EXHIBIT 1

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Heneine et al.

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(54) **INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS**

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A61K 31/675 (2006.01)
A61K 31/505 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61K 45/06*** (2013.01); *A61K 31/675* (2013.01); *A61K 31/513* (2013.01); ***A61K 31/7072*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/675; A61K 31/513; A61K 2300/00
USPC 514/274, 86
See application file for complete search history.

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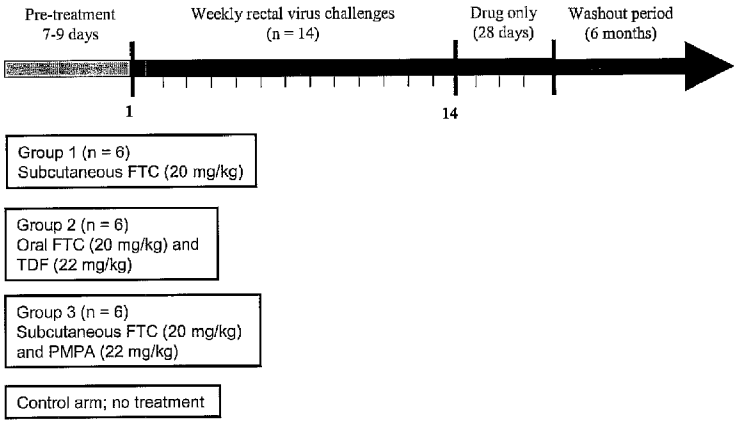
(57) **ABSTRACT**

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.

18 Claims, 4 Drawing Sheets



(51) **Int. Cl.**

A61K 45/06	(2006.01)
A61K 31/7072	(2006.01)
A61K 31/513	(2006.01)

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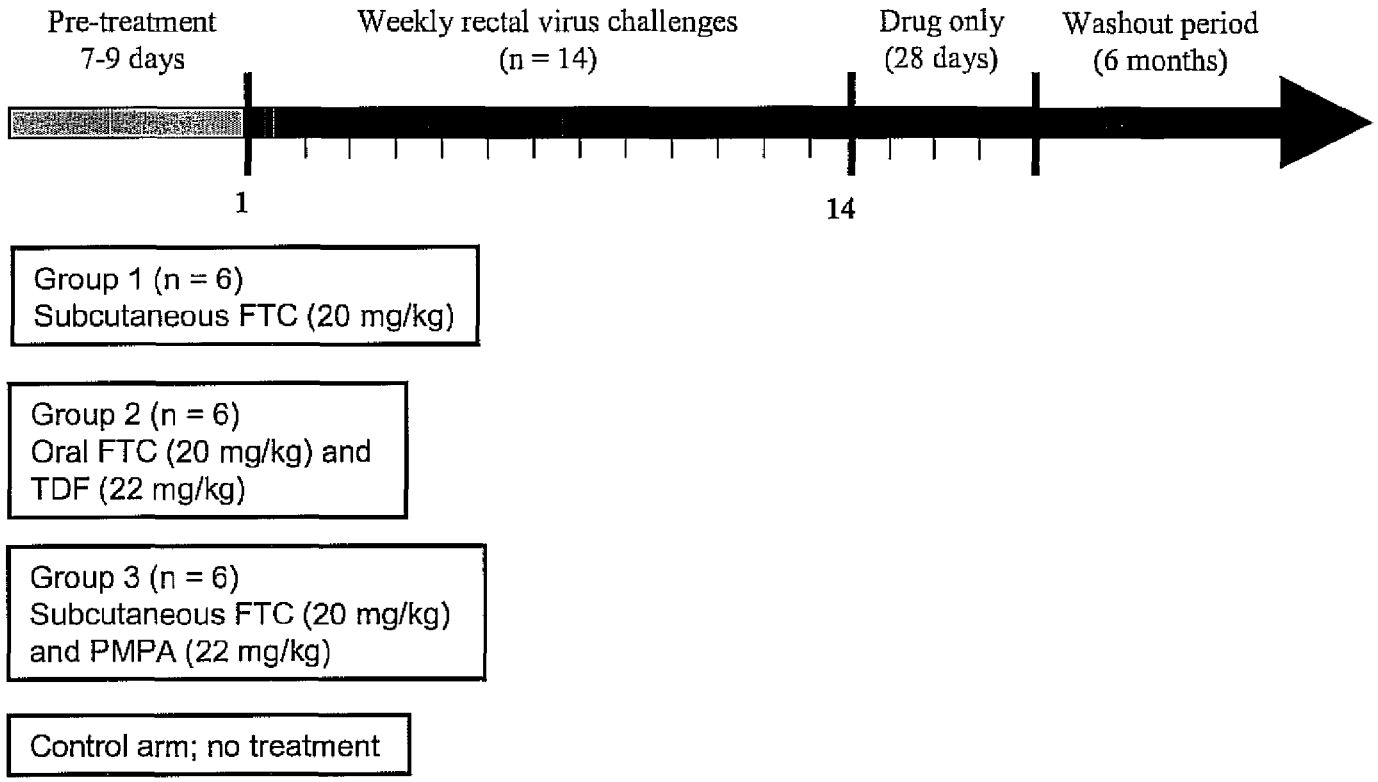
Pre-treatment
7-9 days
Weekly rectal virus challenges
(n = 14)
Drug only
(28 days)
Washout period
(6 months)
1
14
Group 1 (n = 6)
Subcutaneous FTC (20 mg/kg)
Group 2 (n = 6)
Oral FTC (20 mg/kg) and
TDF (22 mg/kg)
Group 3 (n = 6)
Subcutaneous FTC (20 mg/kg)
and PMPA (22 mg/kg)
Control arm; no treatment

Fig 1.

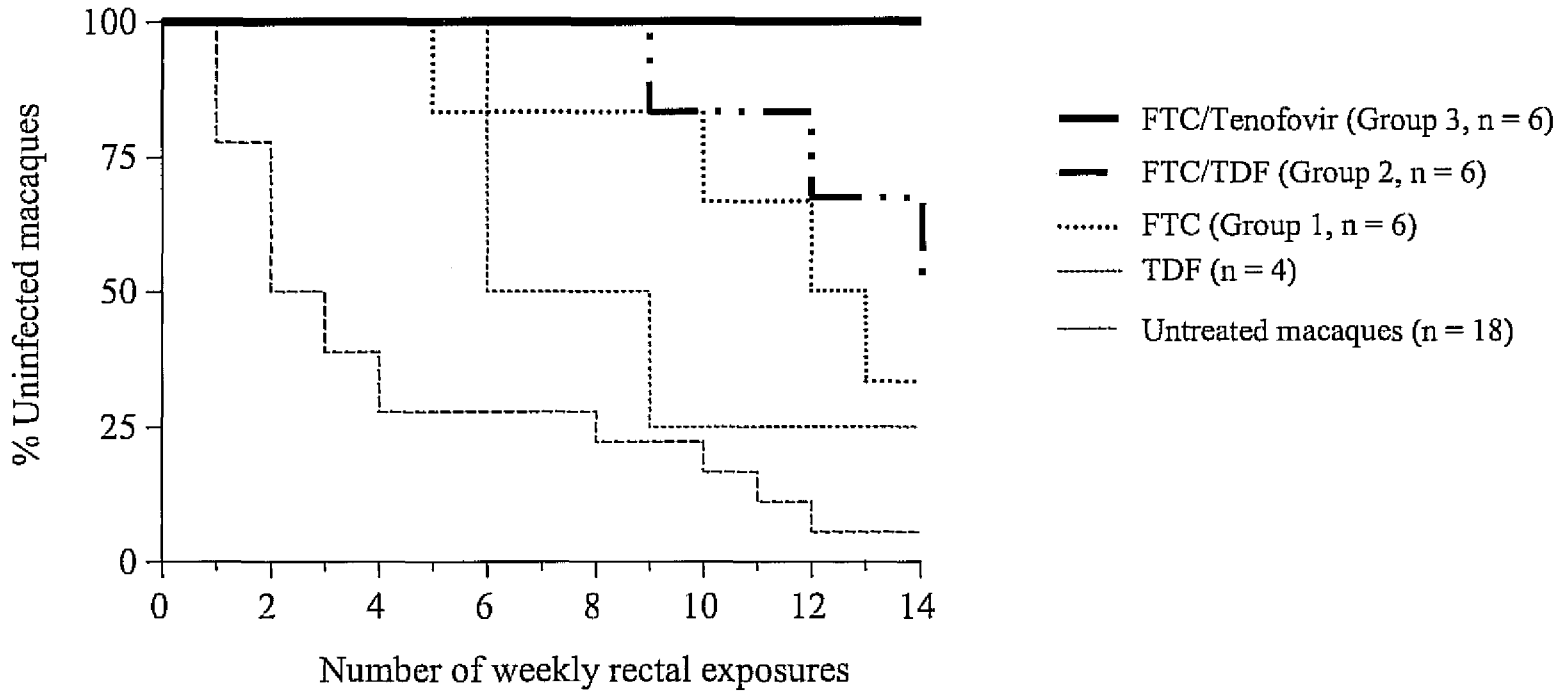
% Uninfected macaques
100
75
50
25
0
0
2
4
6
8
10
12
14
Number of weekly rectal exposures
FTC/Tenofovir (Group 3, n = 6)
FTC/TDF (Group 2, n = 6)
FTC (Group 1, n = 6)
TDF (n = 4)
Untreated macaques (n = 18)

Fig 2.

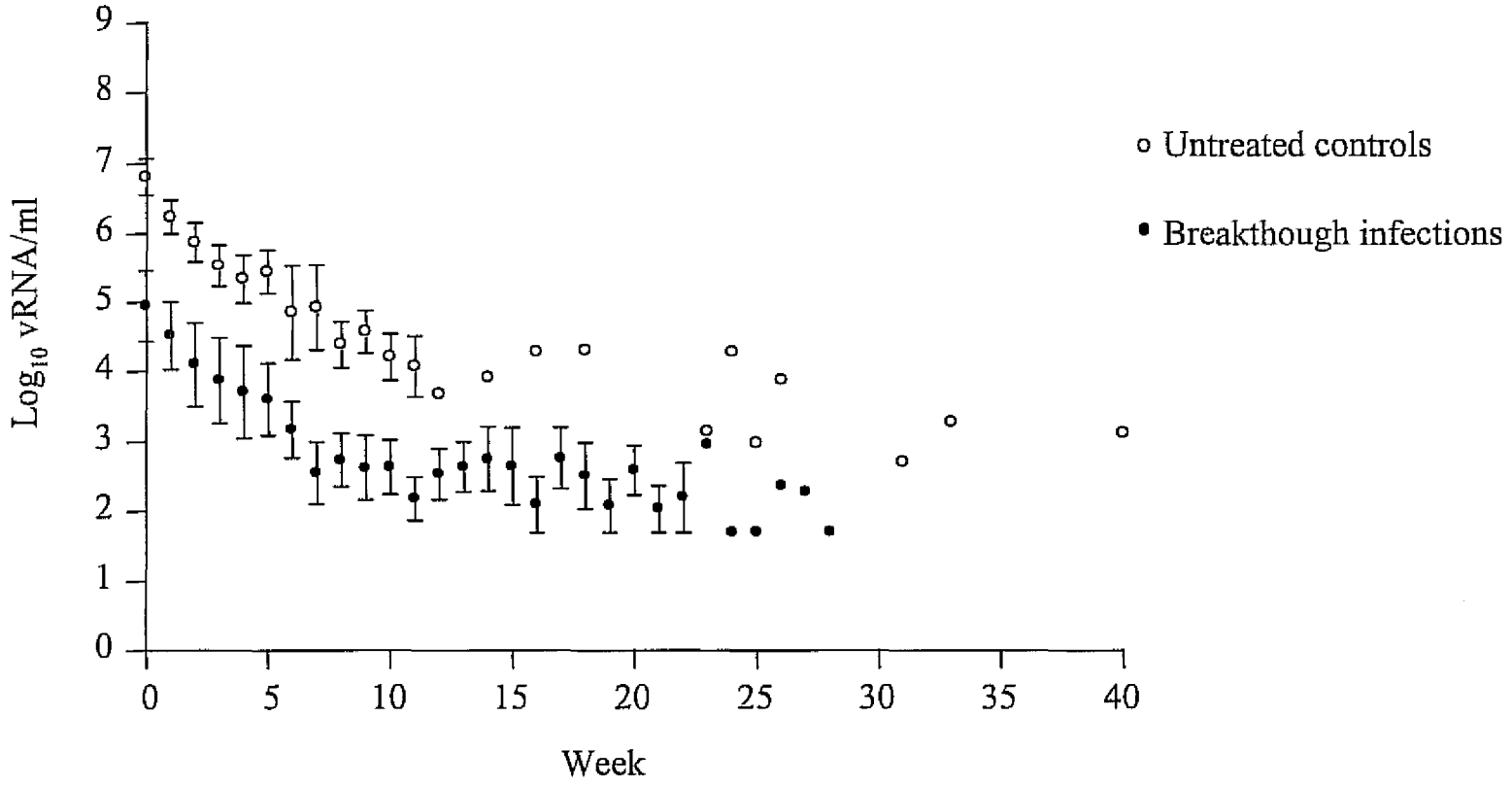
Log10 vRNA/ml
9
8
7
6
5
4
3
2
1
0
0
5
10
15
20
25
30
35
40
Week
Untreated controls
Breakthough infections

Fig. 3.

