121 SW Salmon Street, Suite 1600

Address

Portland, OR, 97205

City, State, Zip Code or Foreign Country as applicable

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	11669547			
Filing Date:	31-Jan-2007			
Title of Invention:	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS			
First Named Inventor/Applicant Name:	Walid M. Heneine			
Filer:	Susan A. Siegel/Adrienne Chocholak			
Attorney Docket Number:	4239-92970-02			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Total in USD (\$)				160

Electronic Acknowledgement Receipt

EFS ID:	37901121
Application Number:	11669547
International Application Number:	
Confirmation Number:	5582
Title of Invention:	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS
First Named Inventor/Applicant Name:	Walid M. Heneine
Customer Number:	46135
Filer:	Susan A. Siegel/Adrienne Chocholak
Filer Authorized By:	Susan A. Siegel
Attorney Docket Number:	4239-92970-02
Receipt Date:	02-DEC-2019
Filing Date:	31-JAN-2007
Time Stamp:	16:25:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$ 160
RAM confirmation Number	E2019B2G26133551
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	4239-92970-02_Transmittal_Letter.pdf	17868	no	1
			419d3573f7b2dbe3b4bb5232d2ef2ae8dc351948		
Warnings:					
Information:					
2	Statutory disclaimers per MPEP 1490	4239-92970-02_Statutory_Disclaimer.pdf	246470	no	2
			c84f0e8e6cb19f49b17f51f1dddf13d87a5194f		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30751	no	2
			9b94e4fcc92029418c927e7abe1997a456407934		
Warnings:					
Information:					
Total Files Size (in bytes):			295089		
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Walid Heneine

Application No. 11/669,547

Filed: January 31, 2007

Patent No: 9,044,509

Issued: June 2, 2015

Confirmation No. 5582

For: INHIBITION OF HIV INFECTION
THROUGH CHEMOPROPHYLAXIS

Examiner: Shengjun Wang

Art Unit: 1627

Attorney Reference No. 4239-92970-02

**FILED VIA EFS
December 2, 2019**

FILED VIA THE ELECTRONIC FILING SYSTEM (EFS)
COMMISSIONER FOR PATENTS

TRANSMITTAL LETTER

Submitted herewith for filing in the application referenced above are the following:

- ☒ Disclaimer in Patent Under 37 C.F.R. § 1.321(a).
- ☒ Statutory Disclaimer Fee of \$160.00 (37 C.F.R. § 1.20(d)).
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Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
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Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By /Susan Alpert Siegel/
Susan Alpert Siegel, Ph.D.
Registration No. 43,121

EXHIBIT L

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DISCLAIMER IN PATENT UNDER 37 CFR 1.321(a)Name of Patentee The United States of America, as represented by the
Secretary, Department of Health and Human ServicesDocket Number (Optional)
4239-92970-12

Patent Number

9,579,333

Date Patent Issued

February 28, 2017

Title of Invention

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXISI hereby disclaim the following complete claims in the above identified patent: _____
12 and 14-17The extent of my interest in said patent is (if assignee of record, state liber and page, or reel and frame, where
assignment is recorded): 100% (Assignments recorded at Reel 035408, Frames 0692-709)

The fee for this disclaimer is set forth in 37 CFR 1.20(d).

- ☐ Patentee claims small entity status. See 37 CFR 1.27.
- ☐ Small entity status has already been established in this case, and is still proper.
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Signature

43,121Registration Number, if
applicableSusan Alpert Siegel

Typed or printed name of patentee/ attorney or agent of record

503-595-5300

Telephone Number

Klarquist Sparkman, LLP, 121 SW Salmon Street, Suite 1600

Address

Portland, OR 97205

City, State, Zip Code or Foreign Country as applicable

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The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
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Electronic Patent Application Fee Transmittal

Application Number:	14679887			
Filing Date:	06-Apr-2015			
Title of Invention:	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYALXIS			
First Named Inventor/Applicant Name:	Walid Heneine			
Filer:	Susan A. Siegel/Adrienne Chocholak			
Attorney Docket Number:	4239-92970-12			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Total in USD (\$)				160

Electronic Acknowledgement Receipt

EFS ID:	37901068
Application Number:	14679887
International Application Number:	
Confirmation Number:	6646
Title of Invention:	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYALXIS
First Named Inventor/Applicant Name:	Walid Heneine
Customer Number:	46135
Filer:	Susan A. Siegel/Adrienne Chocholak
Filer Authorized By:	Susan A. Siegel
Attorney Docket Number:	4239-92970-12
Receipt Date:	02-DEC-2019
Filing Date:	06-APR-2015
Time Stamp:	16:28:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$ 160
RAM confirmation Number	E2019B2G28423609
Deposit Account	
Authorized User	

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File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	4239-92970-12_Transmittal_Letter.pdf	17986	no	1
			f2bbf7f8d511894fa4df3f4f2df639381fd8218		
Warnings:					
Information:					
2	Statutory disclaimers per MPEP 1490	4239-92970-12_Statutory_Disclaimer.pdf	453188	no	2
			464e7b8638e59d245decd3453210cc8a3a147838		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30799	no	2
			91211273aa949302ae194c89f761bd09f6d54c24		
Warnings:					
Information:					
Total Files Size (in bytes):			501973		
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Walid Heneine

Application No. 14/679,887

Filed: April 6, 2015

Patent No. 9,579,333

Issued: February 28, 2017

Confirmation No. 6646

For: INHIBITION OF HIV INFECTION
THROUGH CHEMOPROPHYLAXIS

Examiner: Shengjun Wang

Art Unit: 1627

Attorney Reference No. 4239-92970-12

**FILED VIA EFS
December 2, 2019**

FILED VIA THE ELECTRONIC FILING SYSTEM (EFS)
COMMISSIONER FOR PATENTS

TRANSMITTAL LETTER

Submitted herewith for filing in the application referenced above are the following:

- ☒ Disclaimer in Patent Under 37 C.F.R. § 1.321(a).
- ☒ Statutory Disclaimer Fee of \$160.00 (37 C.F.R. § 1.20(d)).
- ☒ \$160.00 is being submitted herewith via EFS to cover the above-listed fee(s).
- ☒ The Director is hereby authorized to charge any additional fees that may be required in connection with this filing, or credit over-payment, to Deposit Account No. 02-4550.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By /Susan Alpert Siegel/
Susan Alpert Siegel, Ph.D.
Registration No. 43,121

cc: Docketing

EXHIBIT M

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Transmitted herewith for filing is the continuing patent application of:

Applicant: THE UNITED STATES OF AMERICA, as represented by the Secretary,
Department of Health and Human Services

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Jose Gerardo Garcia Lerma

For: INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLLAXIS

Submitted herewith are:

- ☒ 18 pages of specification, 3 pages of claims, and an abstract
- ☒ 4 sheet(s) of drawings
- ☒ 5 pages of an Oath or Declaration
 - ☒ A copy of oath or declaration filed with the prior application (37 C.F.R. § 1.63(d))
- ☒ Information Disclosure Statement
- ☒ Form PTO-1449
- ☒ Application Data Sheet

Continuing Application:

- ☒ Continuation
- ☐ Divisional
- ☐ Continuation-in-part (CIP)

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Total	19	-	# of claims included	20	=	# of extra claims	0	x	\$80.00	=	\$0.00
claims*			in basic fee								
Independent	2	-	# of indep. claims	3	=	# of extra indep.	0	x	\$420.00	=	\$0.00
claims **			included in basic fee			claims					
# of	26	x	.75 EFS	=	20	-	100	=	# of extra pages	0	x \$400.00 = \$0.00
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☒ Assignee for this application is or will be “THE UNITED STATES OF AMERICA, as represented by the Secretary, Department of Health and Human Services,” and it is requested that this information be listed on the published application.

☒ This is a continuation U.S. Patent Application No. 14/679,887, filed on April 6, 2015, which is a continuation of U.S. Patent Application No. 11/669,547, filed on January 31,

2007, issued as U.S. Patent No. 9,044,509, which in turn claims the benefit of U.S. provisional application 60/764,811, filed on February 3, 2006. All of the prior applications are incorporated herein by reference in their entirety.

- ☒ **\$1600.00** is being submitted herewith via EFS to cover the above-listed fee(s).
- ☒ The Director is hereby authorized to charge any additional fees that may be required in connection with this filing, or credit over-payment, to Deposit Account No. 02-4550.
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INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This is a continuation U.S. Patent Application No. 14/679,887, filed on April 6, 2015, which is a continuation of U.S. Patent Application No. 11/669,547, filed on January 31, 2007, issued as U.S. Patent No. 9,044,509, which in turn claims the benefit of U.S. provisional application 60/764,811, filed on February 3, 2006. All of the prior applications are incorporated herein by reference in their entirety.

GOVERNMENT INTEREST

[0002] The invention described herein may be manufactured, used, and licensed by or for the United States Government.

FIELD OF THE INVENTION

[0003] The present invention in general relates to a process for inhibiting initial infection by a retrovirus such as human immunodeficiency virus (HIV) and in particular to a combination of a nucleoside reverse transcriptase inhibitor (NRTI) and a nucleotide reverse transcriptase inhibitor (NtRTI) capable of preventing self-replicating retroviral infection, even in response to multiple viral challenges.

BACKGROUND OF THE INVENTION

[0004] Despite the fact that significant progress has been made slowing the advancement of the symptoms of AIDS associated with HIV infection, in the absence of an effective vaccine, HIV continues to spread globally. The spread of HIV persists in part because an infected individual remains a potential source of infection. It is clear that current treatment of monitoring viral titer and in response to a titer exceeding a preselected threshold commencing treatment with highly active antiretroviral therapy (HAART) has not prevented new infections.

[0005] An attractive method of controlling the spread of HIV would be to provide an individual exposed to a potential source of HIV with a pre-exposure prophylactic treatment. As

HIV and, in particular HIV-1, often begins with a comparatively small population of retroviral particles being transmitted to a new host and within a few days self-replicating into a retroviral titer detectable in host blood serum. If the establishment of a retroviral could be blocked before the HIV burden expands into a self-propagating infection, an individual could avoid contraction of HIV.

[0006] Previous attempts at pre-exposure prophylaxis have met with limited success. Prophylactic activity has been demonstrated with the NtRTI, tenofovir in monkey models challenged with simian immunodeficiency virus (SIV).¹⁻³ Unfortunately, oral daily dosing and pre-exposure prophylaxis with tenofovir at a dose equivalent to that used in humans proved to only be partially protective against rectal SHIV transmission.⁴

[0007] HAART therapy involves the administration of a combination including at least three active compounds classified by the mode of operation as an NRTI, an NtRTIs, a non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitor, and an entry inhibitor. While HAART is effective in lowering retroviral titer in a host, concerns remain as to the long term toxicity and the retained potential to infect others. It is also unknown if initiating HAART therapy in a pre-exposure prophylactic regimen would be efficacious. As a result, society remains devoid of a pre-exposure prophylactic regimen to prevent an individual from developing self-propagating retrovirus infection subsequent to initial exposure.

[0008] Thus, there exists a need for a chemoprophylactic composition and dosing regimen effective in blocking early stage infection by retrovirus in a host founder cell population. There also exists a need for a chemoprophylactic composition formulated with a vehicle amenable to user compliance.

SUMMARY OF THE INVENTION

[0009] A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided

in a single dose prior to the exposure. A regime of multiple temporally spaced doses prior to retroviral exposure is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection a combination of a pharmaceutically effective nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

[0010] A kit is also provided that includes at least one combination dose of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor sufficient to protect a primate host from developing a self-replicating retroviral infection along with instructions for the administration of the at least one dose one prior to and optionally one additional dose subsequent to a potential exposure to an immunodeficiency retrovirus along with dosing modifications associated with subject characteristics and behaviors to further reduce the risk of contracting a self-replicating immunodeficiency retrovirus infection.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Fig. 1 is a schematic depicting one study of the present invention for 4 groups of macaques in which all treated macaques received known antiretroviral medications 7 to 9 days prior to the first virus inoculation and continuing throughout the study with treated animals that remained uninfected throughout the 14 viral challenges receiving 28 additional days of post-exposure prophylactics.

[0012] Fig. 2 is a survival curve graph for macaque Groups 1-4 per Fig. 1, as well as for animals receiving only tenofovir disoproxil fumarate (TDF).

[0013] Fig. 3 is a graph depicting a plot of viremia as a function of time for untreated controls (○) and breakthrough infections (●) where each point represents a mean viremia observed, 0 time

indicates peak plasma virus load observed in a given animal where the arrow bars denote standard error of the mean (SEM).

[0014] Fig. 4 depicts plots of infection dynamics as a function of time during the study per Fig. 1 with plots for animals coded as AG-80, AG-46, AH-04 and AG-07 corresponding to emtricitabine (FTC) treatment alone, or FTC plus TDF treatment (AI-54 and AG-81). The arrow indicates the first detectable antibody response. Grey circles indicate detectable M184V/I mutation; wild type sequences are shown in as black full circles. Open circles indicate the time points where no genotype was undertaken

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0015] The present invention has utility in protecting a primate host from self-propagating immunodeficiency virus infection. The use of a combination of antiretroviral agents as a prophylactic dosing regime is also provided for the manufacture of a medicament is provided for protection against a human immunodeficiency virus infection developing to a level of self-replicating infection. Retroviral transmission through most routes entails a new primate host receiving a small number of viral particles. Common routes of retrovirus transmission illustratively include sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, blood transfusions, birth canal exposure, breastfeeding, and transplacental contact between individuals. Through the administration of at least one nucleoside reverse transcriptase inhibitor (NRTI) and at least one nucleotide reverse transcriptase inhibitor (NtRTI) prior to a retrovirus exposure protection is provided against development of a self-replicating retroviral infection. As the aforementioned exposure routes are characterized by a small number of retrovirus particles being transferred to the new primate host, this initial phase of infection represents a window of opportunity to protect a host from infection. The inventive chemoprophylactic treatment is provided through a dosing regimen. A dosing regimen according to the present invention that provides retroviral protection to a host primate includes at least one single dose administered prior to initial retroviral exposure. An inventive dosing regimen also includes a course of multiple doses administered in advance of exposure to maintain a therapeutic level of NRTI and NtRTI agents in the primate host. The timing of the at least one

does prior to retroviral exposure is dictated by the pharmacokinetics of the NRTI and NtRTI components to assure the presence of a therapeutically effective amount of inventive composition for at least 20 hours subsequent to the exposure to the communicated small retroviral particle population. Multiple doses are administered according to the present invention at regular time intervals and amounts such as for example like formulated daily doses for a period of several days, weeks, or months; or are administered in advance of a likely exposure as a cluster of doses, with the amount of NRTI and NtRTI components in each dose being independent of the amount of NRTI and NtRTI in other doses within the cluster. While most oral, topical, and parenteral existing versions of NRTIs and NtRTIs are fully absorbed and therapeutically active within 1 to 8 hours, it is appreciated that subcutaneous implants and long acting timed release formulations allow for a single dose to sustain therapeutically effective amounts of an inventive prophylactic composition for several days, weeks, or even months. Representative of sustained release compositions and implants are provided in the U.S. Patents 4,122,129; 4,927,687; 4,996,047; 5,169,642; and 5,656,296.