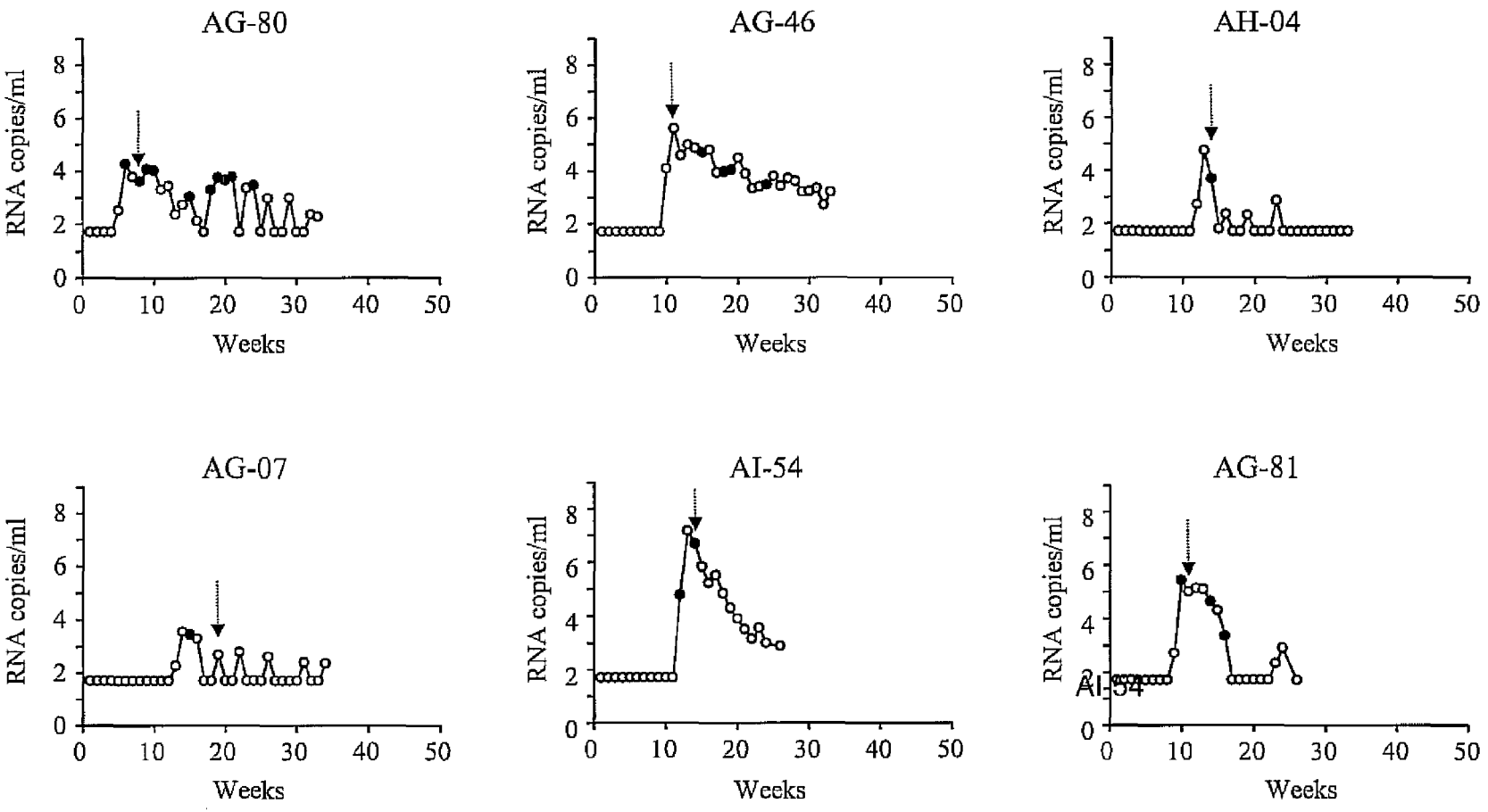
AG-80
AG-46
AH-04
AG-07
AI-54
AG-81
RNA copies/ml
Weeks
0
2
4
6
8
0
10
20
30
40
50
AI-54

Fig. 4

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority of U.S. Provisional Patent Application Ser. No. 60/764,811 filed Feb. 2, 2006, which is incorporated herein by reference.

GOVERNMENT INTEREST

The invention described herein may be manufactured, used, and licensed by or for the United States Government.

FIELD OF THE INVENTION

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

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 injection. 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.

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.

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]

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.

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

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.

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

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.

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).

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).

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

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 of 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. Pat. Nos. 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.

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.

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.

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.

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, C_1-C_6 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.

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. Pat. No. 5,935,946.

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.

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.

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.

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.

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.

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.

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'-fluoroadenosine; 2',3'-dideoxy-3'-fluoroguanosine; 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.

Optionally, an inventive composition also includes within an inventive combination other antiretrovirals such as non-nucleoside 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).

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.

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.

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.

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

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 μg×hr/ml which was similar to the value of 5.02 μg×hr/ml observed in human receiving 300 mg of TDF. The dose of 20 mg/kg of FTC resulted in an AUC value (11 μg×hr/ml), also similar to that observed in humans receiving 200 mg of FTC orally (10.0±3.12 μg×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.

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

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 $HIV\text{-}1_{SF162}$ 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 $TCID_{50}$ 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

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-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

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

Virus-specific serologic responses (IgG and IgM) are measured using a synthetic-peptide EIA (Genetic Systems HrV-1/HIV-2) assay.

Example 6

Statistical Methods

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)×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

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 $TCID_{50}$ 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 (22 mg/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).

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

FIG. **2** shows the survival curves observed for each group of animals per Example 7. Data with TDF (20 mg/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

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 ± 0.5 $\log_{10}$ RNA copies/ml, 2.0 $\log_{10}$ lower than in untreated controls (6.9 ± 0.3 $\log_{10}$ RNA). FIG. **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 ± 0.02 $\log_{10}$/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 FIG. **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.

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

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

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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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.

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.

The invention claimed is:

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 tenofovir disoproxil fumarate,

wherein the combination is administered prior to an exposure of the primate host to the immunodeficiency retrovirus, thereby protecting the primate host from infection with the immunodeficiency retrovirus, wherein the combination is administered orally.

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 primate host is a male adult primate host.

4. The process of claim **1** wherein the pharmaceutically effective amount of emtricitabine and the pharmaceutically effective amount of tenofovir disoproxil fumarate, are administered orally directly to the human in a combined single dosage formulation.

5. The process of claim **1** wherein the immunodeficiency retrovirus is a human immunodeficiency virus.

6. The process of claim **5** wherein the 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 and 300 mg of tenofivir disoproxil fumarate to a human 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 tenofovir ester;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered orally.

13. The process of claim 12 wherein the combination is administered prior to a potential exposure of the primate host to the human immunodeficiency retrovirus.

14. The process of claim 12 wherein the combination is compounded into a single combination formulation suitable for oral administration.

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 tenofovir ester is tenofovir disoproxil fumarate.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 9,044,509 B2
APPLICATION NO. : 11/669547
DATED : June 2, 2015
INVENTOR(S) : Heneine et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1562 days.

Signed and Sealed this
Sixth Day of June, 2017

Michelle K. Lee
Director of the United States Patent and Trademark Office

EXHIBIT 2

US009579333B2

(12) **United States Patent**
Heneine et al.

(10) **Patent No.: US 9,579,333 B2**
(45) **Date of Patent: *Feb. 28, 2017**

(54) **INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYALXIS**

(71) Applicant: **THE UNITED STATES OF AMERICA, as represented by the Secretary, Department of Health and Human Services**, Washington, DC (US)

(72) Inventors: **Walid Heneine**, Atlanta, GA (US); **Thomas M. Folks**, Helotes, TX (US); **Robert Janssen**, Atlanta, GA (US); **Ronald A. Otten**, Villa Rica, GA (US); **Jose Gerardo Garcia Lerma**, Decatur, GA (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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CPC ***A61K 31/683*** (2013.01); ***A61K 31/513*** (2013.01); ***A61K 31/675*** (2013.01);
(Continued)

(58) **Field of Classification Search**
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(Continued)

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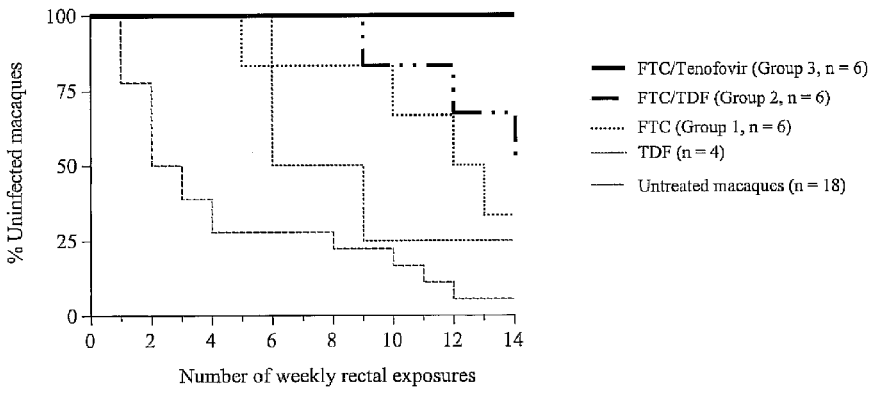
(57) **ABSTRACT**

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
(Continued)



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.

17 Claims, 4 Drawing Sheets

Related U.S. Application Data

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(58) **Field of Classification Search**
USPC 514/81, 274
See application file for complete search history.