The combination of NRTI and NtRTI compounds administered prophylactically according to the present invention are shown to provide a dose-dependent inhibition of HIV self-replicating infection and a therapeutically effective dosing primate host protection against self-replicating HIV infection is provided, even in response to multiple viral challenges. While the present invention is largely detailed with respect to HIV-1 as a prototypical infectious and pathogenic retrovirus, it is appreciated that other retroviruses owing to reliance on reverse transcription for replication are also protected against in a primate host according to the present invention.

[0016] As used herein, “protection” as used in the context of a host primate response to an immunodeficiency virus challenge is defined by the host primate being serologically negative and negative in response to a polymerase chain reaction (PCR) testing for viral genome.

[0017] As used herein, the term “retrovirus” is inclusive of any virus that utilizes reverse transcriptase in the viral replication cycle and therefore is susceptible to the antiviral activity of nucleoside or nucleotide analogs specifically inclusive of HIV (HIV-1 and HIV-2), HTLV-1, HTLV-2, HTLV-3, HTLV-4, and SIV. Also encompassed are viruses such as HBV that

although not technically classified as retroviruses nonetheless utilize a reverse transcriptase and are therefore susceptible to the antiviral activity of nucleoside and/or nucleotide analogs.

[0018] As used herein a “primate host” is defined to include a monkey, baboon, chimpanzee, gorilla, and a human. Nonhuman primates are appreciated to themselves be susceptible to infection by retroviruses and in particular immunodeficiency viruses and represent well-established animal models as to human response with an appreciation that physiological differences often require different doses in milligrams per kilogram for a nonhuman primate animal model relative to a human.

[0019] The compositions of the present invention include administration in combination of an NRTI and NtRTI and are readily compounded by pharmaceutical composition with conventional pharmaceutically acceptable carriers or diluents. Additionally, pharmaceutically acceptable derivatives and prodrugs of active NRTIs and NtRTIs operative in the present invention include salts such as alkali metal salts; esters such as acetate, butyrate, octinoate, palmitate, chlorobenzoates, benzoates, C₁-C₆ benzoates, succinates, and mesylate; salts of such esters; and nitrile oxides. It is appreciated that other analogs of pharmaceutically active NRTIs or NtRTIs that provide within a primate host an active antiviral metabolite residue are also suitable as part of an inventive composition. A pharmaceutically acceptable carrier or diluent includes agents that are compatible with other ingredients of a dosage and not injurious to a primate host. The identity and process for compounding a combination of at least one NRTI and at least one NtRTI into a dosage form suitable for delivery by a route with administration by oral, rectal, topical, vaginal or parenteral routes of administration are provided in Remington’s Science and Practice of Pharmacology, 20th Edition, Chapters 37-47, pages 681-929, where parenteral injection includes subcutaneous, intramuscular, intravenous, and intradermal injection.

[0020] As used herein the term “prodrug” is defined to include a compound that when administered to a primate host generates an active NRTI or NtRTI as a result of spontaneous reaction under physiological conditions, enzymatic catalysis, metabolic clearance, or combinations thereof. An exemplary NtRTI prodrug currently FDA approved for HAART use is tenofovir disoproxil fumarate (TDF) and is detailed in U.S. Patent 5,935,946.

[0021] The present invention provides an alternative to conventional retroviral therapy using HAART, in response to self-propagating HIV infection by protecting a primate host against the establishment of self-replicating retroviral infection that provides an indication for such therapy. Through prophylactic prior dosing with an inventive combination including at least one NRTI and one NtRTI, replication of the comparatively low number of viral particles received by a host primate is prevented.

[0022] To achieve protection against a primate host developing a retroviral self-replicating infection, at least one dosage of an NRTI and NtRTI is administered to the primate host prior to exposure to the retrovirus. Preferably, the at least one NRTI and at least one NtRTI are administered concurrently. More preferably, the combination of reverse transcriptase inhibitors is compounded into a single formulation.

[0023] The process of the present invention demonstrates protection against retroviral self-replicating infection through administration of even a single dosage administered prior to the retroviral exposure. Owing to the known pK rates of specific NRTIs and NtRTIs, a single dosage is administered to assure a therapeutically effective amount of NRTI and NtRTI persist in the primate host for a time of more than 12 hours after viral challenge. With conventional NRTI and NtRTI formulations, currently approved for HAART, preferably an inventive dose is administered within 12 hours prior to retroviral exposure and still more preferably often within 2 hours prior to retroviral exposure. The practice of the inventive process involving the administration of a single dosage in the hours proceeding a likely retroviral exposure is particularly advantageous in assuring compliant dosing in a human and also avoids side effects associated with a regular dosing regime and is particularly well suited for a human engaging in a sporadic behavior likely to bring the person into retroviral exposure. Preferably, an additional dose or doses of a combination of at least one NRTI and at least one NtRTIs is provided subsequent to the retroviral exposure event to assure adequate antiviral reverse transcriptase inhibitor concentration during and immediately subsequent to retroviral infection of the host founder cell population so as to preclude retroviral self-replication to assure NRTI and NtRTI incorporation into a replicating virus genome. Preferably, a dose of an inventive composition

taken after retroviral exposure is administered within 24 hours subsequent to the exposure, and more preferably within 12 hours subsequent to the exposure.

[0024] Alternatively, an individual routinely subjected to retroviral exposure can be protected against the development of a self-replicating retroviral infection through administration of regular prophylactic doses of an inventive combination. As a result, an epidemiological advantage exists in controlling the outbreak and spread of a retrovirus within a population is provided through offering routine doses of an inventive composition prophylactically to high-risk persons such as sex workers and a short course prophylactic inventive composition to uninfected sex trade clientele.

[0025] It is appreciated that hybrid dosing regimes of an inventive composition are also operative herein and include multiple doses prior to retroviral exposure with multiple doses not being administered for a duration or with sufficient periodicity to arise to the level of a routine prophylactic regime.

[0026] The at least one nucleoside reverse transcriptase inhibitor has the attribute of interfering with *in vivo* viral replication. An NRTI operative in an inventive prophylactic process includes emtricitabine, lamivudine, zalcitabine, zidovudine, azidothymidine, didanosine, stavudine, abacavir; with the aforementioned specific NRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

[0027] An at least one nucleotide reverse transcriptase inhibitor (NRTI) present in an inventive composition to protect a primate from developing a self-replicating retroviral infection illustratively includes tenofovir, adefovir; 2',3'-dideoxy-3'-fluoroadenisine; 2',3'-dideoxy-3'-fluoroguanasine; 3'deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine with the aforementioned specific NtRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

[0028] Optionally, an inventive composition also includes within an inventive combination other antiretrovirals such as nonnucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, and combinations thereof. Representative non-nucleoside reverse transcriptase inhibitors operative herein illustratively include delavirdine, efavirenz, nevirapine, and other

diarylpyrimidine (DAPY) derivatives. Representative protease inhibitors operative herein illustratively include amprenavir, tipranavir, indinavir, saquinavir, lopinavir, ritonavir, fosamprenavir calcium, ritonavir, atazanavir sulfate nelfinavir mesylate, and combinations thereof. An entry inhibitor operative herein as an optional active ingredient in an inventive composition illustratively includes enfuvirtide, Schering C (Schering Plough), S-1360 (Shionogi), and BMS806 (Bristol Myers Squibb).

[0029] The dose of individual active components of an inventive prophylactic composition is administered to create a therapeutic concentration of the active composition at the situs of retrovirus initial founder cell population infection prior to viral exposure. It is appreciated that establishing a therapeutic concentration at the time of viral replication for a given NRTI, NtRTI or optional additional active agent in the target cells, includes factors for the therapeutic agent such as the route of administration, pharmacokinetics, absorption rate based on administration route, effects of food on oral absorption, *in vivo* distribution, metabolic pathways, elimination route, race, gender, and age of the subject, single dose incident side effects, long term administration side effects, and synergistic effects with co-administered active agents. Information related to these factors considered in dosing are available from the United States Food and Drug Administration (<http://www.fda.gov/oashi/aids/virals.html>) Preferably, NRTI and NtRTI prophylactic dosing according to the present invention uses as a starting point the maximal recommended tolerated dosing levels for the given active agent combination associated with HAART treatment protocols.

[0030] An inventive kit is provided that includes a 2-dose package of oral doses, such as tablets. In an exemplary embodiment of FDA approved NRTI and NtRTIs, each dose contains between 100 and 2500 milligrams (mg) of emtricitabine and between 100 and 2500 mg of TDF along with instructions to ingest the first dose approximately 1 to 8 hours prior to potential retroviral exposure and preferably about 2 hours there before, and a second dosage to be ingested 20 to 48 hours after potential retroviral exposure, preferably at about 22 hours thereafter. For an adult human, preferably each of the doses includes 200 mg of emtricitabine and 300 mg TDF. A non-human primate dose according to the present invention is typically higher on a mg per kg animal body weight basis by a factor typically ranging from 2 to 10. Additional NRTIs, NtRTIs,

NNRTIs, protease inhibitors or entry inhibitors are optionally provided in concert with either or both of these doses. The kit also includes instructions as to the timing of doses, contraindications, modifications associated with food ingestion, and additional behaviors that the recipient (synonymously described herein as a human primate host) can undertake to reduce the risk of retrovirus exposure and initial infection. It is also appreciated that a carrier illustratively including a gel, jelly, cream, ointment, film, sponge, foam, suppository, vaginal ring or other delivery device is provided containing an NRTI such as emtricitabine, alone or in combination with an NtRTI such as tenofovir or TDF. The carrier is readily applied to mucosal tissue likely to be exposed to viral transmission as an added level of protection in concert with the oral doses.

[0031] An inventive kit is also provided that includes at least one NRTI and at least one NtRTI compounded as a gel, jelly, cream, ointment, film, sponge, foam, suppository, or applied to a vaginal ring or other like antiviral barrier. To prepare such a pharmaceutical compounded form, an effective amount of each of the active agents inclusive of at least one NRTI and NtRTI is combined in admixture with the pharmaceutically acceptable carrier or applied to a surface of the barrier. It is appreciated that the residence time of such a pharmaceutical composition is maintained at the site of administration through the inclusion of an optional bioadhesive that provides adhesion to mucosal tissue or the dermis. An inventive composition compounded for application to the dermis or mucosal tissue is provided along with instructions as to the timing of doses, contraindications, modifications associated with food ingestion, and additional behaviors that the person (synonymously described herein as a human primate host) can undertake to reduce the risk of retrovirus exposure and initial infection. Optionally, a kit containing an oral dosage is combined with a composition compounded for application to the dermis, rectal mucosa or vaginal mucosa so as to assure a therapeutically effective combination of NRTI and NtRTI at the mucosal point of retroviral entry associated with sexual exposure, as well as a therapeutically effective serum circulating quantity of prophylactic antiretrovirals.

[0032] The present invention is further detailed with respect to the following non-limiting examples. These examples are intended to provide exemplary specific embodiments of the present invention and are not intended to limit the scope of the appended claims.

EXAMPLES

Example 1 – Antiretroviral Drugs and Doses

[0033] A dose of 22 mg/kg of tenofovir disoproxil fumarate (TDF) is given orally and 20 mg/kg of emtricitabine (FTC) given orally or subcutaneously to one group of adult male rhesus macaques. The 22 mg/kg TDF dose resulted in an area-under the plasma concentration-time curve over a 24 h interval (AUC) of 4.49 $\mu\text{g} \times \text{hr/ml}$ which was similar to the value of 5.02 $\mu\text{g} \times \text{hr/ml}$ observed in human receiving 300 mg of TDF. The dose of 20 mg/kg of FTC resulted in an AUC value (11 $\mu\text{g} \times \text{hr/ml}$), also similar to that observed in humans receiving 200 mg of FTC orally ($10.0 \pm 3.12 \mu\text{g} \times \text{hr/ml}$)⁶. Subcutaneous administration of FTC results in plasma FTC levels comparable to those achieved during oral administration, indicating a high FTC absorption in rhesus macaques.

[0034] Oral administration of FTC and TDF to macaques is by mixing the drug powders with peanut butter or fruit. Macaques are observed to ensure ingestion.

Example 2 – Virus Inoculations

[0035] A chimeric envelope SHIV_{SF162P3} isolate is used to inoculate the macaques. SHIV_{SF162P3} is a construct that contains the *tat*, *rev*, and *env* coding regions of HIV-1_{SF162} in a background of SIVmac239. This isolate was obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.^{7,8} Virus exposures are performed 2 hours after drug treatment, and involved non-traumatic inoculation of 1 mL of SHIV_{SF162P3} (10 TCID₅₀ or 7.5×10^6 viral RNA copies) into the rectal vault via a sterile gastric feeding tube.⁹ Anesthetized macaques remained recumbent for at least 15 min after each intra-rectal inoculation.

Example 3 – SHIV Viral Load Assay

[0036] Plasma RNA is quantified using a real-time PCR assay as previously described.⁵ This assay has a sensitivity of detection of 50 RNA copies/ml or 10 copies of a pVp1 plasmid carrying the SIVmac239 RT gene. HIV-1 RNA is extracted from 1 mL of plasma using the NucliSens extraction method (bioMérieux). A known amount of virus particles (3×10^5) from an HIV-1 CM240 virus stock is added to each sample prior to extraction to control for the efficiency of extraction. Reverse transcription is performed using 10 microliters (μL) of extracted RNA and the 2-step TaqMan Gold reverse-transcriptase (RT)–PCR kit (Applied Biosystems) according to

the manufacturer's instructions. PCR reactions are performed as described using an ABI 7000 Gene Detection System (Applied Biosystems). Virus loads are calculated from a standard curve generated with known amount of virus particles. All primers and probes used for SIVmac239 and HIV-1 CM240 have been reported elsewhere.⁵ HIV-1 CM240 is obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.

Example 4 – Detection of Genotypic Resistance to FTC and Tenofovir

[0037] Emergence of FTC and tenofovir resistance is monitored by sequence analysis of SIV RT (551 bp; amino acids 52 to 234) and by a more sensitive allele-specific real-time PCR method for the K65R and M184V mutations. Sequence analysis was done from plasma viruses using an RT-PCR procedure as previously described.⁵ The Vector NTI program (Version 7, 2001) is used to analyze the data and to determine deduced amino-acid sequences. Detection of low frequency of K65R and M184V mutants in plasma by real-time PCR is performed as previously described.¹⁰ These assays have a detection limit of 0.4% of K65R and 0.6% of M184V cloned sequences in a background of wild type plasmid.

Example 5 – Virus-Specific Antibody Responses

[0038] Virus-specific serologic responses (IgG and IgM) are measured using a synthetic-peptide EIA (Genetic Systems HIV-1/HIV-2) assay.

Example 6 – Statistical Methods

[0039] The exact log-rank test is used for a discrete-time survival analysis of the treatment and control groups, with use of the number of inoculations as the time variable. The Cox proportional hazards model is used to estimate the relative hazard ratio (HR). Percent protection is calculated from the HR value using the formula: $(1 - 1/HR) \times 100$. All statistical analyses for calculation of the efficacy of the different interventions are performed using SAS software (version 9.1; SAS Institute) and StatXact software (version 6.3; Cytel).

Example 7 – Routine Dosing Experimental Design

[0040] Macaques are exposed rectally once weekly for up to 14 weeks to SHIV162p3 which contains an R5 tropic HIV-1 envelope that resembles naturally transmitted viruses. The SHIV162p3 challenge dose is 10 TCID₅₀ or 7.6×10^5 RNA copies which is similar to HIV-1 RNA levels in semen during acute infection in humans.¹¹ Virus exposures are terminated when a

macaque became infected. Fig. 1 shows the study design and the interventions evaluated in each group of macaques. Three prophylactic drug treatments of increasing drug potency are each given once daily to a group of six macaques. Animals in Group 1 were treated subcutaneously with 20 mg/kg of FTC alone. Animals in Group 2 received orally a combination of FTC (20 mg/kg) and TDF (22mg/kg). Animals in Group 3 had the most protective treatment with subcutaneous 20 mg/kg of FTC and a 22 mg/kg of tenofovir (PMPA). The rate of infection in each group is compared with that seen in 18 untreated control macaques (9 real time and 9 historical controls).

[0041] All treated macaques received the corresponding drugs 7 to 9 days prior to the first virus inoculation to achieve steady-state plasma levels. Treated animals that remained uninfected during the 14 challenges received 28 days of post-exposure prophylaxis after the last challenge. Protection was defined as absence of persistent viremia and seroconversion. Treated animals that became infected continued treatment for an average of 21 weeks (range = 13 to 29) to monitor for plasma viremia and drug resistance development.

Example 8 – Survival Curves

[0042] Fig. 2 shows the survival curves observed for each group of animals per Example 7. Data with TDF (20mg/kg) is also provided for comparison. Untreated macaques are infected after a median of 2 rectal exposures (mean = 4). The majority of the animals (13/18 or 72%) are infected during the first 4 challenges (median= 2); 4 (22%) are infected between exposures 8 and 14 (mean = 10), and only 1 (6%) remained uninfected after 14 exposures. The median 2 exposures for infection in controls suggests that an animal receiving prophylactic treatment and remaining uninfected after 14 virus challenges would have been protected against a median of 7 rounds of transmissions. Treatments of Groups 1-3 are all protective to a degree with a clear dose-response relationship being observed. All 6 macaques in Group 3 that received the most potent inventive composition remained uninfected demonstrating that full protection against repeated challenges is possible. Of the 6 macaques in Group 2, 4 were protected and only 2 (animal reference numbers AI-54 and AG-81) became infected at exposures 9 and 12. Compared to controls, infection in this group is reduced by 7.8-fold (Cox proportional hazard ratio [HR] =7.8, $p = 0.0075$). Infection in both animals is significantly delayed compared to the untreated

controls ($p = 0.0004$). These 2 macaques became seropositive 2 weeks after the first detectable viral RNA in plasma and both were proviral DNA positive at weeks 10 and 12, respectively. Of the 6 macaques in Group 1 receiving FTC only, 2 remained protected after 14 exposures and 4 had the first detectable viral RNA at exposures 5 (AG-80), 10 (AG-46), 12 (AH-04), and 13 (AG-07), respectively. Survival analysis showed a statistically significant difference from untreated controls ($p = 0.004$). Compared to controls, infection is reduced 3.8-fold macaques (Cox proportional hazard ratio [HR] = 3.8, $p = 0.021$). Infection in these 4 animals is also confirmed by PCR amplification of proviral DNA from PBMCs and by serology; antibody responses are detectable 3, 1, 2, and 6 weeks after the first detectable RNA, respectively. Fig. 2 also shows that the protection achieved with FTC alone was higher than that previously seen in 4 animals receiving TDF,⁵ consistent with the slightly higher potency of FTC, although the difference was not statistically significant ($p = 0.5$).

Example 9 – Prophylactic Breakthrough Infections and Drug Resistance Emergence

[0043] Since the dynamics of breakthrough infections that occur during inventive prophylaxis and drug resistance emergence are unknown, the 6 infected animals from Groups 1 and 2 are followed under continued drug treatment. Fig. 3 compares the virus load kinetics in the 6 breakthrough infections with those in 12 untreated macaques that had sufficient follow-up samples. The mean peak viremia in the 6 treated macaques was $4.9 \pm 0.5 \log_{10}$ RNA copies/ml, $2.0 \log_{10}$ lower than in untreated controls ($6.9 \pm 0.3 \log_{10}$ RNA). Figure 3 also shows that such differences in viremia were maintained up to week 11 as indicated by similar rate of virus load decline seen in the two groups of animals ($-0.23 \pm 0.02 \log_{10}/\text{week}$ in treated vs. $-0.29 \pm 0.02 \log_{10}/\text{week}$ in untreated controls). The individual virus load kinetics in the 6 breakthrough infections are shown in Figure 4. Three FTC (AG-80, AH-04, and AG-07) and one of the FTC/TDF (AG-81) failures had undetectable virus loads 3, 4, 7, and 11 weeks after the peak in viremia, respectively; viremia in these animals remained consistently low or undetectable for up to 20 weeks. In contrast, all 12 untreated macaques had detectable virus loads during a median follow-up period of 7 weeks (range = 5-36 weeks). The arrow in Fig. 4 denotes the first detectable antibody response. Grey circles indicate detectable M184V/I mutation; wild type

sequences are shown in black full circles. Open circles are provided for data points not genotyped.

[0044] Drug resistance testing showed that wild type virus initiated all 6 breakthrough infections in Groups 1 and 2 reflecting residual virus replication in target cells not protected by drugs (Fig. 4). Four animals had no evidence of drug resistance despite extended treatment (median= 23 weeks). Only 2 animals had detectable M184V (AG-46, FTC-treated) or M184I (AI-54 FTC/TDF-treated) mutations associated with FTC resistance at week 4 and 10, respectively. The tenofovir-associated K65R mutation is not detected in the 2 Group 2 animals receiving FTC/TDF. Fig. 4 also shows that the 2 macaques that selected M184V/I had the highest peak viremias. Without intending to be bound to a particular theory, it is hypothesized that more virus replication in these animals may have facilitated drug resistance selection. Reductions in acute viremia are proposed to contribute at a population level to a decrease in virus transmissibility.

Example 10 – Single Dosing

[0045] The process of Example 7 is repeated in Group 3 with drugs only being administered 2 hours prior to and 22 hours subsequent to each inoculation. The resultant survival curves are comparable to those detailed in Example 8.

Example 11 – Single Dosing with Suppository

[0046] A group of 6 macaques received the drug treatment of Group 3 per Example 7 in the form of a gel inserted rectally containing 300 mg of tenofovir and 300 mg lamuvidine (3-TC) 1 hour before viral inoculation with observation to assure that the suppository is not voided. The gel is formed by compounding tenofovir and 3-TC in 2% by weight hydroxyethyl cellulose (HEC)-based gel in both a vaginal formulation (pH 4.5) and rectal formulation (pH 6.5) containing (w/v) 3% tenofovir, and 3% 3-TC. The gels are stable at room temperature for at least five months with no loss in activity; and gels retained full activity at both pH 4.5 and pH 6.5 at levels equivalent to those observed for tenofovir and 3-TC preparations in water. Using an MT4/MTT phenotypic assay, all gels were tested for activity against wild-type HIV-1_{HXB2}, and resistant HIV-1 viruses containing the K65R or M184V mutations. No significant cytotoxicity is seen in the cervical explant model.

Viral protection of the macaques is maintained throughout the study.

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[0047] Patent documents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. These documents and publications are incorporated herein by reference to the same extent as if each individual document or publication was specifically and individually incorporated herein by reference.

[0048] The foregoing description is illustrative of particular embodiments of the invention, but is not meant to be a limitation upon the practice thereof. The following claims, including all equivalents thereof, are intended to define the scope of the invention.

CLAIMS

1. A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:

- (a) selecting a primate host not infected with the immunodeficiency retrovirus, and
- (b) administering directly to an uninfected primate host a combination comprising:

- i. a pharmaceutically effective amount of emtricitabine; and
- ii. a pharmaceutically effective amount of tenofovir or a tenofovir prodrug,

wherein the combination is administered orally prior to the exposure of the primate host to the immunodeficiency retrovirus,

thereby protecting the primate host from infection with the immunodeficiency retrovirus.

2. The process of claim 1, wherein selecting a primate host comprises selecting an adult human not infected with the immunodeficiency retrovirus.

3. The process of claim 2, wherein the adult human is a male.

4. The process of claim 2, wherein the pharmaceutically effective amount of emtricitabine and the pharmaceutically effective amount of tenofovir or the tenofovir prodrug, are administered directly to the human in a combined single dosage formulation.

5. The process of claim 2, wherein the immunodeficiency retrovirus is a human immunodeficiency virus.

6. The process of claim 5, wherein a human immunodeficiency virus (HIV) is HIV-1.

7. The process of claim 1, wherein the combination is administered as preexposure prophylactic treatment prior to rectal and/or vaginal exposure of the primate host to the immunodeficiency retrovirus.

8. The process of claim 1, comprising administering 200 milligrams (mg) of emtricitabine to the primate host.

9. The process of claim 1, wherein the combination is administered daily for several days, weeks or months.

10. The process of claim 9, wherein the combination is administered daily for several days, weeks or months both before and after an exposure of the primate host to the immunodeficiency retrovirus.

11. The process of claim 1, wherein administration of the combination results in an absence of persistent viremia and seroconversion of the primate host.

12. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection;

and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine; and

ii. a pharmaceutically effective amount of tenofovir or a tenofovir prodrug;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human.

13. The process of claim 12, wherein the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus.

14. The process of claim 12, wherein the combination is compounded into a single combination formulation.

15. The process of claim 12, wherein an inhibition of infection in the host is determined by an absence of persistent viremia and seroconversion in the human following the exposure to the immunodeficiency retrovirus.

16. The process of claim 12, wherein the combination is administered following potential exposure of the primate host to the human immunodeficiency retrovirus.

17. The process of claim 16, wherein the potential exposure to the human immunodeficiency retrovirus comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.

18. The process of claim 12, wherein the combination comprises the tenofovir prodrug.

19. The process of claim 1, wherein the combination comprises the tenofovir prodrug.

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

ABSTRACT OF THE DISCLOSURE

A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided in a single dose within 24 hours of the exposure. A regime of regular daily doses is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection the detailed combination prior to sexual exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