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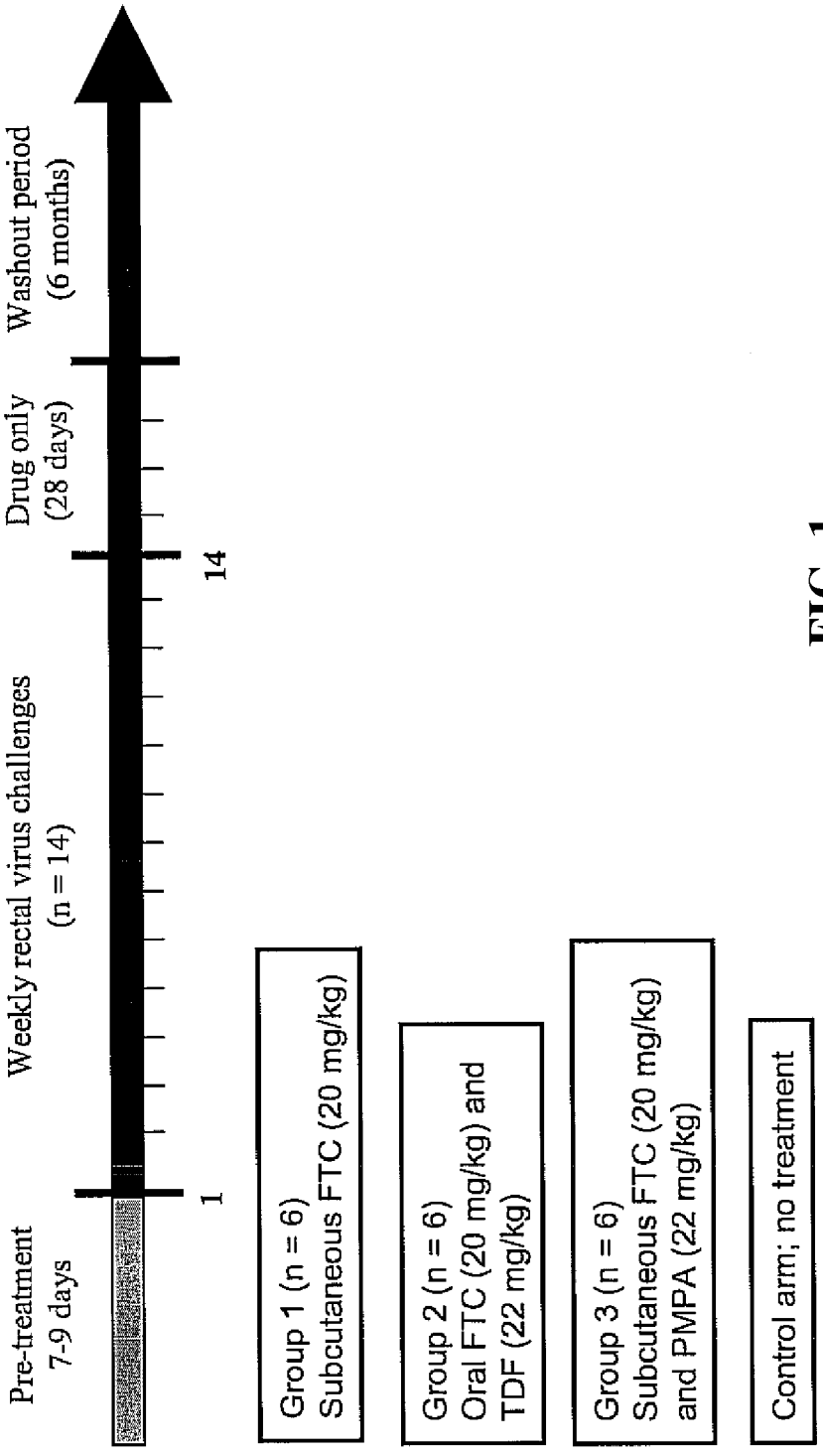
Pre-treatment
7-9 days
Weekly rectal virus challenges
(n = 14)
Drug only
(28 days)
Washout period
(6 months)
1
14
Group 1 (n = 6)
Subcutaneous FTC (20 mg/kg)
Group 2 (n = 6)
Oral FTC (20 mg/kg) and
TDF (22 mg/kg)
Group 3 (n = 6)
Subcutaneous FTC (20 mg/kg)
and PMPA (22 mg/kg)
Control arm; no treatment

FIG. 1

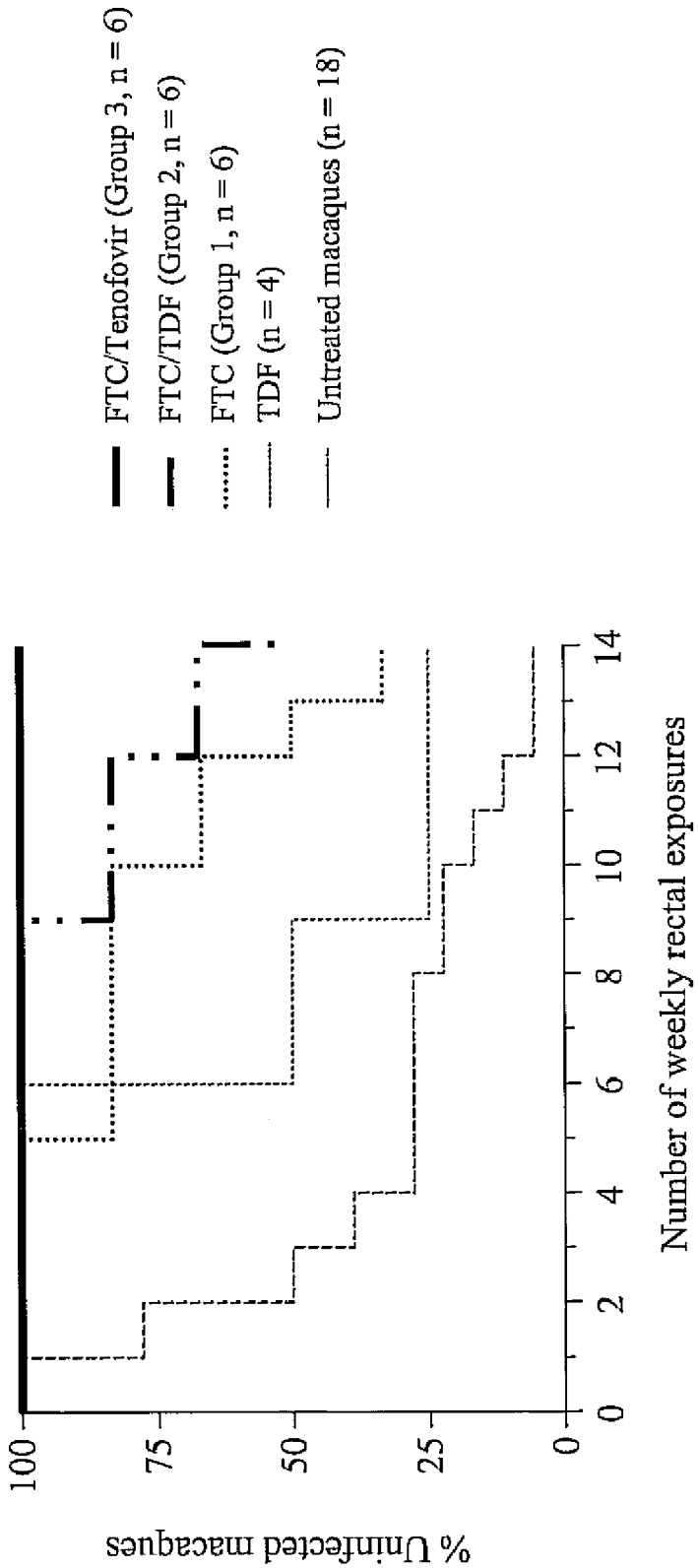
FTC/Tenofovir (Group 3, n = 6)
FTC/TDF (Group 2, n = 6)
FTC (Group 1, n = 6)
TDF (n = 4)
Untreated macaques (n = 18)
% Uninfected macaques
100
75
50
25
0
0
2
4
6
8
10
12
14
Number of weekly rectal exposures

FIG. 2

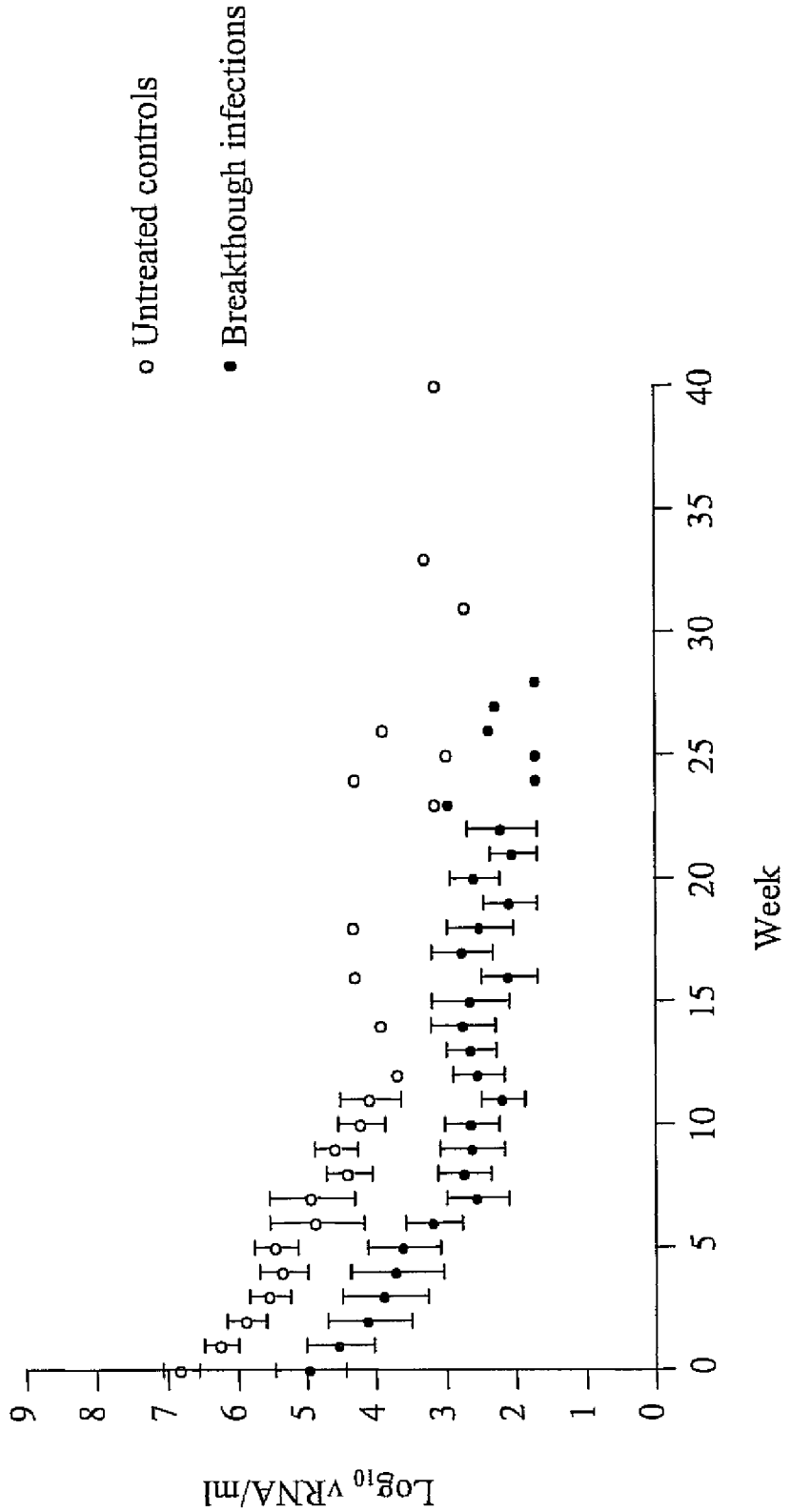
o Untreated controls
• Breakthough infections
Log10 vRNA/ml
0
1
2
3
4
5
6
7
8
9
0
5
10
15
20
25
30
35
40
Week