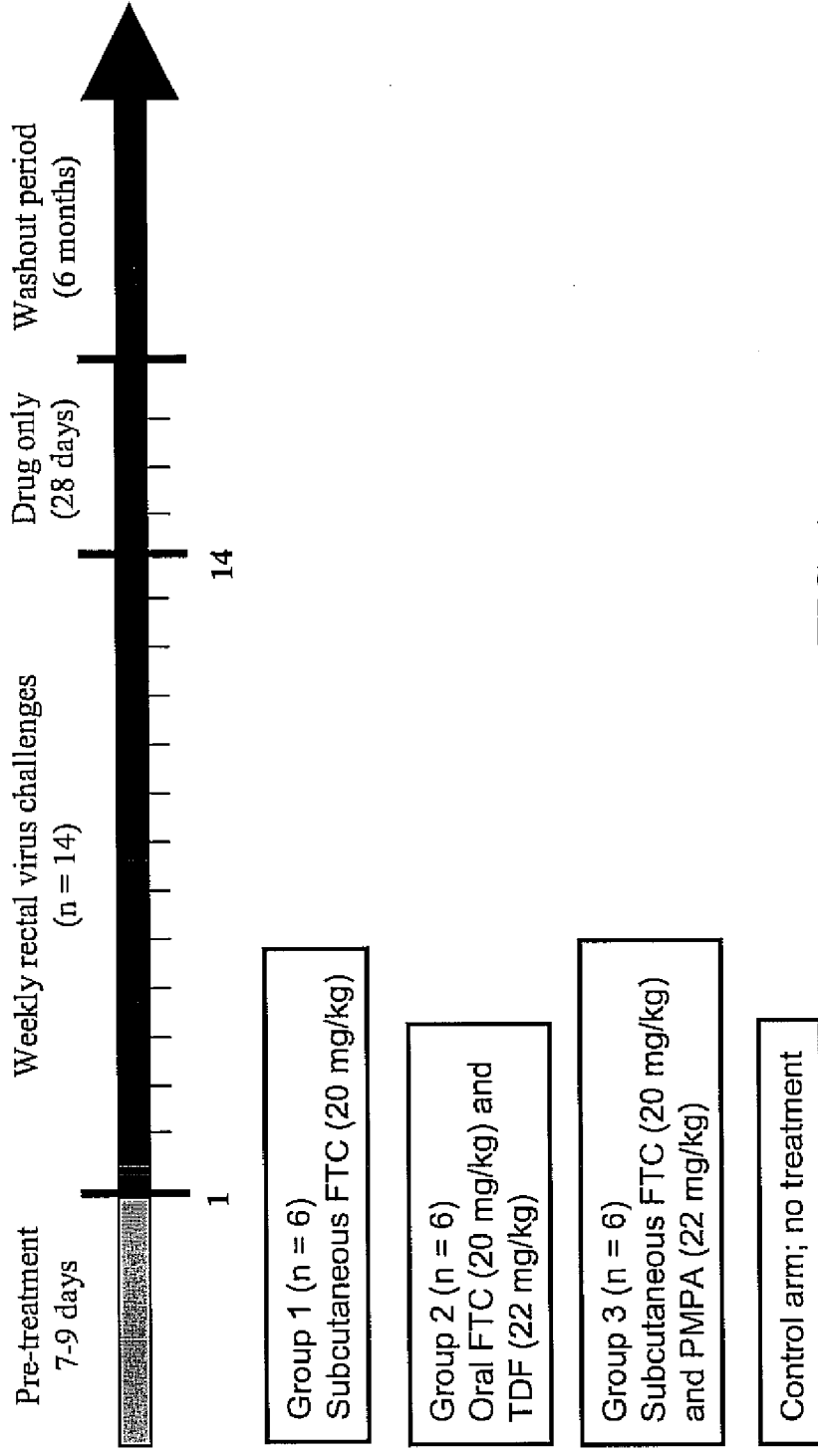


FIG. 1

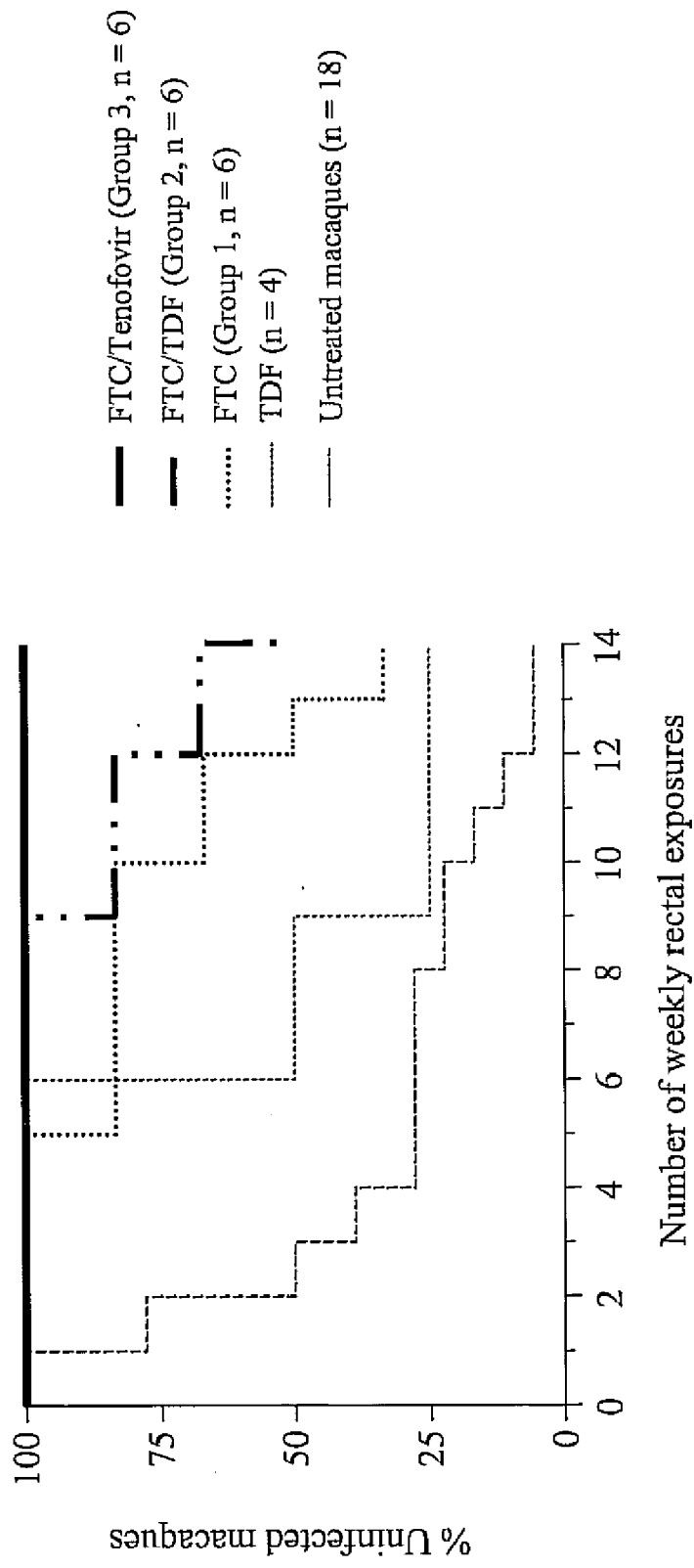


FIG. 2

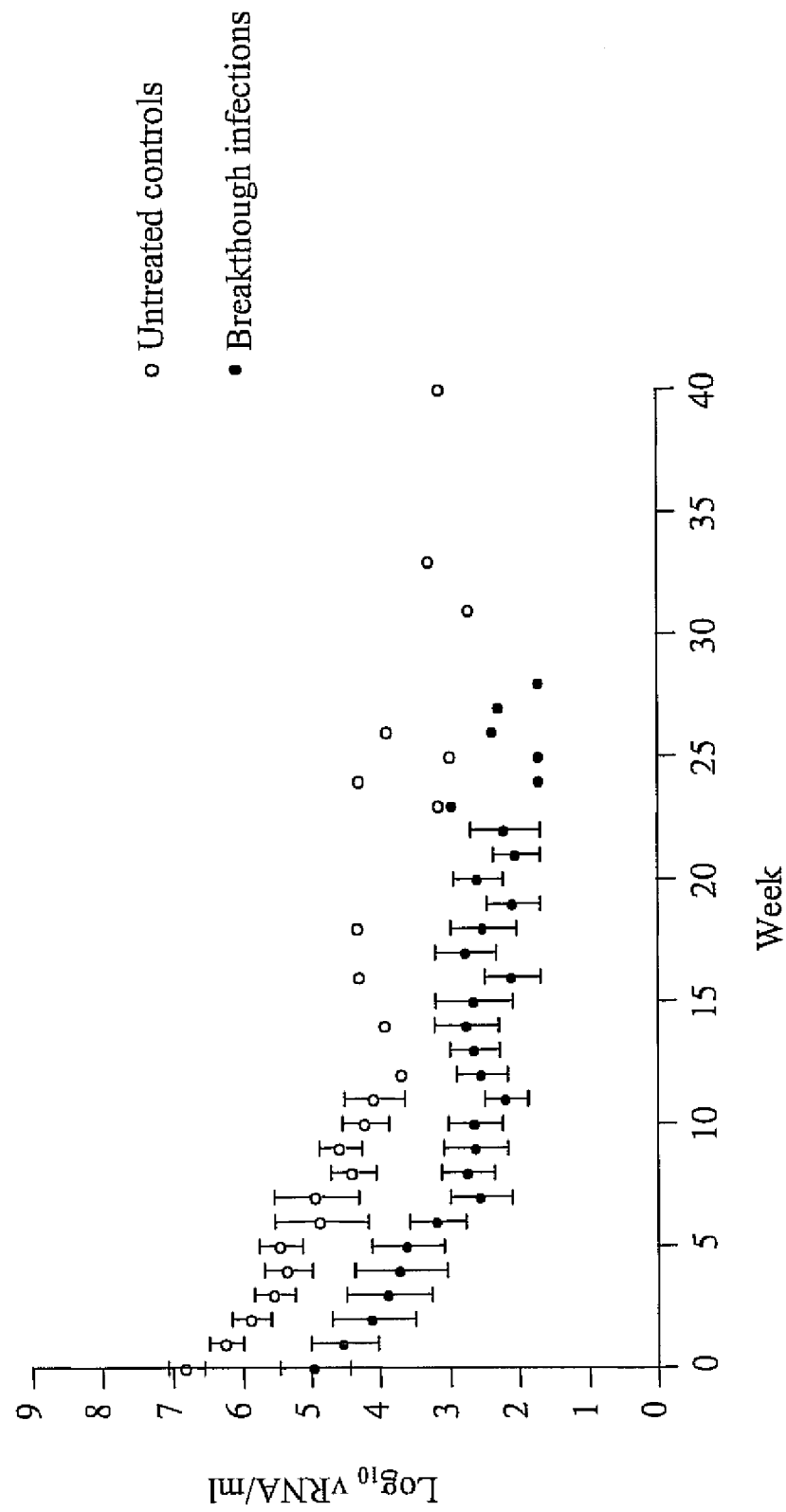


FIG. 3

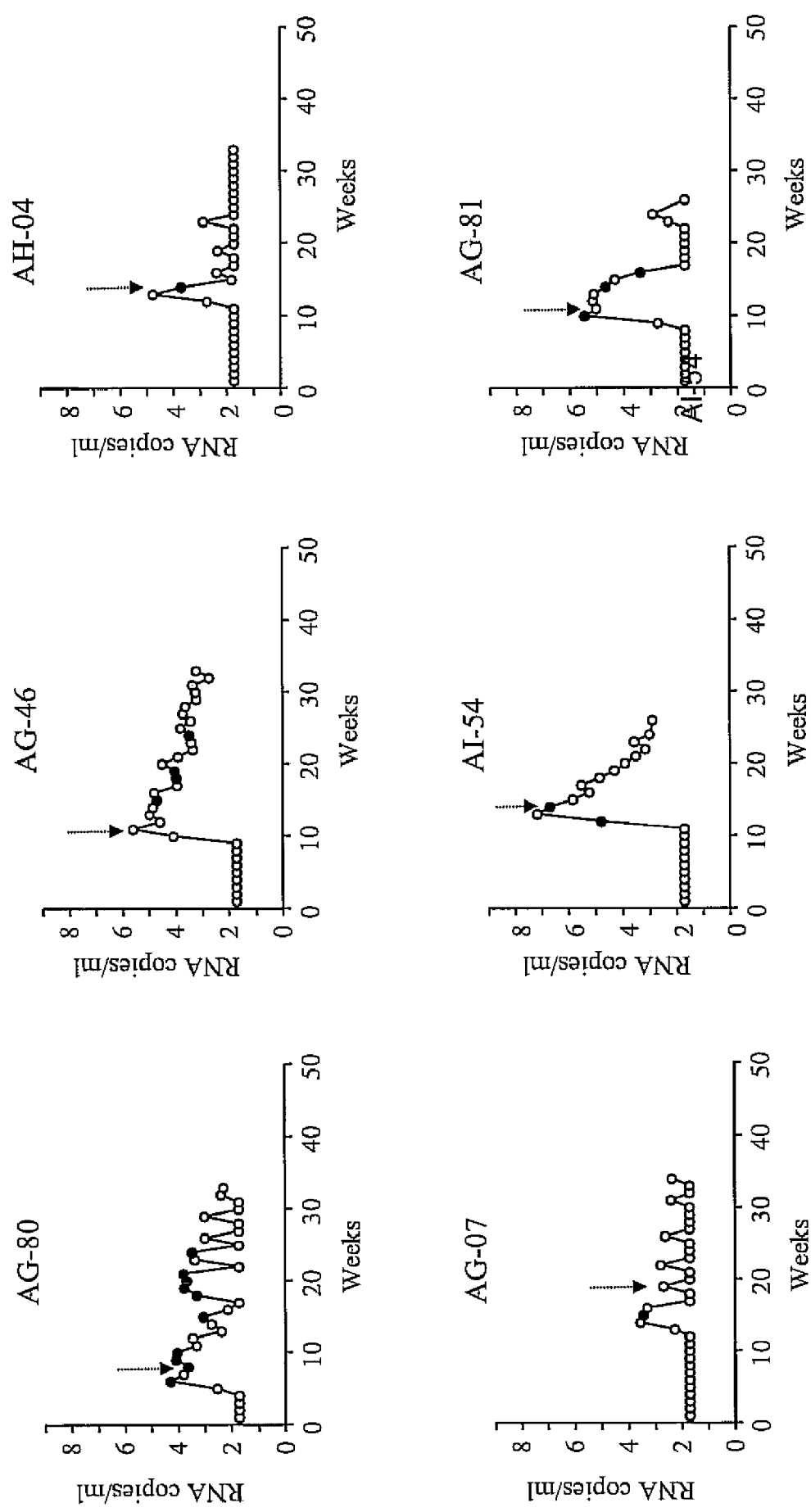


FIG. 4

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INFORMATION DISCLOSURE STATEMENT
FOR CONTINUING APPLICATIONS

Listed on the accompanying form PTO-1449 are several English-language documents. Applicant respectfully requests that such documents be listed as references cited on the issued patent.

The present application relies upon U.S. Patent Application No. 14/679,887, which was filed April 6, 2015, for an earlier filing date under 35 U.S.C. § 120. Furthermore, documents listed on the accompanying form PTO-1449 were disclosed to or cited by the Patent Office in the earlier U.S. application.

Copies of the documents listed on the accompanying form PTO-1449 that were submitted by applicant or cited by the Patent Office in an earlier application need not be sent to the Patent Office pursuant to 37 C.F.R. § 1.98. The documents listed on the accompanying form PTO-1449 were all submitted or cited in U.S. Patent Application No. 14/679,887. Applicant will furnish the Patent Office with copies of the previously submitted documents upon request.

The filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, prior art or otherwise material to patentability as defined in 37 C.F.R. § 1.56.

Please charge any fees that may be required in connection with filing this Information Disclosure Statement, or credit any overpayment, to Deposit Account No. 02-4550.

Respectfully submitted,

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		WANG et al., "Single-dose sertaconazole vaginal tablet treatment of vulvovaginal candidiasis," <i>J. Chin. Med. Assoc.</i> 69(6):259-63 (June 2006).	
		WINSTON et al., "The Use of a Triple Nucleoside-nucleotide Regimen for Nonoccupational HIV Post-exposure Prophylaxis," <i>HIV Medicine</i> 6:191-97 (2005).	

EXAMINER SIGNATURE:	DATE CONSIDERED:
* Examiner: Initial if reference considered, whether or not in conformance with MPEP 609. Draw line through cite if not in conformance and not considered. Include copy of this form with next communication to applicant. **Please place an "X" in this column if English translation is attached.	

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	4239-92970-14
		Application Number	
Title of Invention	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor	1				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Walid		Heneine		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Atlanta	State/Province	GA	Country of Residence	US

Mailing Address of Inventor:

Address 1	2830 Woodland Park Drive				
Address 2					
City	Atlanta	State/Province	GA		
Postal Code	30345	Country	US		

Inventor	2				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Thomas	M.	Folks		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Helotes	State/Province	TX	Country of Residence	US

Mailing Address of Inventor:

Address 1	14014 French Park				
Address 2					
City	Helotes	State/Province	TX		
Postal Code	78023	Country	US		

Inventor	3				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Robert		Janssen		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	4239-92970-14
		Application Number	
Title of Invention	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS		

City	Atlanta	State/Province	GA	Country of Residence	US

Mailing Address of Inventor:

Address 1	106 Inman Circle				
Address 2					
City	Atlanta	State/Province	GA		
Postal Code	30309	Country	US		
Inventor	4				Remove
Legal Name					

Prefix	Given Name	Middle Name	Family Name	Suffix	
	Ronald	A.	Often		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Villa Rica	State/Province	GA	Country of Residence	US

Mailing Address of Inventor:

Address 1	9795 Lakefall Ct.				
Address 2					
City	Villa Rica	State/Province	GA		
Postal Code	30180	Country	US		
Inventor	5				Remove
Legal Name					

Prefix	Given Name	Middle Name	Family Name	Suffix	
	Jose	Gerardo	Garcia Lerma		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Decatur	State/Province	GA	Country of Residence	US

Mailing Address of Inventor:

Address 1	1170 Larch Lane				
Address 2					
City	Decatur	State/Province	GA		
Postal Code	30033	Country	US		
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button.					

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ An Address is being provided for the correspondence information of this application.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	4239-92970-14
		Application Number	
Title of Invention	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS		

Customer Number	46135		
Email Address	docketing@klarquist.com	Add Email	Remove Email

Application Information:

Title of the Invention	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS		
Attorney Docket Number	4239-92970-14	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.			
Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	46135		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	4239-92970-14
		Application Number	
Title of Invention	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
	Continuation of	14679887	2015-04-06		
Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14679887	Continuation of	11669547	2007-01-31	9044509	2015-06-02
Prior Application Status	Expired		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
11669547	Claims benefit of provisional	60764811	2006-02-03		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.					Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the Add button.			Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	4239-92970-14
		Application Number	
Title of Invention	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS		

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
 NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	4239-92970-14
		Application Number	
Title of Invention	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	4239-92970-14
		Application Number	
Title of Invention	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant	1	Remove
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section. Clear		
☒ Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:		
Name of the Deceased or Legally Incapacitated Inventor:		
If the Applicant is an Organization check here. ☒		
Organization Name	THE UNITED STATES OF AMERICA, as represented by the Secretary, Department of Health and Human Services	
Mailing Address Information For Applicant:		
Address 1	6011 Executive Boulevard, Suite 325, MSC 7660	
Address 2	Office of Technology Transfer	
City	Bethesda	State/Province MD
Country	US	Postal Code 20892-7660
Phone Number		Fax Number
Email Address		
Additional Applicant Data may be generated within this form by selecting the Add button. Add		

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	4239-92970-14
		Application Number	
Title of Invention	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS		

Assignee	1		
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.			
Remove			
If the Assignee or Non-Applicant Assignee is an Organization check here. ☒			
Organization Name	THE UNITED STATES OF AMERICA, as represented by the Secretary, Department of Health and Human Services		
Mailing Address Information For Assignee including Non-Applicant Assignee:			
Address 1	6011 Executive Boulevard, Suite 325, MSC 7660		
Address 2	Office of Technology Transfer		
City	Bethesda	State/Province	MD
Country	US	Postal Code	20892-7660
Phone Number		Fax Number	
Email Address			
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add			

Signature:[Remove](#)

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application and either box A or B is **not** checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Susan Alpert Siegel/		Date (YYYY-MM-DD)	2017-01-13	
First Name	Susan	Last Name	Siegel	Registration Number	43121
Additional Signature may be generated within this form by selecting the Add button. Add					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	4239-92970-14
		Application Number	
Title of Invention	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

- 1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
- 2 A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
- 3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
- 4 A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
- 5 A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
- 6 A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
- 7 A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
- 8 A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
- 9 A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:

Filing Date:

Title of Invention:

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

First Named Inventor/Applicant Name:

Walid M. Heneine

Filer:

Susan A. Siegel/Adrienne Chocholak

Attorney Docket Number:

4239-92970-14

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	280	280
UTILITY SEARCH FEE	1111	1	600	600
UTILITY EXAMINATION FEE	1311	1	720	720

Pages:

Claims:

Miscellaneous-Filing:

Petition:

Patent-Appeals-and-Interference:

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1600

Electronic Acknowledgement Receipt

EFS ID:	28058794
Application Number:	15406344
International Application Number:	
Confirmation Number:	5617
Title of Invention:	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS
First Named Inventor/Applicant Name:	Walid M. Heneine
Customer Number:	46135
Filer:	Susan A. Siegel
Filer Authorized By:	
Attorney Docket Number:	4239-92970-14
Receipt Date:	13-JAN-2017
Filing Date:	
Time Stamp:	17:41:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$ 1600
RAM confirmation Number	011717INTEFSW00004922024550
Deposit Account	024550
Authorized User	Susan Siegel

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:
37 CFR 1.16 (National application filing, search, and examination fees)

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	4239-92970-14_New_App_Trans_CONT.pdf	24775	no	2
			7f80fe336f15430d99ffd6b737468a996cf5fa6d		
Warnings:					
Information:					
2		4239-92970-14_Specification.pdf	128149	yes	22
			5dd3b1196d2a71e957501aa2293b08449acabbd9		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	18	
	Claims		19	21	
	Abstract		22	22	
Warnings:					
Information:					
3	Drawings-only black and white line drawings	4239-92970-14_Drawings.pdf	288384	no	4
			2d5ee4f5dcd44bd03b5e365780ec0806c3e1b3ac		
Warnings:					
Information:					
4	Transmittal Letter	4239-92970-14_IDS.pdf	19627	no	2
			b208753f802bb994e482ee8a01c69c2a272f0d8b		
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Form (SB08)	4239-92970-14_1449.pdf	60642	no	5
			8d25c1190c92a261434ac4b7b314fb1da2244c94		

Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
6	Application Data Sheet	4239-92970-14_ADS.pdf	1823595 9e9d20b8707b68672392ada3215ab1208896b643	no	10
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	35075 03fed05b87b77e90e80344c95e31ea30a8432ab2	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			2380247		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

Document code: WFEE

United States Patent and Trademark Office
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EXHIBIT N

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Attorney Docket Number	4239-92970-14
	Application Number	15/406,344
	Filing Date	January 13, 2017
	First Named Inventor	Walid Heneine
	Art Unit	1629
	Examiner Name	Not yet assigned

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. (optional)	Foreign Patent Document Country Code-Number-Kind Code (if known)	Issue or Publication Date MM-DD-YYYY	Name of Patentee or Applicant	T**

Examiner Initials*	Cite No. (optional)	OTHER DOCUMENTS			T**
		Collins "Tenofovir/FTC backbone outperforms AZT/3TC (Combivir) with efavirenz in treatment naive patients; reduced toxicity drives ITT viral efficacy," <i>HIV Treatment Bulletin</i> (2 pages printed from http://i-base.info/htb/7665)(January 29, 2005).			
		Panlilio et al., "Updated U.S. public health guidelines for the management of occupational exposure to HIV and recommunication for post exposure prophylaxis," <i>MMWR</i> 54(RR09): (25 pages) (September 30, 2005).			
		Smith et al., "Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States," <i>MMRW</i> 54(RR-2) (28 pages)(January 21, 2005).			
		Szekeres et al., "Anticipating the efficacy of HIV pre-exposure prophylaxis," (PrEP) and the needs of at-risk Californians," <i>PrEP and the Needs of At-risk Californians</i> (40 pages)(November 2004).			
		Van Rompay et al., "Two low doses of tenofovir protect newborn macaques against oral simian immunodeficiency virus infection," <i>Journal of Infectious Diseases</i> 184: 429-438 (August 15, 2001).			

EXAMINER SIGNATURE:	DATE CONSIDERED:
* Examiner: Initial if reference considered, whether or not in conformance with MPEP 609. Draw line through cite if not in conformance and not considered. Include copy of this form with next communication to applicant. **Please place an "X" in this column if English translation is attached.	

Electronic Acknowledgement Receipt

EFS ID:	28561450
Application Number:	15406344
International Application Number:	
Confirmation Number:	5617
Title of Invention:	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS
First Named Inventor/Applicant Name:	Walid Heneine
Customer Number:	46135
Filer:	Susan A. Siegel
Filer Authorized By:	
Attorney Docket Number:	4239-92970-14
Receipt Date:	07-MAR-2017
Filing Date:	13-JAN-2017
Time Stamp:	17:29:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	4239-92970-14_IDS.pdf	18967	no	1
			51631e704cd5ae7a313a3d50042bb587ddc15c8b		

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	4239-92970-14_1449.pdf	25681	no	1
			3fd2c687b69aca4f3a76421f72a8be231b9ccc16		
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	Collins_2005.pdf	93645	no	2
			78ae6939a8e387fd6e52c9d0c9f168ea201d2335		
Warnings:					
Information:					
4	Non Patent Literature	Panlilio_et_al_2005.pdf	697380	no	25
			994e67a616c97653b1df340b5dda9ef9543677e1		
Warnings:					
Information:					
5	Non Patent Literature	Smith_et_al_2005.pdf	303146	no	28
			22e5f15b57021ca925b991f309cf5d15e45f9168		
Warnings:					
Information:					
6	Non Patent Literature	van_rompay.pdf	151466	no	10
			1180d9fdb92d6785ec6aff7acb8961e5d68aaba6		
Warnings:					
Information:					
7	Non Patent Literature	Szekeres.pdf	3600129	no	40
			47c0ab3d1235a50584a965f046c27f310cbd00b3		
Warnings:					
Information:					
Total Files Size (in bytes):			4890414		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Walid Heneine

Application No. 15/406,344

Filed: January 13, 2017

Confirmation No. 5617

For: INHIBITION OF HIV INFECTION
THROUGH CHEMOPROPHYLAXIS

FILED VIA EFS
March 7, 2017

Examiner: Not yet assigned

Art Unit: Not yet assigned

Attorney Reference No. 4239-92970-14

FILED VIA THE ELECTRONIC FILING SYSTEM (EFS)
COMMISSIONER FOR PATENTS

INFORMATION DISCLOSURE STATEMENT
PURSUANT TO 37 C.F.R. § 1.97(b)(1)

Listed on the accompanying form PTO-1449 and submitted herewith are several English-language documents. Applicant respectfully requests that these documents be listed as references cited on the issued patent.

Applicant filed this Information Disclosure Statement (IDS) within three months of the filing date of a national application. As a result, no fee should be required to file this IDS. However, if the Patent Office determines that a fee is required for Applicant to file this IDS, please charge any such fees, or credit overpayment, to Deposit Account No. 02-4550.

The filing of this IDS shall not be construed to be an admission that the information cited in the statement is, or is considered to be, prior art or otherwise material to patentability as defined in 37 C.F.R. § 1.56.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

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121 S.W. Salmon Street
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By /Susan Alpert Siegel/
Susan Alpert Siegel, Ph.D.
Registration No. 43,121

EXHIBIT O



UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/406,344	01/13/2017	Walid Heneine	4239-92970-14	5617

46135 7590 08/08/2017
KLARQUIST SPARKMAN, LLP (NIH-CDC)
121 S.W. SALMON STREET
SUITE 1600
PORTLAND, OR 97204

EXAMINER

WANG, SHENGJUN

ART UNIT	PAPER NUMBER

1627

NOTIFICATION DATE	DELIVERY MODE

08/08/2017

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@klarquist.com
nicole.salazar@klarquist.com
ASCChair@klarquist.com

Office Action Summary	Application No. 15/406,344	Applicant(s) HENEINE ET AL.	
	Examiner SHENGJUN WANG	Art Unit 1627	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 1-19 is/are pending in the application.
5a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) _____ is/are allowed.
- 7) ☒ Claim(s) 1-19 is/are rejected.
- 8) ☐ Claim(s) _____ is/are objected to.
- 9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)	3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____	4) ☐ Other: _____

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Double Patenting Rejections

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor

Art Unit: 1627

to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

2. Claims 1-19 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 9,044,509. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims herein are generic to the claims of '059.

3. Claims 1-19 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 9,579,333. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims herein are generic to the claims of '333.

Claim Rejections 35 U.S.C. 103

4. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stephenson (IDS), and Dahl et al. (US 20040224917, IDS) in view of Shapiro et al. (IDS), Smith et al. (IDS), Szekeres et al. (IDS), Keller et al. (WO 2004/002498, IDS), and AIDS PATIENT CARE and STDs

6. Stephenson teaches that is known in the art that antiretroviral agents reduce the risk of HIV infection of those at high risk of such infection. Stephenson also reveals that vaginal application of antiviral composition in the form of gel and cream for preventing HIV infection is known. See, the entire document. Dahl et al. teach combinations of antiviral compounds, in particular compositions and methods for inhibition of HIV (including HIV-1). In an exemplary aspect, the invention includes a composition including tenofovir disoproxil fumarate (a prodrug of tenofovir) and emtricitabine which has anti-HIV activity. The composition of tenofovir DF and emtricitabine is both chemically stable and either synergistic and/or reduces the side effects of one or both of tenofovir DF and emtricitabine. Increased patient compliance is likely in view of the lower pill burden and simplified dosing schedule. (paragraphs [0003], [0004], [0011] to [0013]. Dahl et al. also reveal that tenofovir has been known for both treatment and prophylaxis of HIV infection. (paragraph [0090]. The combination may be in a variety of dosage forms, include oral, rectal, nasal, topical, vaginal or parenteral. The composition is particularly in the form of genital application forms, which may be administered for either therapeutic or prophylactic use. (paragraphs [0098 to [0108].

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7. The primary references as a whole do not teach expressly treatment of a subject who has not infected with the immunodeficiency virus with the particular combination of emtricitabine and tenofovir.

8. However, Szekeres et al. teach that it is widely believed in the art that biomedical approaches to HIV prevention is required to adequately curb the spread of the virus, both by post exposure prophylaxis (PEP) and pre exposure prophylaxis (PrEP). Known anti-HIV agents are used as the biomedical agents, tenofovir disoproxil fumarate (TDF), and a prodrug of tenofovir. See, particularly, pages 4-7. Smith et al. reveal US DHHS recommend PEP treatment of those exposed to HIV with the known anti-HIV drugs, including emtricitabine, tenofovir, and their combination, Truvada), (200mgemtricitabine/300 mg tenofovir). See, particularly, pages 8-10. Keller et al. teach a method of treating or preventing HIV infection by administering to the subject a combination of zidovudine, an old and well-known nucleoside reverse transcriptase inhibitor, and tenofovir, an old and well-known nucleotide reverse transcriptase inhibitor. Other anti-HIV agents recited herein, such as abacavir and lamivudine are also known. See, particularly, claims 12 and 14. Shapiro et al. further disclose that highly active antiretroviral therapy (HAART) reduces the risk of mother-to-child transmission of HIV via breast-feeding, wherein the HAART is composed of nevirapine, lamivudine and zidovudine. See, particularly, pages 713 and 714. AIDS PATIENT CARE and STDs reveals that tenofovir gel has been used to help women avoid HIV infection. See, the entire documents.

9. Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to treat a subject, or a subpopulation, who have

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not been infected by HIV, but are exposed to or at risk of exposure to HIV, an composition comprising emtricitabine and tenofovir, such as Truvada®.

10. A person of ordinary skill in the art would have been motivated , to treat a subject, or a subpopulation, who have not been infected by HIV, but are exposed to or at risk of exposure to HIV, an composition comprising emtricitabine and tenofovir, such as Truvada® with a reasonable expectation that the risk of infection by HIV will be reduced because it is known that anti-HIV agents will reduce the risk of HIV infection and emtricitabine, tenofovir or their combination, Truvada, is known for treatment/prophylaxis of HIV infection. Furthermore, "[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007). In instant case, the employment of anti-HIV agents for prophylactic purpose against HIV infection is old and well-known, the employment of particular known anti-HIV agents would have been obvious.

11. Furthermore, the optimization of a result effective parameter, e.g., effective amounts of therapeutic agents and the schedule for administration of the agents, is considered within the skill of the artisan. See, In re Boesch and Slaney (CCPA) 204 USPQ 215. The timing for administering the anti-HIV regimen would have been within the purview of ordinary skill in the art, particularly for the vaginal application. Furthermore, treatment of any subject who is at risk of HIV infection, man or woman, homosexual or heterosexual, would have been obvious since the method is for such purpose regardless the way of exposing to HIV.

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12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHENGJUN WANG whose telephone number is (571)272-0632.