FIG. 3

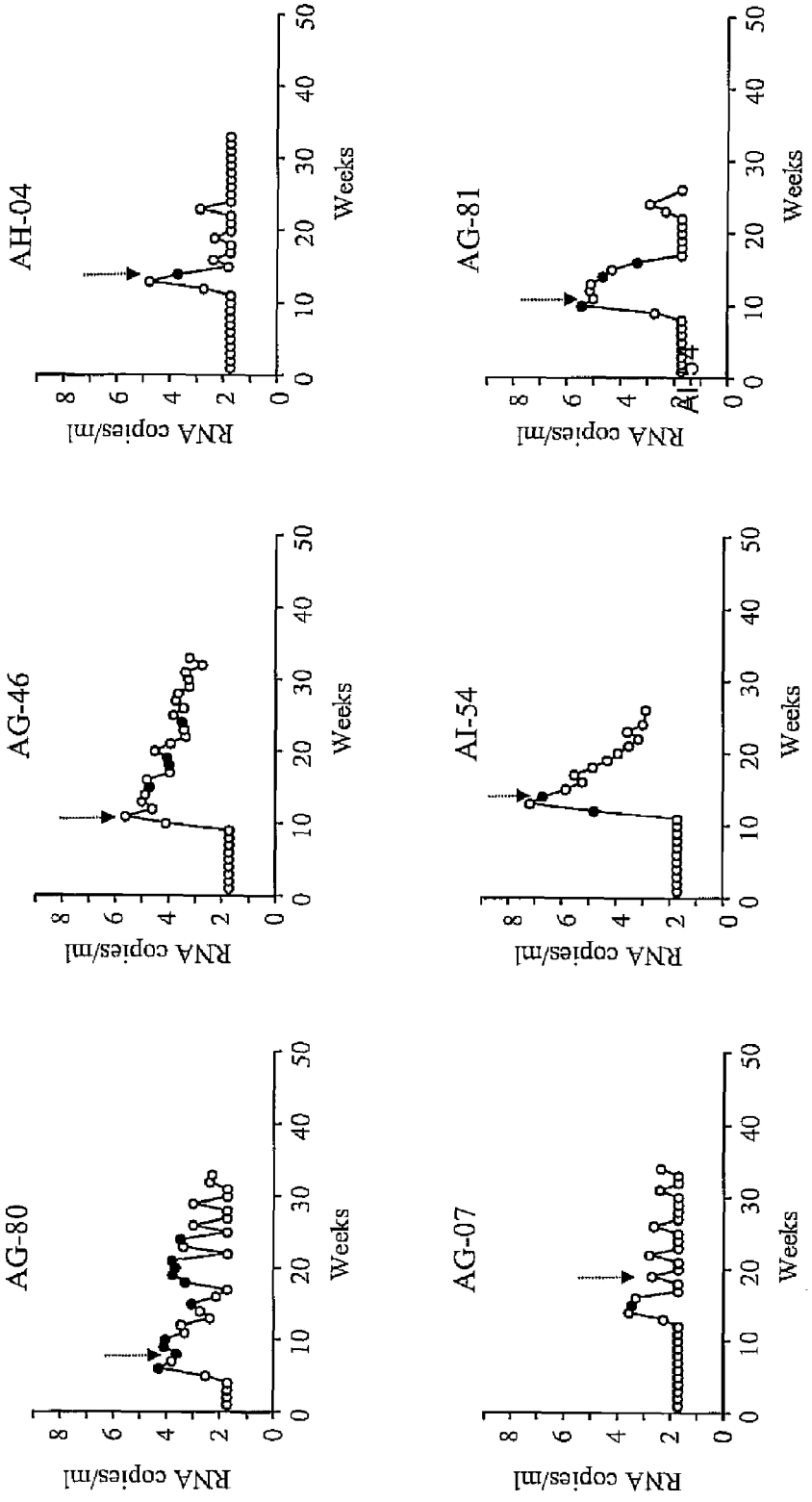
AH-04
AG-81
AG-46
AI-54
AG-80
AG-07
RNA copies/ml
Weeks
0
2
4
6
8
0
10
20
30
40
50

FIG. 4

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYALXIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of U.S. patent application Ser. No. 11/669,547, filed on Jan. 31, 2007, which in turn claims the benefit of U.S. provisional application 60/764,811, filed on Feb. 3, 2006. Both of the prior applications are incorporated herein by reference in their entirety.

GOVERNMENT INTEREST

The invention described herein may be manufactured, used, and licensed by or for the United States Government.

FIELD OF THE INVENTION

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

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 injection. 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.

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.

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]

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.

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

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.

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

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.

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).

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).

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

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 of 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. Pat. Nos. 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.

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.

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.

As used herein a "primate host" is defined to include a monkey, baboon, chimpanzee, gorilla, and a human. Non-human 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.

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, C_1-C_6 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, 20^{th} Edition, Chapters 37-47, pages 681-929, where parenteral injection includes subcutaneous, intramuscular, intravenous, and intradermal injection.

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. Pat. No. 5,935,946.

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.

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.

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.

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.

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.

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.

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.

Optionally, an inventive composition also includes within an inventive combination other antiretrovirals such as non-nucleoside 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).

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.

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.

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.

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

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 μg×hr/ml which was similar to the value of 5.02 μg×hr/ml observed in human receiving 300 mg of TDF. The dose of 20 mg/kg of FTC resulted in an AUC value (11 μg×hr/ml), also similar to that observed in humans receiving 200 mg of FTC orally (10.0±3.12 μg×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.

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

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 $HIV\text{-}1_{SF162}$ 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 $SHIV_{SF162P3}$ ($10\ TCID_{50}$ 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 intrarectal inoculation.

Example 3

SHIV Viral Load Assay

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

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

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

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)×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

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 $TCID_{50}$ 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 (22 mg/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).

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

FIG. **2** shows the survival curves observed for each group of animals per Example 7. Data with TDF (20 mg/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

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±0.5 $\log_{10}$ RNA copies/ml, 2.0 $\log_{10}$ lower than in untreated controls (6.9±0.3 $\log_{10}$ RNA). FIG. **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±0.02 $\log_{10}$/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 FIG. **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.

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 M1841 (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

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

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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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.

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.

The invention claimed is:

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, wherein the pharmaceutically effective amount of the emtricitabine is administered orally, subcutaneously or vaginally; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate, wherein the pharmaceutically effective amount of the tenofovir or tenofovir disoproxil fumarate is administered orally, subcutaneously or vaginally,

and wherein the combination is administered 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 primate host is a male adult primate host.

4. The process of claim 1, wherein the pharmaceutically effective amount of emtricitabine and the pharmaceutically effective amount of tenofovir disoproxil fumarate, are administered directly to a human in a combined single dosage formulation.

5. The process of claim 1, 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 and 300 mg of tenofovir disoproxil fumarate to a human 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 wherein the pharmaceutically effective amount of the emtricitabine is administered orally, subcutaneously or vaginally; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate wherein the pharmaceutically effective amount of the tenofovir or tenofovir disoproxil fumarate is administered orally, subcutaneously or vaginally;

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.

* * * * *

EXHIBIT 3

US009937191B2

(12) **United States Patent**
Heneine et al.

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(45) **Date of Patent: *Apr. 10, 2018**

(54) **INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS**

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(73) Assignee: **The United States of America, as represented by the Secretary, Department of Health and Human Services**, Washington, DC (US)

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This patent is subject to a terminal disclaimer.

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CPC ***A61K 31/675*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 31/513*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/7072; A61K 31/676
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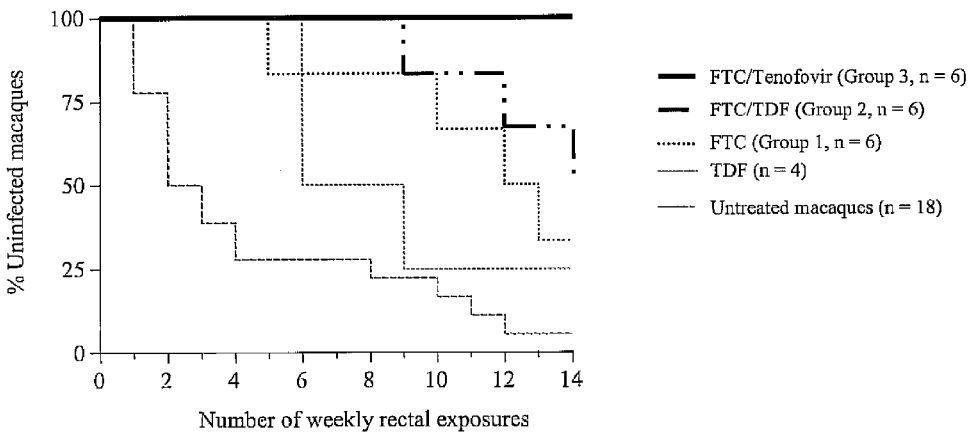
(57) **ABSTRACT**

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
(Continued)



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.

19 Claims, 4 Drawing Sheets

Related U.S. Application Data

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See application file for complete search history.

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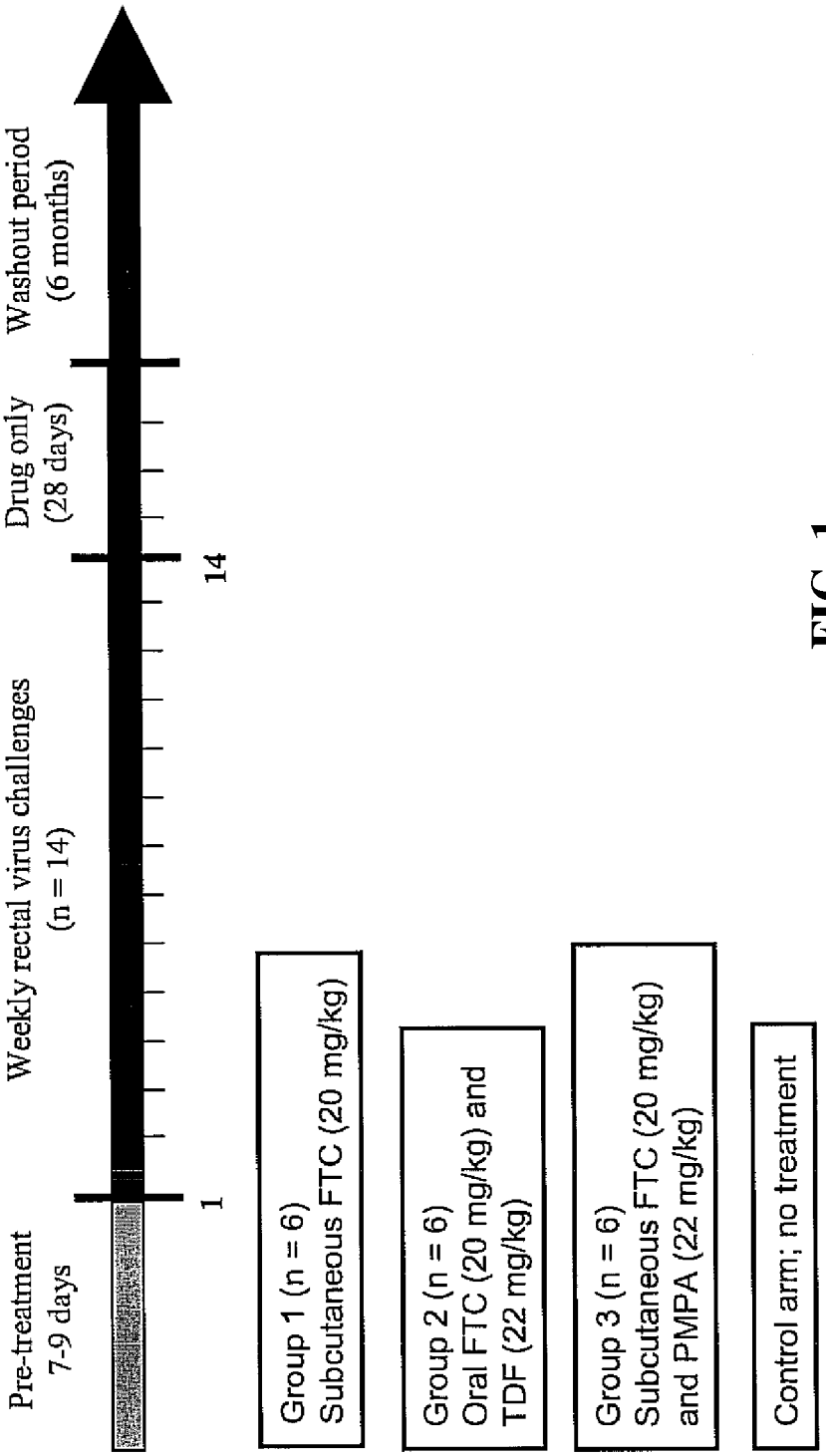
Pre-treatment
7-9 days
Weekly rectal virus challenges
(n = 14)
Drug only
(28 days)
Washout period
(6 months)
1
14
Group 1 (n = 6)
Subcutaneous FTC (20 mg/kg)
Group 2 (n = 6)
Oral FTC (20 mg/kg) and
TDF (22 mg/kg)
Group 3 (n = 6)
Subcutaneous FTC (20 mg/kg)
and PMPA (22 mg/kg)
Control arm; no treatment

FIG. 1

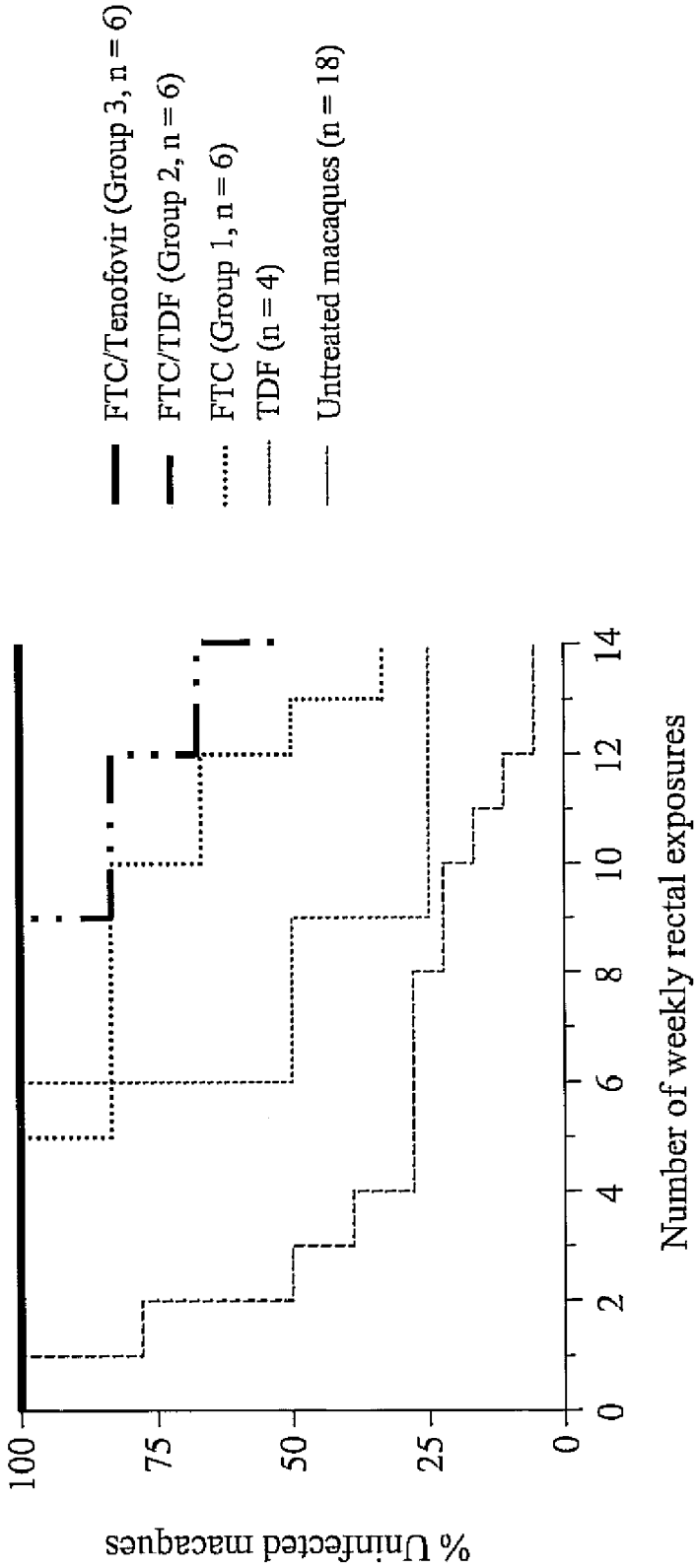
FTC/Tenofovir (Group 3, n = 6)
FTC/TDF (Group 2, n = 6)
FTC (Group 1, n = 6)
TDF (n = 4)
Untreated macaques (n = 18)
% Uninfected macaques
100
75
50
25
0
0
2
4
6
8
10
12
14
Number of weekly rectal exposures

FIG. 2

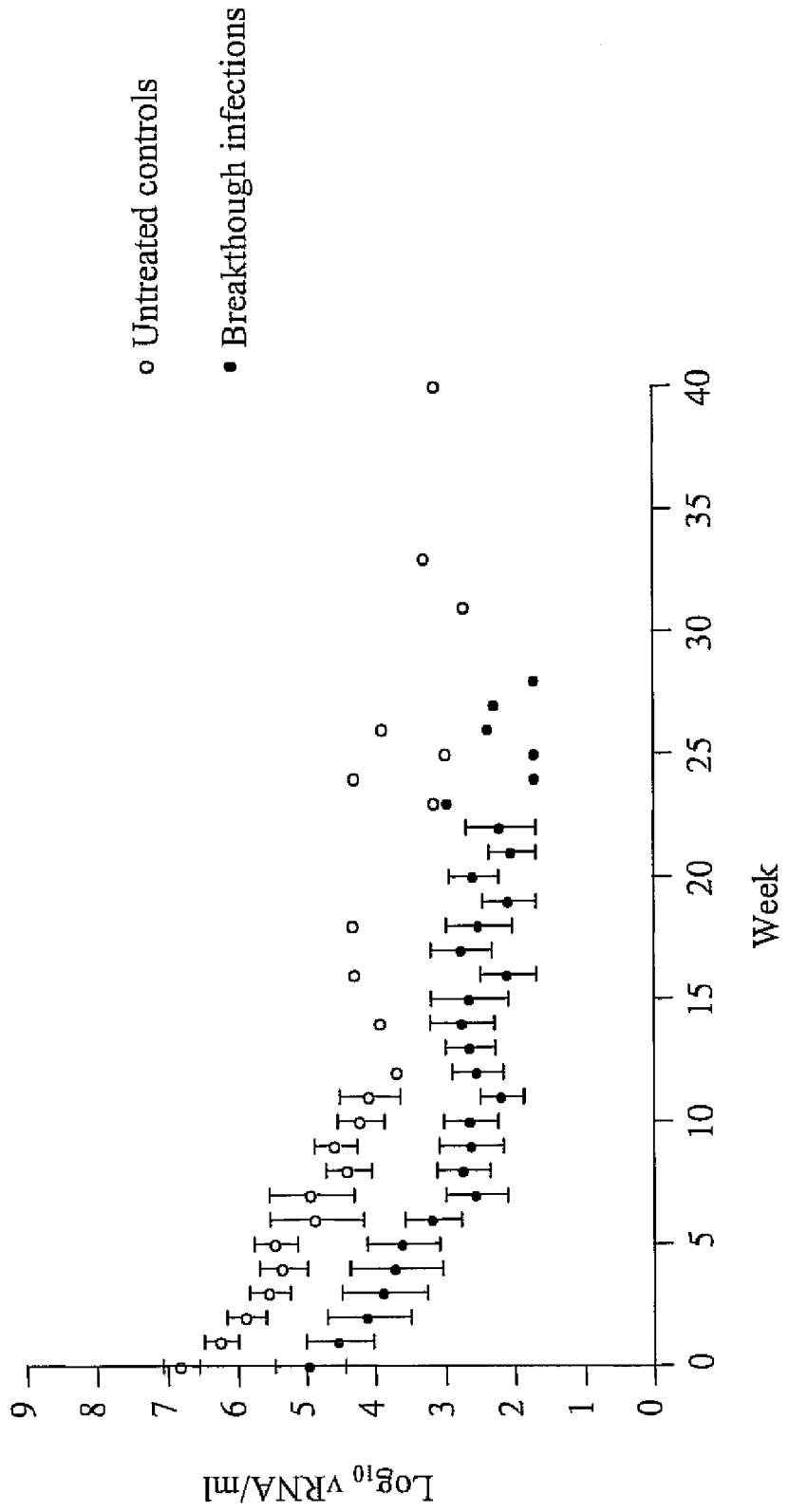
o Untreated controls
• Breakthough infections
Log10 vRNA/ml
0
1
2
3
4
5
6
7
8
9
0
5
10
15
20
25
30
35
40
Week

FIG. 3

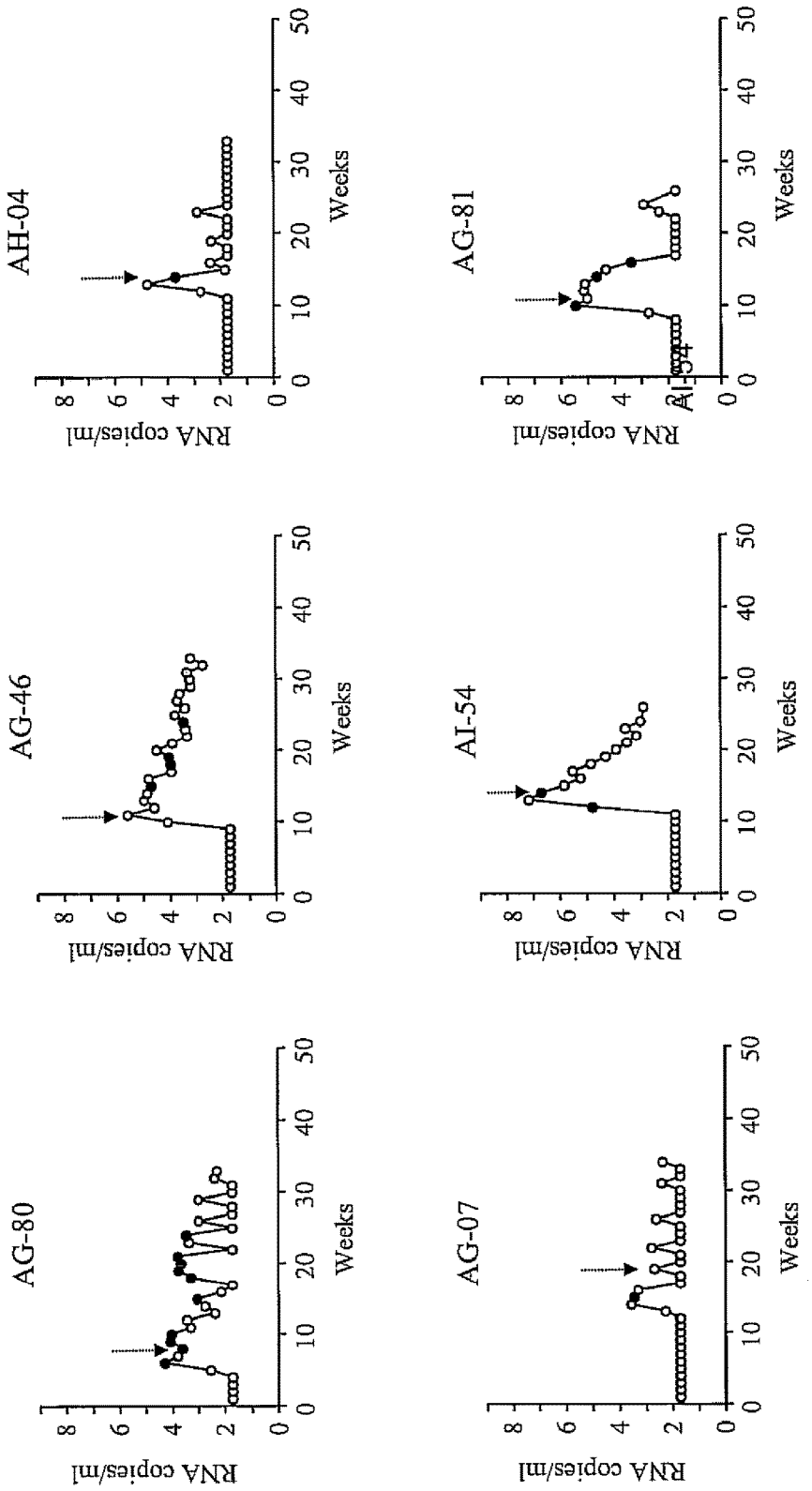
AH-04
AG-81
AG-46
AI-54
AG-80
AG-07
RNA copies/ml
Weeks
0
2
4
6
8
0
10
20
30
40
50