The examiner can normally be reached on Monday to Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://portal.uspto.gov/external/portal>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHENGJUN WANG/
Primary Examiner, Art Unit 1627

<i>Index of Claims</i> 	Application/Control No. 15406344	Applicant(s)/Patent Under Reexamination HENEINE ET AL.
	Examiner SHENGJUN WANG	Art Unit 1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47										
CLAIM		DATE								
Final	Original	08/01/2017								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
	12	✓								
	13	✓								
	14	✓								
	15	✓								
	16	✓								
	17	✓								
	18	✓								
	19	✓								



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BIB DATA SHEET

CONFIRMATION NO. 5617

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
15/406,344	01/13/2017	514	1627	4239-92970-14		
RULE						
APPLICANTS THE UNITED STATES OF AMERICA, as represented by the Secretary, Department of Health and Human Serv, Bethesda, MD;						
INVENTORS Walid Heneine, Atlanta, GA; Thomas M. Folks, Helotes, TX; Robert Janssen, Atlanta, GA; Ronald A. Otten, Villa Rica, GA; Jose Gerardo Garcia Lerma, Decatur, GA;						
** CONTINUING DATA ***** This application is a CON of 14/679,887 04/06/2015 PAT 9579333 which is a CON of 11/669,547 01/31/2007 PAT 9044509 which claims benefit of 60/764,811 02/03/2006						
** FOREIGN APPLICATIONS *****						
** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 02/14/2017						
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and /SHENGJUN WANG/ Acknowledged Examiner's Signature		☐ Met after Allowance Initials	STATE OR COUNTRY GA	SHEETS DRAWINGS 4	TOTAL CLAIMS 19	INDEPENDENT CLAIMS 2
ADDRESS KLARQUIST SPARKMAN, LLP (NIH-CDC) 121 S.W. SALMON STREET SUITE 1600 PORTLAND, OR 97204 UNITED STATES						
TITLE INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLLAXIS						
FILING FEE RECEIVED 1740	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit		

```
=> s emtricitabine
L1      17581 EMTRICITABINE

=> s tenofovir
L2      37680 TENOFOVIR

=> s l2 and l1
L3      15747 L2 AND L1

=> s l3 and (pre-exposure or post-exposure)
L4      1353 L3 AND (PRE-EXPOSURE OR POST-EXPOSURE)

=> s l4 and (prophylaxis or prophyla? or prevent?)
L5      1348 L4 AND (PROPHYLAXIS OR PROPHYLA? OR PREVENT?)

=> dup remov l5
PROCESSING COMPLETED FOR L5
L6      923 DUP REMOV L5 (425 DUPLICATES REMOVED)

=> s l6 and py<=2006
L7      8 L6 AND PY<=2006

=> d ibib abs 1-8
```

WEST Search History for Application 15406344

Creation Date: 2017080118:35

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
emtricitabine	PGPB, USPT, USOC, EPAB, JPAB, DWPI	5078	AND	YES		08-01-2017
(emtricitabine) and tenofovir	PGPB, USPT, USOC, EPAB, JPAB, DWPI	4197	AND	YES		08-01-2017
(emtricitabine and tenofovir) and prophyla\$	PGPB, USPT, USOC, EPAB, JPAB, DWPI	2650	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$)	EPAB, JPAB, DWPI	54	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$) and emtricitabine.clm.	PGPB, USPT	339	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$ and emtricitabine.clm.) and tenofovir.clm.	PGPB, USPT	338	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$ and emtricitabine.clm. and tenofovir.clm.) and (HIV or immunodeficien\$).clm.	PGPB, USPT	225	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$ and emtricitabine.clm. and tenofovir.clm. and (HIV or immunodeficien\$).clm.) and (prophyla\$ or prevent\$).clm.	PGPB, USPT	83	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$ and emtricitabine.clm. and tenofovir.clm. and (HIV or immunodeficien\$).clm. and (prophyla\$ or prevent\$).clm.)	USPT	8	AND	YES		08-01-2017

Search Notes 	Application/Control No. 15406344	Applicant(s)/Patent Under Reexamination HENEINE ET AL.
	Examiner SHENGJUN WANG	Art Unit 1627

CPC- SEARCHED		
Symbol	Date	Examiner
A61K31/7072;A61K31/676	7/31/2017	SW

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner
A61K31/7072;A61K2300/00	7/31/2017	SW

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	81,274	7/31/2017	sw

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

SEARCH NOTES		
Search Notes	Date	Examiner
INVENTOR SEARCH	8/1/2017	SW
PARENT APPLICATIONS	8/1/2017	SW
CAPLUS MEDLINE BIOSIS EMBASE searched terms: EMTRICITABINE, tenofovir	8/1/2017	sw

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		Attorney Docket Number	4239-92970-14
		Application Number	15/406,344
		Filing Date	January 13, 2017
		First Named Inventor	Walid Heneine
		Art Unit	Not yet assigned
		Examiner Name	Not yet assigned
		Grant et al., "Promote HIV chemoprophylaxis research, don't prevent it," <i>Science</i> 309(5744): 2170-2171 (September 29, 2005).	
		Youle et al., "Could chemoprophylaxis be used as an HIV prevention strategy while we wait for an effective vaccine?," <i>AIDS</i> 17(6): 937-938 (April 11, 2003).	
		Youle et al., "Pre-exposure chemoprophylaxis (PREP) as an HIV prevention strategy," <i>JIAPAC</i> 2(3): 102-105 (July/September 2003).	

EXAMINER SIGNATURE: /SHENGJUN WANG/	DATE CONSIDERED: 07/31/2017
* Examiner: Initial if reference considered, whether or not in conformance with MPEP 609. Draw line through cite if not in conformance and not considered. Include copy of this form with next communication to applicant. **Please place an "X" in this column if English translation is attached.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Attorney Docket Number	4239-92970-14
	Application Number	15/406,344
	Filing Date	January 13, 2017
	First Named Inventor	Walid Heneine
	Art Unit	1629
	Examiner Name	Not yet assigned

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. (optional)	Foreign Patent Document Country Code-Number-Kind Code (if known)	Issue or Publication Date MM-DD-YYYY	Name of Patentee or Applicant	T**

Examiner Initials*	Cite No. (optional)	OTHER DOCUMENTS			T**
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EXAMINER SIGNATURE:	/SHENGJUN WANG/	DATE CONSIDERED:	07/31/2017

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT		Attorney Docket Number	4239-92970-14	
		Application Number	15/406,344	
		Filing Date	January 13, 2017	
		First Named Inventor	Walid Heneine	
		Art Unit	1629	
		Examiner Name	Not yet assigned	
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/S.W/		Kellerman et al., "Knowledge and use of HIV pre-exposure prophylaxis among attendees of minority gay pride events, 2004," <i>J. Acquir. Immune. Defic .Syndr.</i> 43(3): 376-377 (November 1, 2006).		

EXAMINER SIGNATURE: /SHENGJUN WANG/	DATE CONSIDERED: 08/01/2017
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	Filing Date	January 13, 2017
	First Named Inventor	Walid Heneine
	Art Unit	Not yet assigned
	Examiner Name	Not yet assigned

U.S. PATENT DOCUMENTS

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		WO 2005/021001	03-10-2005	Stoffels	

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	Examiner Name	Not yet assigned

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	Art Unit	Not yet assigned
	Examiner Name	Not yet assigned

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EXHIBIT P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Walid Heneine

Application No. 15/406,344

Filed: January 13, 2017

Confirmation No. 5617

For: INHIBITION OF HIV INFECTION
THROUGH CHEMOPROPHYLAXIS

Examiner: Shengjun Wang

Art Unit: 1627

Attorney Reference No. 4239-92970-14

**FILED VIA EFS ON
October 24, 2017**

FILED VIA THE ELECTRONIC FILING SYSTEM (EFS)
COMMISSIONER FOR PATENTS

AMENDMENT AND RESPONSE TO THE NON-FINAL OFFICE ACTION

This Amendment responds to the Office action dated August 8, 2017, for which a three-month period of response was set, making a reply timely if filed on or before November 8, 2017. It is believed that no fees are required for this filing. However, if the Commissioner determines that any additional fees are required, such as extension of time, excess page charges or claims fees, Applicant hereby gives permission to deduct such fees from Deposit Account 02-4550.

Amendments to the Claims are reflected in the listing of claims, which begins on page 2.

Remarks begin on page 6.

An e-Terminal Disclaimer is submitted electronically via EFS.

Listing of Claims

1. (Currently Amended) A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:
 - (a) selecting a primate host not infected with the immunodeficiency retrovirus, and
 - (b) administering directly to an uninfected primate host a combination comprising:
 - i. a pharmaceutically effective amount of emtricitabine; and
 - ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate ~~a tenofovir prodrug~~,wherein the combination is administered orally in tablet form prior to the exposure of the primate host to the immunodeficiency retrovirus, thereby protecting the primate host from infection with the immunodeficiency retrovirus.
2. (Original) The process of claim 1, wherein selecting a primate host comprises selecting an adult human not infected with the immunodeficiency retrovirus.
3. (Original) The process of claim 2, wherein the adult human is a male.
4. (Currently Amended) The process of claim 2, wherein the pharmaceutically effective amount of emtricitabine and the pharmaceutically effective amount of tenofovir or the tenofovir prodrug, are administered directly to the human in a combined single tablet dosage formulation.
5. (Original) The process of claim 2, wherein the immunodeficiency retrovirus is a human immunodeficiency virus.
6. (Original) The process of claim 5, wherein a human immunodeficiency virus (HIV) is HIV-1.

7. (Original) The process of claim 1, wherein the combination is administered as preexposure prophylactic treatment prior to rectal and/or vaginal exposure of the primate host to the immunodeficiency retrovirus.

8. (Original) The process of claim 1, comprising administering 200 milligrams (mg) of emtricitabine to the primate host.

9. (Original) The process of claim 1, wherein the combination is administered daily for several days, weeks or months.

10. (Original) The process of claim 9, wherein the combination is administered daily for several days, weeks or months both before and after an exposure of the primate host to the immunodeficiency retrovirus.

11. (Original) The process of claim 1, wherein administration of the combination results in an absence of persistent viremia and seroconversion of the primate host.

12. (Currently Amended) A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection;
and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine in a tablet; and

ii. a pharmaceutically effective amount of tenofovir or a tenofovir disoproxil fumarate in a tablet ~~prodrug~~;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus.

13. (Canceled).

14. (Currently Amended) The process of claim 12, wherein the combination is compounded into a single tablet combination formulation.

15. (Original) The process of claim 12, wherein an inhibition of infection in the host is determined by an absence of persistent viremia and seroconversion in the human following the exposure to the immunodeficiency retrovirus.

16. (Canceled).

17. (Original) The process of claim [[16]] 12, wherein the potential exposure to the human immunodeficiency retrovirus comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.

18. (Canceled).

19. (Canceled).

20. (New) The process of claim 12, wherein:
(i) the pharmaceutically effective amount of emtricitabine; and
(ii) the pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate;
are formulated in a single tablet.

21. (New) The process of claim 20, wherein the tablet comprises 200 milligrams of emtricitabine and 300 mg of tenofovir disoproxil fumarate.

22. (New) The process of claim 4, wherein the tablet comprises 200 milligrams of emtricitabine and 300 mg of tenofovir disoproxil fumarate.

23. (New) The process of claim 20, wherein the tablet is administered daily for several days, weeks or months both before and after an exposure of the primate host to the immunodeficiency retrovirus.

Remarks

Claims 1, 4, 12 and 14 are amended herein. Claim 12 is amended to incorporate the limitations of claim 13. Additional support for the amendment of claims 1, 4, 12 and 14 can be found throughout the specification, such as, but not limited to, paragraph [0030].

New claims 20-23 are added herein. Support for the new claims can be found throughout the specification, such as, but not limited to, paragraphs [0021] to [0030] and the examples. Applicant believes no new matter is added. Reconsideration of the subject application is respectfully requested. Claims 13, 16 and 18-19 are canceled herein, solely to reduce the fees that are due. New claim 23 parallels claim 9, but depends from claim 20.

Applicant believes no new matter is added herein. Reconsideration and allowance of the present application is respectfully requested.

Examiner Interview

Applicant thanks the Examiner for the helpful interview of October 3, 2017, wherein the claims and the outstanding rejections were briefly discussed. The undersigned indicated that the claims would be amended to correspond with the claims of U.S. Patent No. 9,044,509, but to state that the composition was administered in tablet form, as supported by the specification. The Examiner agreed that this would place the application in condition for allowance, and confirmed that it was not necessary to address the rejection under 35 U.S.C. § 103 if the proposed claim amendments were made in the response. The Examiner also confirmed it would not be necessary to resubmit any evidence provided during the prosecution of U.S. Patent No. 9,044,509. However, the Examiner stated that the obviousness-type double patenting rejections would be maintained (see below). The undersigned confirmed terminal disclaimers would be submitted to render these rejections moot.

Double Patenting

Claims 1-19 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable in view of claims 1-18 of U.S. Patent No. 9,044,509. Claims 1-19 were also rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable in view of claims 1-17 of U.S. Patent No. 9,579,333.

Submitted herewith is an electronic Terminal Disclaimer (e-TD) that disclaims the terminal portion of any patent that issue from the present application that would extend beyond the term of U.S. Patent No. 9,044,509 or the term of U.S. Patent No. 9,579,333. The submission of this e-TD renders the rejection moot.

Claim Rejections under 35 U.S.C. § 103

Claims 1-19 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Stephenson (“New HIV Prevention Strategies Urged,” *JAMA*) and Dahl *et al.* (U.S. Publication No. 2004/0224917) in view of Shapiro *et al.* (“Highly Active Antiretroviral Therapy Started During Pregnancy or Postpartum Suppresses HIV-1 RNA, but not DNA, in Breast Milk,” *Journal of Infectious Diseases*), Smith *et al.* (“Antiretroviral postexposure prophylaxis after sexual, injection drug-use, or other non-occupational exposure to HIV in the United States,” *MMRW*), Szekeres *et al.* (“Anticipating the efficacy of HIV pre-exposure prophylaxis” (PrEP) and the needs of at-risk Californians” *PrEP and the Needs of At-risk Californians*), Keller *et al.* (International Publication No. WO 2004/002498) and AIDS PATIENT CARE and STDs. Applicants respectfully disagree with this rejection.

However, to expedite prosecution, the claims have been amended to correspond with the claims of U.S. Patent No. 9,044,509, and to include the limitation that the compositions are in tablet form. The amendment of the claims to correspond with the claims of U.S. Patent No. 9,044,509 renders the rejection moot.

Conclusion and Formal Request for Interview

Applicant believes the present application is in condition for allowance. *If any issues remain prior to allowance, the Examiner is formally requested to contact the undersigned attorney prior to issuance of the next Office Action in order to arrange a telephonic interview.* It is believed that a brief discussion of the merits of the present application will expedite prosecution. This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

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Respectfully submitted,

KLARQUIST SPARKMAN, LLP

cc: Docketing

By /Susan Alpert Siegel/
Susan Alpert Siegel, Ph.D.
Registration No. 43,121

Electronic Acknowledgement Receipt

EFS ID:	30749319
Application Number:	15406344
International Application Number:	
Confirmation Number:	5617
Title of Invention:	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS
First Named Inventor/Applicant Name:	Walid Heneine
Customer Number:	46135
Filer:	Susan A. Siegel
Filer Authorized By:	
Attorney Docket Number:	4239-92970-14
Receipt Date:	24-OCT-2017
Filing Date:	13-JAN-2017
Time Stamp:	19:06:59
Application Type:	Utility under 35 USC 111(a)

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		4239-92970-14_Amendment_and_Response.pdf	54689	yes	8
			d37537d9aff409e980c3ce5daecfc6128da7eb5c		

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	8

Warnings:

Information:

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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed		PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce	
Electronic Petition Request	TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT		
Application Number	15406344		
Filing Date	13-Jan-2017		
First Named Inventor	Walid Heneine		
Attorney Docket Number	4239-92970-14		
Title of Invention	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS		
☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action ☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.			
Owner		Percent Interest	
THE UNITED STATES OF AMERICA, as represented by the Secretary, Department of Health and Human Services		100%	
The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s) 9579333 9044509 as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns. In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later: - expires for failure to pay a maintenance fee; - is held unenforceable; - is found invalid by a court of competent jurisdiction; - is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321; - has all claims canceled by a reexamination certificate; - is reissued; or - is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.			

☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

☐ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicant claims the following fee status:

☐ Small Entity

☐ Micro Entity

☒ Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

☒ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 43121

☐ A sole inventor

☐ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

☐ A joint inventor; all of whom are signing this request

Signature	/Susan Alpert Siegel/
Name	Susan Alpert Siegel

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	15406344			
Filing Date:	13-Jan-2017			
Title of Invention:	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS			
First Named Inventor/Applicant Name:	Walid Heneine			
Filer:	Susan A. Siegel			
Attorney Docket Number:	4239-92970-14			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				160

Doc Code: DISQ.E.FILE

Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 15406344

Filing Date: 13-Jan-2017

Applicant/Patent under Reexamination: Heneine

Electronic Terminal Disclaimer filed on October 24, 2017

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	30740351
Application Number:	15406344
International Application Number:	
Confirmation Number:	5617
Title of Invention:	INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS
First Named Inventor/Applicant Name:	Walid Heneine
Customer Number:	46135
Filer:	Susan A. Siegel
Filer Authorized By:	
Attorney Docket Number:	4239-92970-14
Receipt Date:	24-OCT-2017
Filing Date:	13-JAN-2017
Time Stamp:	19:09:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$ 160
RAM confirmation Number	102517INTEFSW00005682024550
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	33706	no	2
			9467cb6eada0f9d99452f7104c9a692a0c3dd770		

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30468	no	2
			0bbc5acf0be48325ea9fc1e64beb515114afd676		

Warnings:

Information:

Total Files Size (in bytes):			64174

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/406,344	Filing Date 01/13/2017	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

(Column 1)

(Column 2)

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

(Column 1)

(Column 2)

(Column 3)

AMENDMENT	10/24/2017	CLAIMS REMAINING AFTER AMENDMENT	Minus	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	* 19	Minus	** 20	= 0	X \$80 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X \$420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
TOTAL ADD'L FEE						0	

(Column 1)

(Column 2)

(Column 3)

AMENDMENT	CLAIMS REMAINING AFTER AMENDMENT	Minus	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	*	Minus	**	X \$ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	X \$ =	
	☐ Application Size Fee (37 CFR 1.16(s))					
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					
TOTAL ADD'L FEE						

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

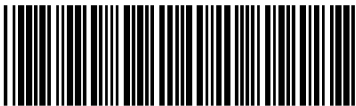
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
LINDA HUMES

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

EXHIBIT Q

Search Notes 	Application/Control No. 15/406,344	Applicant(s)/Patent Under Reexamination Heneine et al.
	Examiner SHENGJUN WANG	Art Unit 1627

CPC - Searched*		
Symbol	Date	Examiner
A61K31/7072;A61K31/676	7/31/2017	SW

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
A61K31/7072; A61K2300/00	7/31/2017	SW

US Classification - Searched*			
Class	Subclass	Date	Examiner
514	81,274	7/31/2017	sw

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
INVENTOR SEARCH	8/1/2017	SW
PARENT APPLICATIONS	8/1/2017	SW
CAPLUS MEDLINE BIOSIS EMBASE searched terms: EMTRICITABINE , tenofovir	8/1/2017	sw

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
514	81,274	12/02/2017	swang
A61K	31/7072,A61K31/676	12/02/2017	SW

Issue Classification 	Application/Control No. 15/406,344	Applicant(s)/Patent Under Reexamination Heneine et al.
	Examiner SHENGJUN WANG	Art Unit 1627

CPC						
Symbol					Type	Version
A61K	/	31	/	675	F	2013-01-01
A61K	/	31	/	513	I	2013-01-01
A61K	/	9	/	0053	I	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
A61K	/	31	/	7072	I	1	1	2013-01-01
A61K	/	2300	/	00	A	1	2	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	19	
/SHENGJUN WANG/ Primary Examiner, Art Unit 1627	02 December 2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	2

Issue Classification 	Application/Control No. 15/406,344	Applicant(s)/Patent Under Reexamination Heneine et al.
	Examiner SHENGJUN WANG	Art Unit 1627

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	675
A61K	/	31	/	505

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
514	81

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					
514	274					

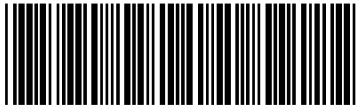
NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	19	
/SHENGJUN WANG/ Primary Examiner, Art Unit 1627	02 December 2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	2

Issue Classification 	Application/Control No. 15/406,344	Applicant(s)/Patent Under Reexamination Heneine et al.
	Examiner SHENGJUN WANG	Art Unit 1627

☐ Claims renumbered in the same order as presented by applicant
 ☐ CPA
 ☒ T.D.
 ☐ R.1.47

CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	10	10	19	23										
2	2	11	11												
3	3	13	12												
4	4	14	14												
5	5	15	15												
6	6	16	17												
7	7	17	20												
8	8	18	21												
9	9	12	22												

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	19	
/SHENGJUN WANG/ Primary Examiner, Art Unit 1627	02 December 2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	2

<i>Index of Claims</i> 	Application/Control No. 15/406,344	Applicant(s)/Patent Under Reexamination Heneine et al.
	Examiner SHENGJUN WANG	Art Unit 1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS									
☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47									
CLAIM		DATE							
Final	Original	08/01/2017	12/02/2017						
1	1	✓	=						
2	2	✓	=						
3	3	✓	=						
4	4	✓	=						
5	5	✓	=						
6	6	✓	=						
7	7	✓	=						
8	8	✓	=						
9	9	✓	=						
10	10	✓	=						
11	11	✓	=						
13	12	✓	=						
	13	✓	-						
14	14	✓	=						
15	15	✓	=						
	16	✓	-						
16	17	✓	=						
	18	✓	-						
	19	✓	-						
17	20		=						
18	21		=						
12	22		=						
19	23		=						

WEST Search History for Application 15406344

Creation Date: 2017120210:26

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
emtricitabine	PGPB, USPT, USOC, EPAB, JPAB, DWPI	5078	AND	YES		08-01-2017
(emtricitabine) and tenofovir	PGPB, USPT, USOC, EPAB, JPAB, DWPI	4197	AND	YES		08-01-2017
(emtricitabine and tenofovir) and prophyla\$	PGPB, USPT, USOC, EPAB, JPAB, DWPI	2650	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$)	EPAB, JPAB, DWPI	54	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$) and emtricitabine.clm.	PGPB, USPT	339	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$ and emtricitabine.clm.) and tenofovir.clm.	PGPB, USPT	338	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$ and emtricitabine.clm. and tenofovir.clm.) and (HIV or immunodeficien\$).clm.	PGPB, USPT	225	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$ and emtricitabine.clm. and tenofovir.clm. and (HIV or immunodeficien\$).clm.) and (prophyla\$ or prevent\$).clm.	PGPB, USPT	83	AND	YES		08-01-2017
(emtricitabine and tenofovir and prophyla\$ and emtricitabine.clm. and tenofovir.clm. and (HIV or immunodeficien\$).clm. and (prophyla\$ or prevent\$).clm.)	USPT	8	AND	YES		08-01-2017

9579333	PGPB, USPT	2	AND	YES		12-02-2017
9044509	PGPB, USPT	4	AND	YES		12-02-2017
TENOFOVIR	PGPB, USPT	5984	AND	YES		12-02-2017
(TENOFOVIR) AND EMTRICITABINE	PGPB, USPT	3945	AND	YES		12-02-2017
(TENOFOVIR) AND EMTRICITABINE.CLM.	PGPB, USPT	510	AND	YES		12-02-2017
(TENOFOVIR AND EMTRICITABINE.CLM.) AND TENOFOVIR	PGPB, USPT	510	AND	YES		12-02-2017
(TENOFOVIR AND EMTRICITABINE.CLM.) AND TENOFOVIR.CLM.	PGPB, USPT	502	AND	YES		12-02-2017
(TENOFOVIR AND EMTRICITABINE.CLM. AND TENOFOVIR.CLM.)	USPT	116	AND	YES		12-02-2017
(TENOFOVIR AND EMTRICITABINE.CLM. AND TENOFOVIR.CLM.) AND DISOPROXIL ADJ FUMARATE.CLM.	USPT	30	AND	YES		12-02-2017
(TENOFOVIR AND EMTRICITABINE.CLM. AND TENOFOVIR.CLM.) AND DISOPROXIL ADJ FUMARATE.CLM.	PGPB, USPT	121	AND	YES		12-02-2017



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

46135 7590 12/07/2017
KLARQUIST SPARKMAN, LLP (NIH-CDC)
121 S.W. SALMON STREET
SUITE 1600
PORTLAND, OR 97204

EXAMINER

WANG, SHENGJUN

ART UNIT

PAPER NUMBER

1627

DATE MAILED: 12/07/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/406,344	01/13/2017	Walid Heneine	4239-92970-14	5617

TITLE OF INVENTION: INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	03/07/2018

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

46135 7590 12/07/2017
KLARQUIST SPARKMAN, LLP (NIH-CDC)
121 S.W. SALMON STREET
SUITE 1600
PORTLAND, OR 97204

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/406,344	01/13/2017	Walid Heneine	4239-92970-14	5617

TITLE OF INVENTION: INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	03/07/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
WANG, SHENGJUN	1627	514-086000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

- (1) The names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____
- (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____
- 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/406,344	01/13/2017	Walid Heneine	4239-92970-14	5617

46135 7590 12/07/2017
KLARQUIST SPARKMAN, LLP (NIH-CDC)
121 S.W. SALMON STREET
SUITE 1600
PORTLAND, OR 97204

EXAMINER

WANG, SHENGJUN

ART UNIT	PAPER NUMBER

1627

DATE MAILED: 12/07/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

<i>Notice Requiring Inventor's Oath or Declaration</i>	Application No. 15/406,344	Applicant(s) Walid Heneine	
	Examiner WANG, SHENGJUN	Art Unit 1627	

This notice is an attachment to the Notice of Allowability (PTOL-37), or the Notice of Allowability For A Design Application (PTOL-37D).

An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor has not yet been submitted.

An oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each inventor (for any inventor for which a compliant oath, declaration, or substitute statement has not yet been submitted) **MUST** be filed no later than the date on which the issue fee is paid. See 35 U.S.C. 115(f). Failure to timely comply will result in ABANDONMENT of this application.

A properly executed inventor's oath to declaration has not been received for the following inventor(s):

If applicant previously filed one or more oaths, declarations, or substitute statements, applicant may have received an informational notice regarding deficiencies therein.

The following deficiencies are noted:

INFORMAL ACTION PROBLEMS

- A properly executed inventor's oath or declaration has not been received for the following inventor(s): **Walid Heneine, Thomas M. Folks , Robert Janssen, Ronald A. Otten, and Jose Gerardo Garcia Lerma.**

Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Questions relating to this Notice should be directed to the Application Assistance Unit at 571-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/406,344	Applicant(s) Heneine et al.	
	Examiner SHENGJUN WANG	Art Unit 1627	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 10/24/2017.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are See Continuation Sheet. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov**.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
Certified copies:
a) ☐ All b) ☐ Some *c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
* Certified copies not received: ____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)	5. ☒ Examiner's Amendment/Comment
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date ____	6. ☐ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material ____	7. ☐ Other ____
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. ____	

/SHENGJUN WANG/
Primary Examiner, Art Unit 1627

Continuation of 3. The allowed claim(s) is/are: 1-12,14-15,17 and 20-23

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

2. The terminal disclaimer filed on October 24, 2017 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US 9,044,509 and 9,579,333 has been reviewed and is accepted. The terminal disclaimer has been recorded.

EXAMINER'S AMENDMENT

3. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Susan Siegel on November 1, 2017.

The application has been amended as follows:

In the claims:

Claim 4, line 3, after "tenofovir", delete "prodrug" and insert "disoproxil fumarate".

Reasons for Allowance

4. The following is an examiner's statement of reasons for allowance:
5. Applicants' amendments and remarks submitted October 24, along with the terminal disclaimer, are persuasive to put the application in conditions for allowance. The claims are allowable for reasons as set forth in parent application 11/669,547. See, the interview summary of October 4, 2017.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHENGJUN WANG whose telephone number is (571)272-0632. The examiner can normally be reached on Monday to Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://portal.uspto.gov/external/portal>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHENGJUN WANG/
Primary Examiner, Art Unit 1627

EXHIBIT R



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/913,750	03/06/2018	Walid Heneine	4239-92970-15	1309
46135	7590	01/23/2019	EXAMINER	
KLARQUIST SPARKMAN, LLP (NIH-CDC)			WANG, SHENGJUN	
121 S.W. SALMON STREET			ART UNIT	PAPER NUMBER
SUITE 1600			1627	
PORTLAND, OR 97204			NOTIFICATION DATE	DELIVERY MODE
			01/23/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ASCChair@klarquist.com
docketing@klarquist.com
nicole.salazar@klarquist.com

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Double Patenting Rejection

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor

to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

3. Claims 1-19 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 9,044,509. Although the claims at issue are not identical, they are not patentably distinct from each other because ‘509 claims the method of protecting primate host from a selfreplicating infection by an immunodeficiency retrovirus comprising administering a combination of emtricitabine and tenofovir. The claimed scope of ‘509 substantially overlaps the claimed scope herein.

4. Claims 1-19 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 9,579,333. Although the claims at issue are not identical, they are not patentably distinct from each other because ‘333 claims the method of protecting primate host from a selfreplicating infection by an immunodeficiency retrovirus comprising administering a combination of emtricitabine and tenofovir. The claimed scope of ‘333 substantially overlaps the claimed scope herein.

5. Claims 1-19 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 9,937,191. Although the claims at issue are not

identical, they are not patentably distinct from each other because '191 claims the method of protecting primate host from a selfreplicating infection by an immunodeficiency retrovirus comprising administering a combination of emtricitabine and tenofovir. The claimed scope of '191 substantially overlaps the claimed scope herein.