FIG. 4

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation U.S. patent application Ser. No. 14/679,887, filed on Apr. 6, 2015, which is a continuation of U.S. patent application Ser. No. 11/669,547, filed on Jan. 31, 2007, issued as U.S. Pat. No. 9,044,509, which in turn claims the benefit of U.S. provisional application 60/764,811, filed on Feb. 3, 2006. All of the prior applications are incorporated herein by reference in their entirety.

GOVERNMENT INTEREST

The invention described herein may be manufactured, used, and licensed by or for the United States Government.

FIELD OF THE INVENTION

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

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 injection. 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.

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.

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]

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.

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

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.

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

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.

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).

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).

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

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 of 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. Pat. Nos. 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.

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.

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.

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.

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, C_1-C_6 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, 20^{th} Edition, Chapters 37-47, pages 681-929, where parenteral injection includes subcutaneous, intramuscular, intravenous, and intradermal injection.

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. Pat. No. 5,935,946.

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.

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.

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.

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.

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.

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.

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.

Optionally, an inventive composition also includes within an inventive combination other antiretrovirals such as non-nucleoside 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).

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.

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, contraindi-

cations, 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.

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.

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

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 μg×hr/ml which was similar to the value of 5.02 μg×hr/ml observed in human receiving 300 mg of TDF. The dose of 20 mg/kg of FTC resulted in an AUC value (11 μg×hr/ml), also similar to that observed in humans receiving 200 mg of FTC orally (10.0±3.12 μg×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.

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

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 $HIV\text{-}1_{sF162}$ 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 intrarectal inoculation.

Example 3—SHIV Viral Load Assay

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

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

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

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)×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

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 (22 mg/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).

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

FIG. **2** shows the survival curves observed for each group of animals per Example 7. Data with TDF (20 mg/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

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 ± 0.5 $\log_{10}$ RNA copies/ml, 2.0 $\log_{10}$ lower than in untreated controls (6.9 ± 0.3 $\log_{10}$ RNA). FIG. **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 ± 0.02 $\log_{10}$/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 FIG. **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.

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 M1841 (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

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

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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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.

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.

The invention claimed is:

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 tenofovir disoproxil fumarate,

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. 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 disoproxil fumarate, are administered directly to the human in a combined single tablet.

5. The process of claim **2**, wherein the immunodeficiency retrovirus is a human immunodeficiency virus.

6. The process of claim **5**, wherein a humans 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 emtricitabinc 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. The process of claim 4, wherein the tablet comprises 200 milligrams of emtricitabine and 300 mg of tenofovir disproxil fumarate.

13. 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 fumerate in a tablet;

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.

14. The process of claim 13, wherein the combination is compounded into a single tablet.

15. The process of claim 13, 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 13, wherein the potential exposure to the human immunodeficiency retrovirus comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.

17. The process of claim 13, 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.

18. The process of claim 17, wherein the tablet comprises 200 milligrams of emtricitabine and 300 mg of tenofovir disproxil fumarate.

19. The process of claim 17, 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.

* * * * *

EXHIBIT 4

US010335423B2

(12) **United States Patent**
Heneine et al.

(10) **Patent No.: US 10,335,423 B2**
(45) **Date of Patent: *Jul. 2, 2019**

(54) **INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS**

(71) Applicant: **THE UNITED STATES OF AMERICA, as represented by the Secretary, Department of Health and Human**, Washington, DC (US)

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(73) Assignee: **THE UNITED STATES OF AMERICA, as represented by the Secretary, Department of Health and Human Services**, Washington, DC (US)

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This patent is subject to a terminal disclaimer.

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CPC ***A61K 31/675*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 31/513*** (2013.01);
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(Continued)

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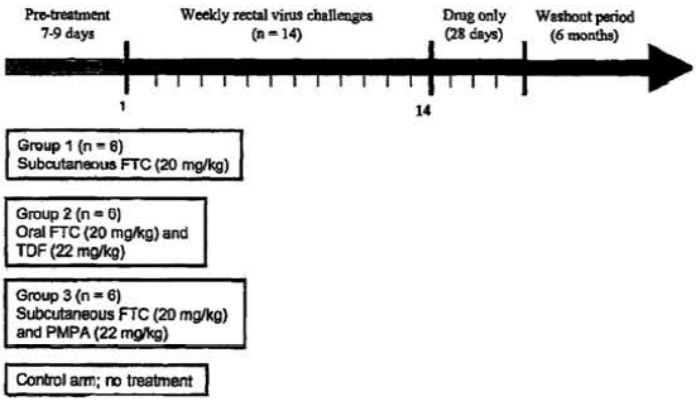
(57) **ABSTRACT**

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
(Continued)



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.

19 Claims, 4 Drawing Sheets

Related U.S. Application Data

continuation of application No. 14/679,887, filed on Apr. 6, 2015, now Pat. No. 9,579,333, which is a continuation of application No. 11/669,547, filed on Jan. 31, 2007, now Pat. No. 9,044,509.

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A61K 9/00	(2006.01)

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USPC 514/81, 274
See application file for complete search history.

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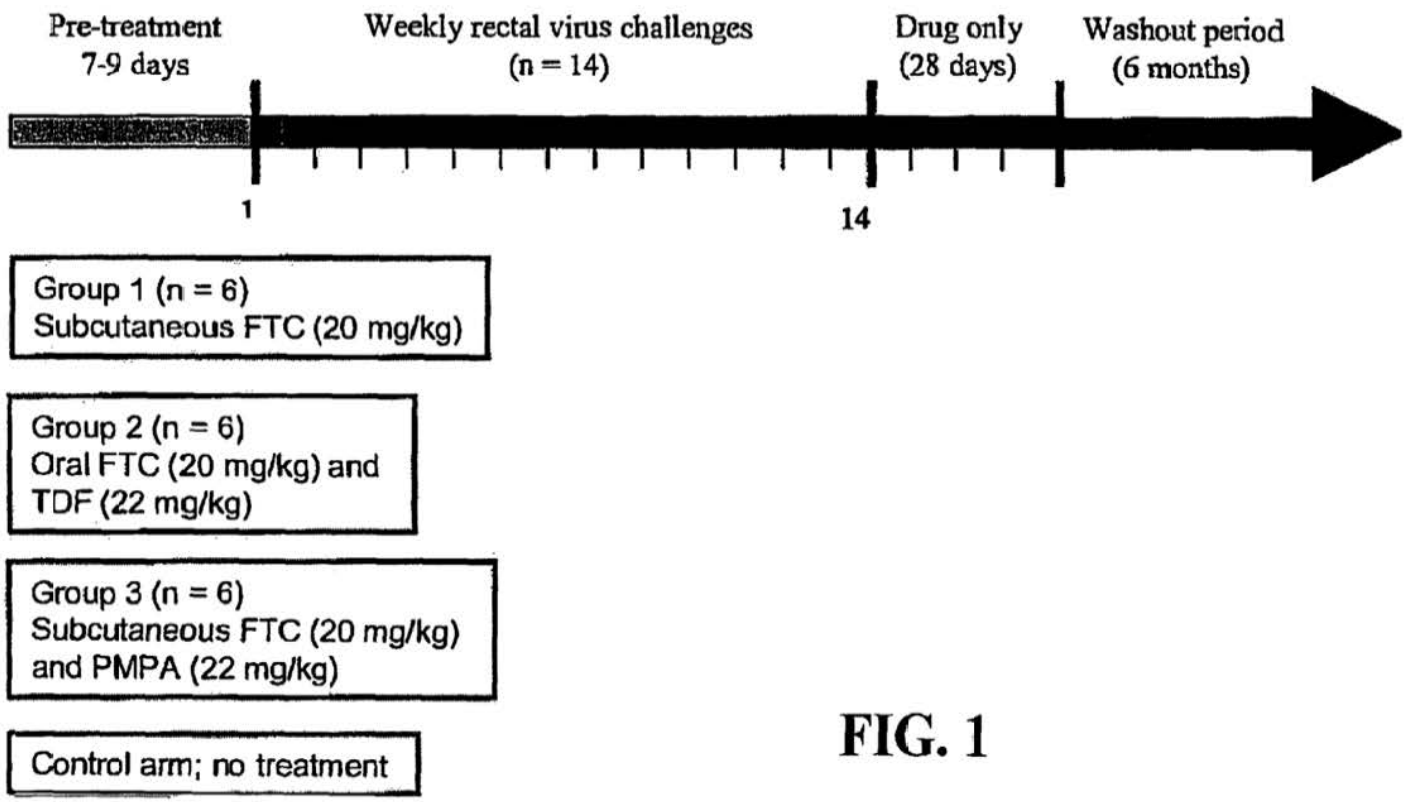
Pre-treatment
7-9 days
Weekly rectal virus challenges
(n = 14)
Drug only
(28 days)
Washout period
(6 months)
1
14
Group 1 (n = 6)
Subcutaneous FTC (20 mg/kg)
Group 2 (n = 6)
Oral FTC (20 mg/kg) and
TDF (22 mg/kg)
Group 3 (n = 6)
Subcutaneous FTC (20 mg/kg)
and PMPA (22 mg/kg)
Control arm; no treatment

FIG. 1

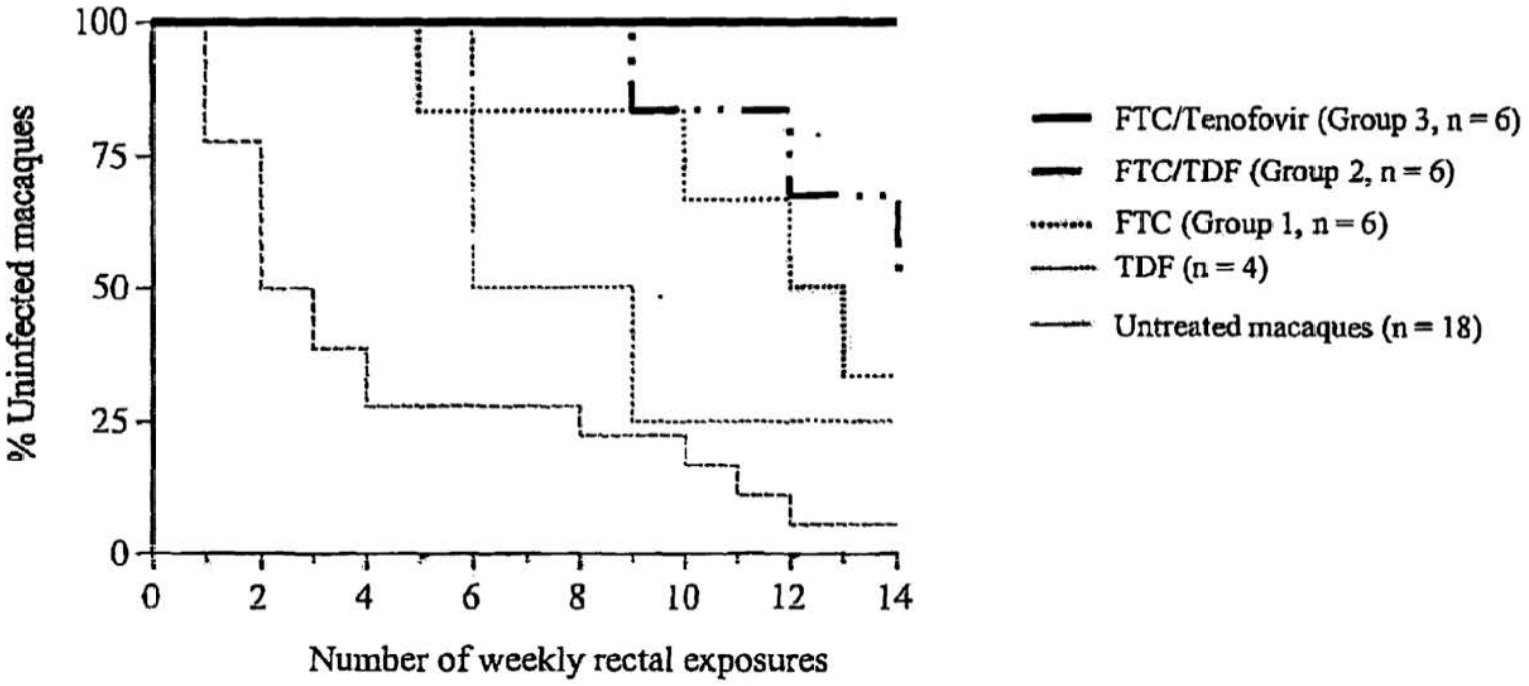
100
75
50
25
0
% Uninfected macaques
0
2
4
6
8
10
12
14
Number of weekly rectal exposures
FTC/Tenofovir (Group 3, n = 6)
FTC/TDF (Group 2, n = 6)
FTC (Group 1, n = 6)
TDF (n = 4)
Untreated macaques (n = 18)

FIG. 2

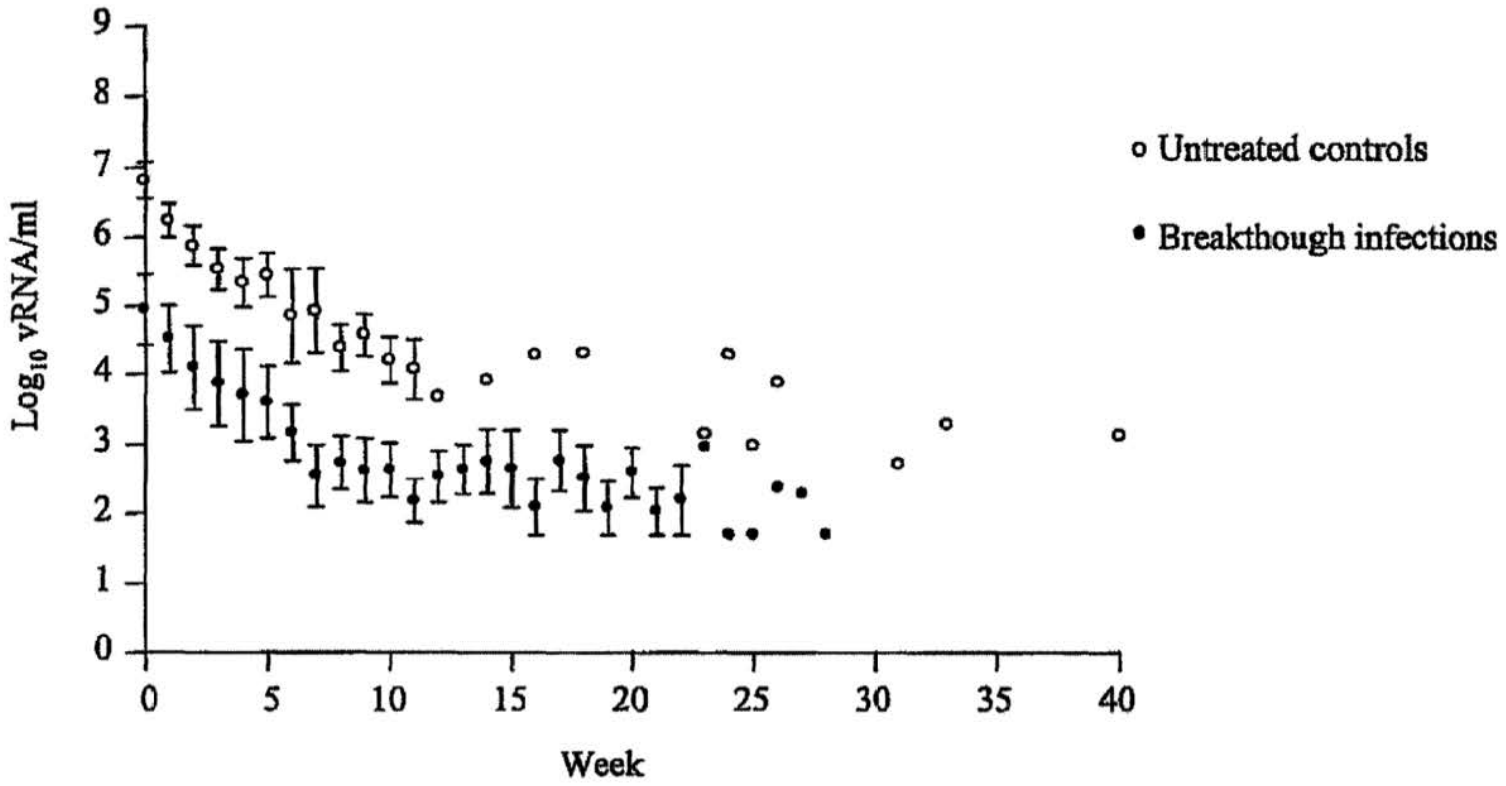
Log10 vRNA/ml
9
8
7
6
5
4
3
2
1
0
0
5
10
15
20
25
30
35
40
Week
Untreated controls
Breakthough infections

FIG. 3

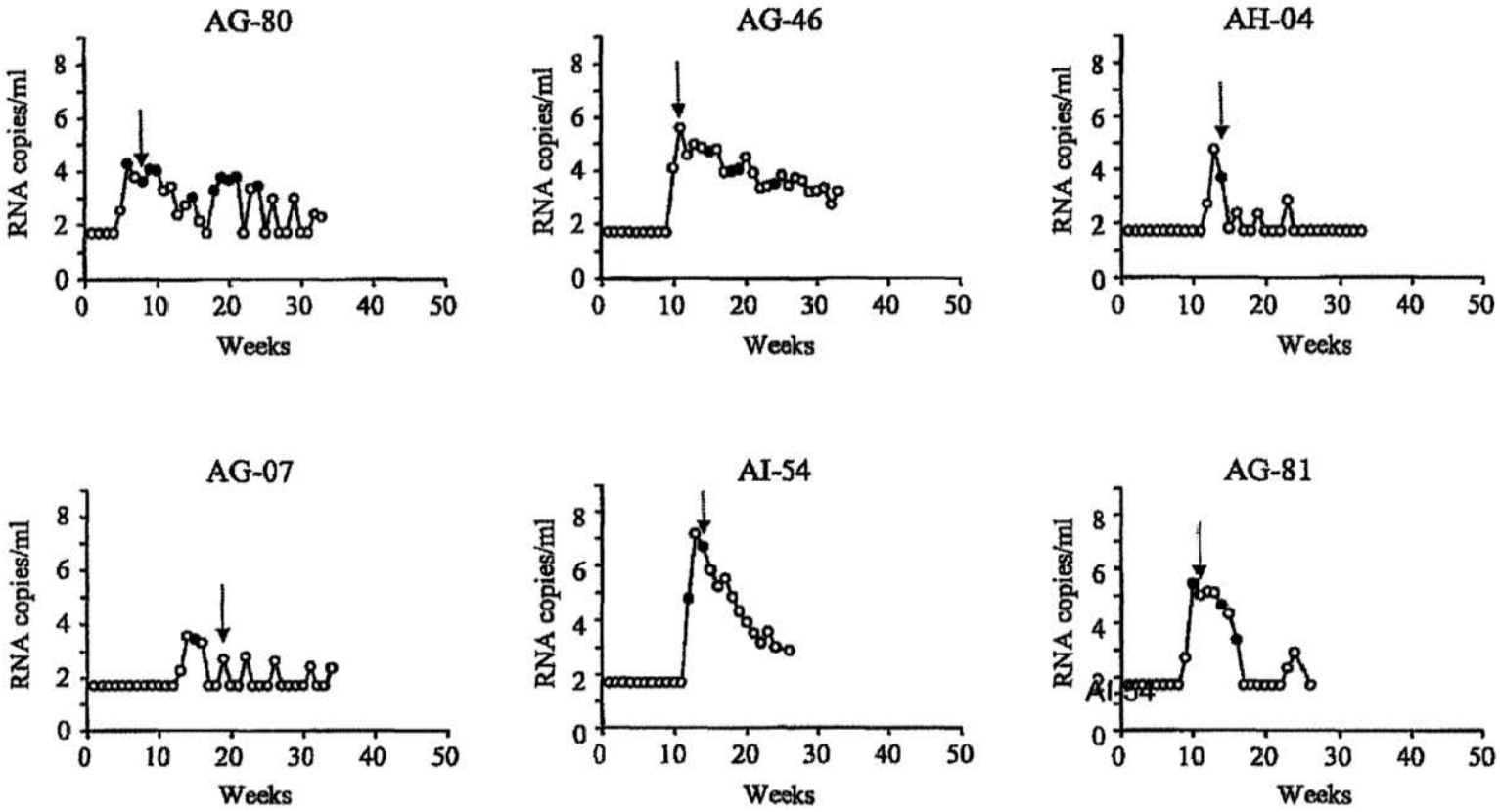
AG-80
AG-46
AH-04
AG-07
AI-54
AG-81
RNA copies/ml
Weeks
0
2
4
6
8
0
10
20
30
40
50

FIG. 4

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of U.S. patent application Ser. No. 15/406,344, filed on Jan. 13, 2017, which is a continuation U.S. patent application Ser. No. 14/679,887, filed on Apr. 6, 2015, issued as U.S. Pat. No. 9,579,333, which is a continuation of U.S. patent application Ser. No. 11/669,547, filed on Jan. 31, 2007, issued as U.S. Pat. No. 9,044,509, which in turn claims the benefit of U.S. provisional application 60/764,811, filed on Feb. 3, 2006. All of the prior applications are incorporated herein by reference in their entirety.

GOVERNMENT INTEREST

The invention described herein may be manufactured, used, and licensed by or for the United States Government.

FIELD OF THE INVENTION

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

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 injection. 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.

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.

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]

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.

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

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.