Remarks

The claims are allowable over prior art for reasons as set forth in parent applications.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHENGJUN WANG whose telephone number is (571)272-0632. The examiner can normally be reached on 8:00 AM to 3:30 PM M-F.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

**/SHENGJUN WANG/
Primary Examiner, Art Unit 1627**

<i>Notice of References Cited</i>	Application/Control No. 15/913,750		Applicant(s)/Patent Under Reexamination	
	Examiner SHENGJUN WANG		Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-9579333-B2	02-2017	Heneine; Walid	A61K31/7072	1/1
*	B	US-9937191-B2	04-2018	Heneine; Walid	A61K31/7072	1/1
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

<i>Index of Claims</i> 	Application/Control No. 15/913,750	Applicant(s)/Patent Under Reexamination Heneine et al.
	Examiner SHENGJUN WANG	Art Unit 1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS										
☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47										
CLAIM			DATE							
Final	Original	01/14/2019								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
	12	✓								
	13	✓								
	14	✓								
	15	✓								
	16	✓								
	17	✓								
	18	✓								
	19	✓								

<i>Search Notes</i> 	Application/Control No. 15/913,750	Applicant(s)/Patent Under Reexamination Heneine et al.
	Examiner SHENGJUN WANG	Art Unit 1627

CPC - Searched*		
Symbol	Date	Examiner
A61K31/7072;A61K31/676	01/14/2019	SW

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
A61K31/7072; A61K2300/00	01/14/2019	SW

US Classification - Searched*			
Class	Subclass	Date	Examiner
514	81,274	01/14/2019	sw

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
INVENTOR SEARCH	01/14/2019	SW
PARENT APPLICATIONS	01/14/2019	SW
CAPLUS, MEDLINE, BIOSIS EMBASE searched terms: tenofovir, emtricitabine	01/14/2019	sw

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

=> d hist

(FILE 'HOME' ENTERED AT 10:50:36 ON 14 JAN 2019)

FILE 'REGISTRY' ENTERED AT 10:50:45 ON 14 JAN 2019

L1 28 S TENOFOVIR
L2 8 S EMTRICITABINE

FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 10:51:15 ON 14 JAN 2019

L3 32284 S L1
L4 13478 S L2
L5 11334 S L4 AND L3
L6 3812 S L5 AND (PROPHYLA? OR PREVENT? OR PREEXPOS?)
L7 258 S L6 AND PY<=2006
L8 249 DUP REM L7 (9 DUPLICATES REMOVED)
L9 0 S L8 AND PREEXPOS?/TI
L10 1 S L8 AND PRE-EXPOS?/TI
L11 3818 S L5 AND (PROPHYLA? OR PREVENT? OR PRE-EXPOS?)
L12 258 S L11 AND PY<=2006
L13 249 DUP REM L12 (9 DUPLICATES REMOVED)
L14 20 S L13 AND (PROPHYLA? OR PREVENT?)/TI

Bibliographic Data

Application No: 15/913,750

Foreign Priority claimed: ☐ Yes ☒ No

35 USC 119 (a-d) conditions met: ☐ Yes ☒ No ☐ Met After Allowance

Verified and Acknowledged: /SHENGJUN WANG/

Examiner's Signature

Initials

Title:

INHIBITION OF HIV INFECTION THROUGH
CHEMOPROPHYLLAXIS

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
03/06/2018	514	1627	4239-92970-15
RULE			

APPLICANTS

THE UNITED STATES OF AMERICA, as represented by the Secretary, Department of Health and Human, Bethesda, MD, UNITED STATES

INVENTORS

Walid Heneine Atlanta, GA, UNITED STATES

Thomas M. Folks Helotes, TX, UNITED STATES

Robert Janssen Atlanta, GA, UNITED STATES

Ronald A. Otten Villa Rica, GA, UNITED STATES

Jose Gerardo Garcia Lerma Decatur, GA, UNITED STATES

CONTINUING DATA

This application is a CON of 15406344 01/13/2017 PAT 9937191

15406344 is a CON of 14679887 04/06/2015 PAT 9579333

14679887 is a CON of 11669547 01/31/2007 PAT 9044509

11669547 has PRO of 60764811 02/03/2006

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

04/03/2018

STATE OR COUNTRY

UNITED STATES

ADDRESS

KLARQUIST SPARKMAN, LLP (NIH-CDC)

121 S.W. SALMON STREET

SUITE 1600

PORTLAND, OR 97204

UNITED STATES
FILING FEE RECEIVED
\$1,720

WEST Search History for Application 15913750

Creation Date: 2019011410:49

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
tenofovir.clm.	PGPB, USPT	922	AND	YES		01-14-2019
(tenofovir.clm.) and emtricitabine.clm.	PGPB, USPT	578	AND	YES		01-14-2019
(tenofovir.clm. and emtricitabine.clm.) and (prevent\$ or prophyla\$ or protect\$ or risk).clm.	PGPB, USPT	227	AND	YES		01-14-2019
(tenofovir.clm. and emtricitabine.clm. and (prevent\$ or prophyla\$ or protect\$ or risk).clm.)	USPT	30	AND	YES		01-14-2019

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	Art Unit	Not yet assigned
	Examiner Name	Not yet assigned

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. (optional)	Document Number Number-Kind Code (if known)	Issue or Publication Date MM-DD-YYYY	Name of Patentee or Applicant
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		5,914,331	06-22-1999	Liotta et al.
		5,922,695	07-13-1999	Arimilli et al.
		5,935,946	08-10-1999	Munger Jr. et al.
		5,977,089	11-02-1999	Arimilli et al.
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		9,044,509	06-2-2015	Heneine et al.
		2004/0224917 A1	11-11-2004	Dahl et al.

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		WO 2004/002498	01-08/2004	Keller et al.	
		WO 2004/064845	08-05-2004	Dahl et al.	
		WO 2005/021001	03-10-2005	Stoffels	

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EXHIBIT S

CLINICAL TRIAL AGREEMENT

Date: November 1, 2004

Parties: (1) Centers for Disease Control and Prevention, 1600 Clifton Rd., MS E-45, Atlanta, GA 30333 ("CDC")
(2) Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 ("Gilead")

The Centers for Disease Control and Prevention (“CDC”), and Gilead Sciences, Inc., (“Gilead”) have agreed to cooperate on the conduct of the clinical trial titled “Study of the Safety and Efficacy of Daily Tenofovir Disoproxil Fumarate (“TDF”) for the Prevention of HIV Infection in Heterosexually-Active Young adults in Botswana” for Gilead’s study drug TDF (the “Study Drug”), hereafter referred to as the “Trial”.

If, prior to the start of the Trial, Gilead is deemed to be a sponsor of the Trial, Gilead will have the right to terminate this agreement and its support of the Trial. Gilead also reserves the right to terminate support of this Trial if either Institutional Review Board (“IRB”) approval is not obtained or the first participant is not enrolled within a reasonable period of time.

The Trial will be conducted under the terms and conditions of the Agreement outlined below.

The understanding by both parties to the Agreement is as follows:

1. TRIAL CONDUCT

CDC will be responsible for the conduct of the Trial and will obtain all necessary regulatory approvals for the Trial and will conduct the Trial in accordance with: all applicable laws, rules and regulations (including any applicable Food and Drug Administration (FDA) guidelines); the protocol, standard operating procedures, any investigator’s brochure for the Trial and applicable IRB requirements. CDC will obtain proper informed consent from each participant in the Trial.

Protocol development and management, evaluation of data, proposal of amendments, responsibility for research subjects recruited, recommendations for early termination, etc. shall be the responsibility of CDC. CDC will consult with Gilead on the Trial protocol development, data analysis and design.

When the protocol, informed consent, and standard operating procedures are in final draft form and if any later changes are made thereto, CDC will provide Gilead with copies of the same and a reasonable opportunity for review and comment prior to submission to the IRB. CDC will, however, have the full and final discretion and responsibility over the protocol, informed consent and standard operating procedures, including any changes thereto. Once CDC has obtained IRB approval, CDC will send Gilead final copies of the aforementioned documents.

2. DATA COLLECTION, MANAGEMENT, ANALYSIS AND REPORTING

CDC shall assume responsibility for the collection, management, analysis, and initial reporting of all data obtained from the Trial. CDC will deliver to Gilead all grouped interim and final results from the Trial and relevant supporting data within 24 weeks after the final analyses dataset is completed by CDC or at such time that CDC provides the results from the Trial to a third party, whichever is the earliest data.

CDC will provide Gilead with copies of all reports submitted to government regulatory agencies that are related to the Trial, as well as any correspondence with such authorities related to the Trial.

Information or results from the Trial which may be released to the public shall not be released without prior discussion of the information with Gilead and by mutual agreement of Gilead and CDC.

3. MONITORING

CDC shall be responsible for clinical site monitoring at its sites and the quality assurance of all data. Monitoring shall be done in compliance with FDA Good Clinical Practices Guidelines.

4. ADVERSE EXPERIENCE REPORTING

CDC shall collect adverse experience and serious adverse events (SAE) data in its case report forms. CDC shall report any SAE arising during the Trial to the Gilead Global Drug Safety Department within 24 hours of CDC staff being notified of the event. The reporting to Gilead will follow the same guidelines for reporting SAEs to CDC’s

IRB as outlined in the protocol. CDC will promptly make available to Gilead upon request such records as Gilead may deem necessary or useful to investigate an adverse event or death associated with the use of Study Drug during the Trial. Any report of a SAE or death addressed to Gilead will be sent to the attention of:

Global Drug Safety Associate
Fax: 650-522-5477
E-mail: Safety_FC@gilead.com

Gilead shall, in a timely manner and during the term of the Trial, provide CDC with any information it now has or may obtain in the future regarding the safety and/or the toxicity of the Study Drug.

5. DRUG SUPPLY AND DISTRIBUTION

Gilead will supply 8,500 bottles (30 tablets/bottle) of tenofovir disoproxil fumarate and 8,500 bottles of matching placebo. If, by mutual agreement of Gilead and CDC, the Trial is extended beyond the initial term and CDC determines that additional supply of the Study Drug is required to conduct the extended trial term, then CDC shall request in writing an additional quantity of the Study Drug from Gilead sufficient to complete the extended trial. In addition, if the Study proves to be safe and effective those patients on placebo will be offered open-label drug for up to one year.

Gilead shall be responsible for distributing the Study Drug to the participating sites. CDC will limit access to the Study Drug to only those persons who, under the CDC's direct control, will be engaged in employing the Study Drug for purposes of conducting the Trial. At no time shall CDC, any investigator or any persons under CDC's direct control employ the Study Drug for any purpose other than as described in the Protocol, or provide it to any third party, without the prior written approval of Gilead.

CDC will further ensure that the Study Drug will be handled, secured and stored properly, and that it is not transferred, misbranded, sold, administered, handled or used by any unauthorized third party. CDC will be responsible for obtaining any required proper import licenses and clearance, and will comply with all applicable laws, rules and regulations. If Gilead's assistance or participation is necessary in order to obtain such licenses or comply with such laws, rules or regulations, CDC will promptly notify Gilead and provide reasonable assistance to enable Gilead to comply. Promptly upon Gilead's request, CDC will provide copies of licenses, approvals, reports and records.

Gilead shall provide CDC with the necessary Material Safety Data Sheet (MSDS) for the Study Drug together with any specific storage or shipping instructions. At the conclusion of the Trial, CDC will return to Gilead or destroy all unused Study Drug at Gilead's direction.

6. CONFIDENTIALITY

CDC, to the extent permissible by the Freedom of Information Act, 5 U.S.C. section 552, will not disclose information relating to the Trial or the Study Drug including, but not limited to data and information generated during the conduct of the Trial, without Gilead's prior review in accordance with clause 14.

CDC will maintain in confidence, and only use for the Trial, any confidential or proprietary information Gilead provides or discloses in connection with the Trial.

7. INTELLECTUAL PROPERTY

Ownership of inventions from the Trial shall be determined in accordance with inventorship under U.S. patent law. The Study Drug and any related confidential information disclosed to CDC by Gilead will remain Gilead's property. CDC agrees to put the results of the Trial, patentable or otherwise, in the public domain for all to use without obligation or compensation to CDC. For clarity, CDC agrees not to seek patent protection in connection with any inventions that derive from the use of the Study Drug in the Trial.

8. TRIAL DATA

All raw data obtained from the Trial shall be the property of CDC. These data shall not be released to the public by CDC except to the extent required by law. No persons or party other than Gilead, its subsidiaries, affiliates, contractors, and/or its designees or other corporate sponsors of the Trial or their designated agents shall have any rights to review and/or use the raw data obtained by CDC from the Trial for purposes of filing an NDA without the prior written permission of Gilead.

The data shall be controlled by CDC and shall not be released to the public without prior notice to and appropriate consultation with Gilead. The database will be made available to Gilead as described in Section 2 above. Gilead will be provided a copy of the complete CRF analysis data set and other raw data as required in a machine-readable format to be determined jointly.

9. PUBLICATION

Any publications based on the results of the Trial shall conform to the CDC guidelines. Gilead shall receive copies of any abstract or manuscript prior to their submission for publication for review and comment. For manuscripts, a maximum of thirty (30) days for review and comment by Gilead will be provided. For abstracts, Gilead will be provided with a review period of seven days (7) prior to submission of the abstract to the meeting organizer. Upon Gilead's reasonable request, CDC will remove any of Gilead's confidential or proprietary information.

Gilead shall have the right to delay by written request such publication, presentation or use of the manuscript for up to thirty (30) days after receipt to preserve U.S. or foreign patent or other intellectual property rights.

CDC will give reasonable consideration to any request Gilead may make to change the publication or presentation, but the final decision will be made by CDC.

10. INDEMNIFICATION

There is no indemnification for damages provided under this Agreement. Each party shall be liable for damages it incurs as a result of its own activities under this Agreement.

11. ENDORSEMENT

Gilead acknowledges that the involvement of CDC in the Trial shall not be construed as an endorsement by CDC for the Study Drug. However, this does not prohibit Gilead from indicating in presentations or written material that it is providing support for the Trial conducted by CDC as the sponsor, or from referring or using publications and reports based on the Trial for legitimate business and regulatory purposes.

12. TERMINATION

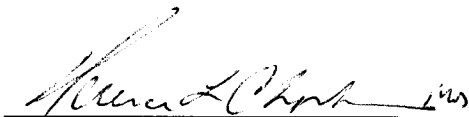
Either Gilead or CDC shall have the right to terminate this Agreement at any time in the event of a material breach by the other party if that party fails to remedy the breach within thirty (30) days of the receipt of the notice specifying the breach.

The provisions governing access to trial results, confidentiality, publication, and liability shall survive termination or expiry of this Agreement.

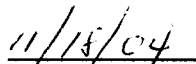
13. APPLICABLE LAW

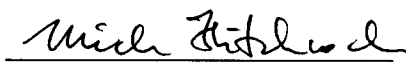
The construction, interpretation, and performance of this agreement shall be governed by and construed in accordance with the federal laws of the United States of America.

The foregoing represents the entire agreement between us regarding the Trial, and there are no further commitments, obligations or understandings of any nature regarding the Trial. This agreement will be effective on the latest date indicated below, and will terminate upon the completion of CDC's obligations under the protocol and this agreement and Gilead's payment of any amounts identified above, if applicable. This letter agreement may only be amended with the mutual written consent of the parties.

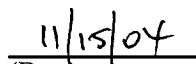

(Signature)

Terence L. Chorba, MD
Associate Director for Science
National Center for HIV, STD and TB Prevention
Centers for Disease Control and Prevention


(Date)


(Signature)

Mick Hitchcock
Vice President, Medical Affairs
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, California 94404


(Date)

 **GILEAD**
Approved by Legal Department