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

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.

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).

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).

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

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 of 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. Pat. Nos. 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.

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.

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.

As used herein a "primate host" is defined to include a monkey, baboon, chimpanzee, gorilla, and a human. Non-human 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.

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, C_1-C_6 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.

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 cataly-

sis, 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. Pat. No. 5,935,946.

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.

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.

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.

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.

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.

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.

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.

Optionally, an inventive composition also includes within an inventive combination other antiretrovirals such as non-nucleoside 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).

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.

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.

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.

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

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 μg×hr/ml which was similar to the value of 5.02 μg×hr/ml observed in human receiving 300 mg of TDF. The dose of 20 mg/kg of FTC resulted in an AUC value (11 μg×hr/ml), also similar to that observed in humans receiving 200 mg of FTC orally (10.0±3.12 μg×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.

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

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 $HIV\text{-}1_{SF162}$ 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 $TCID_{50}$ 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 intrarectal inoculation.

Example 3

SHIV Viral Load Assay

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 (bioMerieux). 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

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

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

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)×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

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 $TCID_{50}$ 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 (22 mg/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).

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

FIG. **2** shows the survival curves observed for each group of animals per Example 7. Data with TDF (20 mg/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 4animals 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

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 ± 0.5 $\log_{10}$ RNA copies/ml, 2.0 $\log_{10}$ lower than in untreated controls (6.9 ± 0.3 $\log_{10}$ RNA). FIG. **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 ± 0.02 $\log_{10}$/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 FIG. **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.

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 M1841 (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

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

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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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.

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.

The invention claimed is:

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 the 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 s 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 a 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, wherein the combination is administered prior to potential exposure the human to the human immunodeficiency retrovirus.

13. The process of claim **12**, wherein combination is compounded into a single formulation.

14. The process of claim **13**, wherein the single formulation is administered daily for several days, weeks or months both before and after an exposure of the primate host to the immunodeficiency retrovirus.

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:

(i) the pharmaceutically effective amount of emtricitabine; and

(ii) the pharmaceutically effective amount of tenofovir or the tenoforvir prodrug; are formulated in a single tablet.

17. The process of claim **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. The process of claim **12**, wherein the combination comprises the tenofovir prodrug.

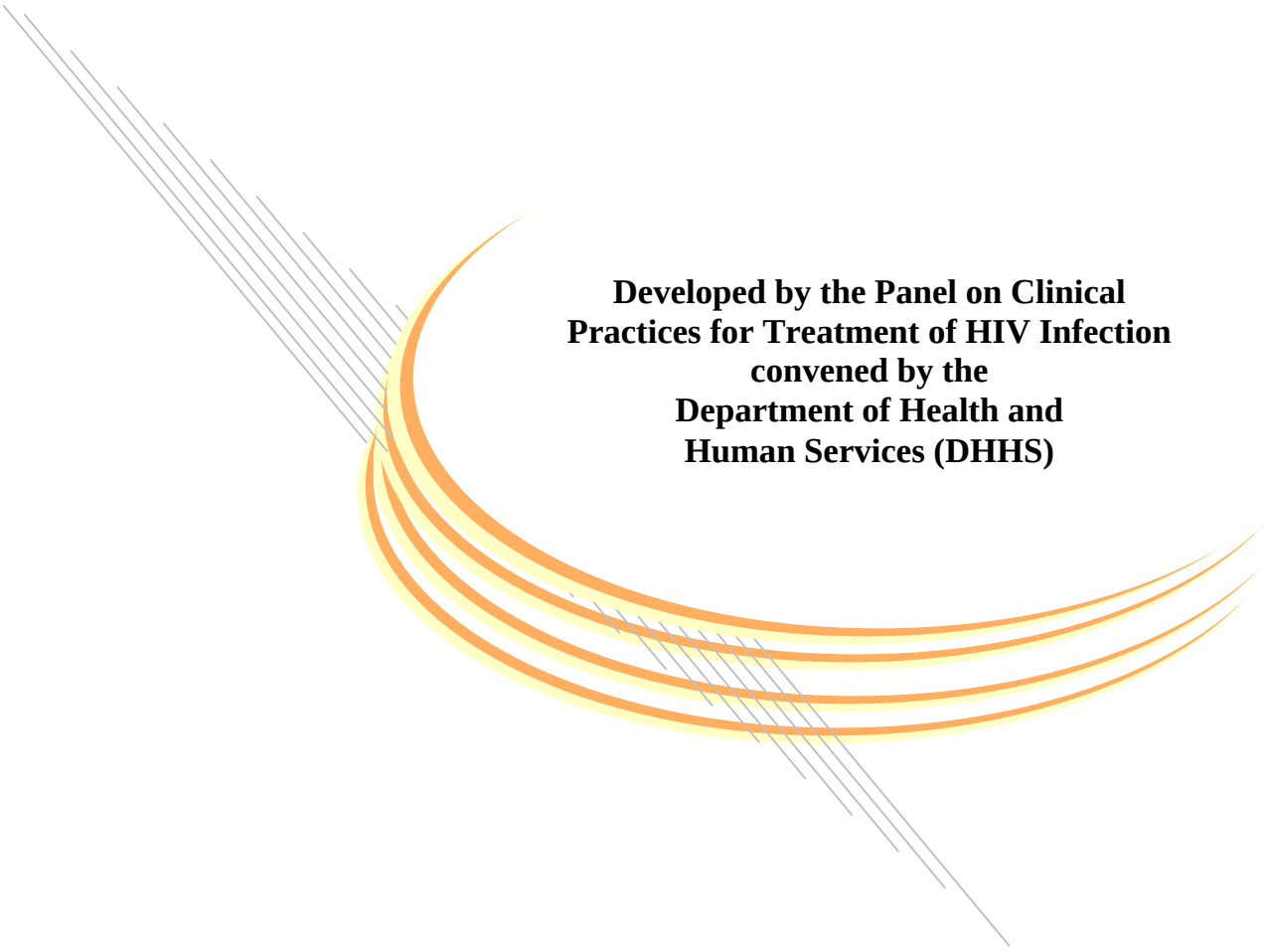
19. The process of claim **1**, wherein the combination comprises the tenofovir prodrug.

* * * * *

EXHIBIT 5

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

April 7, 2005



Developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS)

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the ***AIDSinfo*** **Web site** (**http://*AIDSinfo*.nih.gov**).

What's New in the Document?

The following changes have been made to the October 29, 2004 version of the guidelines:

1. **New recommendations for initiation of NNRTI therapy -** based on increased risk of symptomatic hepatotoxicity when nevirapine is initiated in men and women with high $CD4^+$ T cell counts:

   - Nevirapine-based regimens are recommended as alternatives for adult females with $CD4^+$ T cell counts $\leq$250 cells/mm^3 and adult males with $CD4^+$ T cell counts $\leq$400 cells/mm^3. **(BII)**

   - The Panel does not recommend initiation of nevirapine in adult females with $CD4^+$ T cell counts >250 cells/mm^3 and adult males with $CD4^+$ T cell counts >400 cells/mm^3 unless the benefit clearly outweighs the risk. **(DI)**

2. **Removal of prior recommendation for the use of rifampin with ritonavir-boosted saquinavir** - based on reports of significant elevation (up to 20 x upper limit of normal) of serum transaminases in a Phase I study evaluating the pharmacokinetic interaction of this drug combination in healthy volunteers.

3. **Revision of Tables 28 and 29 (per Perinatal Guidelines) to reflect the recent FDA labeling change for efavirenz from Pregnancy Category C to Category D.**

4. **Addition of a table entitled "Antiretroviral Agent Available Through Expanded Access Program."**

5. **Revision of Table 19 to reflect the FDA labeling change for ritonavir and lopinavir/ritonavir listing new warnings and contraindications.**

April 7, 2005

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Guidelines Acknowledgement List
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Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Introduction

Summary of Guidelines

Antiretroviral therapy for treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection has improved steadily since the advent of combination therapy in 1996. More recently, new drugs have been approved, offering added dosing convenience and improved safety profiles, while some previously popular drugs are being used less often as their drawbacks become better defined. Resistance testing is used more commonly in clinical practice and interactions among antiretroviral agents and with other drugs have become more complex.

The Panel on Clinical Practices for Treatment of HIV (the Panel) develops these guidelines which outline current understanding of how clinicians should use antiretroviral drugs to treat adult and adolescents with HIV infections. The Panel considers new evidence and adjusts recommendations accordingly. The primary areas of attention and revision have included: when to initiate therapy, which drug combinations are preferred and which drugs or combinations should be avoided, and means to continue clinical benefit in the face of antiretroviral drug resistance. In contrast, some aspects of therapy, while important, have seen less rapid data evolution and thus fewer changes, such as medication adherence. Yet other topics have warranted more in-depth attention by separate guidelines groups, like the treatment of HIV during pregnancy.

Key Clinical Questions Addressed By Guidelines. For ease of use, these guidelines are organized so as to answer the following series of clinical questions clinicians are most likely to face in making treatment decisions:

- ***When should therapy be started in patients with established asymptomatic infection?*** The Panel reaffirms the desirability of initiating therapy before the CD4 cell count falls below 200 cells/mm^3. In addition, there are inconsistent data documenting added value in treating before the count falls below 350 cell/mm^3, but some clinicians opt to consider treatment in patients with CD4 count >350 cell/mm^3 and HIV-RNA >100,000 copies/mL. A review of the literature on this issue can been seen in the **When to Treat: Indications for Antiretroviral Therapy** section.
- ***Which regimens are preferred for initial therapy?*** The Panel continues to select several regimens as preferred, while appreciating that patient or provider preferences, or underlying co-morbidities, may make an alternative regimen better in such instances. The Panel recommends that an initial regimen contain two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted or unboosted protease inhibitor (PI).
- ***What drugs or drug combinations should not be used?*** The Panel notes that certain drugs are so similar, for example, lamivudine and emtricitabine, that they should not be combined. Others have additive or synergistic toxicity, such as stavudine with didanosine, and should generally be avoided. Still others have intracellular interactions that decrease their antiviral activities, notably zidovudine with stavudine, and should thus be avoided.
- ***What are some limitations to the safety and efficacy of antiretroviral therapy?*** The Panel notes the high degree of medication adherence with all ARV regimens needed to prevent the selection of drug resistance. It also appreciates that short term and, even more concerning, longer term toxicity may limit the duration of treatment needed in what can be seen as a chronic disease. Finally, drug interactions among the antiretroviral drugs and with other necessary drugs are challenging and require special attention in prescribing and monitoring.
- ***What is the role of resistance testing in guiding therapy decisions?*** Resistance testing continues to be an important component of optimizing drug selection after treatment failure. However, its role in previously untreated persons is less clear. The Panel recognizes that there is a growing sense that such applications are of value, but little evidence exists to guide such use.

- ***What are the goals of therapy in treatment experienced patients?*** When possible, suppression of viremia to less than detection limits remains the goal of therapy. When this is not possible, the Panel recommends maintenance of even partial viremic suppression by selection of an optimal regimen based on resistance testing results. Either way, the ultimate goals are to prevent further immune deterioration and to avoid HIV-associated morbidity and mortality. The Panel recommends against complete antiretroviral cessation in late failure as this has resulted in rapid progression to AIDS and death.

- ***Are there special populations which may require specific considerations when using antiretroviral therapy?*** The Panel recognizes that there are subgroups of patients where specific considerations are critical when selecting and monitoring antiretroviral therapy, in order to assure safe and effective treatment. The Panel addresses some important antiretroviral related issues for these special populations, which include patients with acute HIV infection, HIV-infected adolescents, injection drug users, women of child bearing potential and pregnant women, and those with hepatitis B, hepatitis C, or tuberculosis co-infections.

Guidelines Process

These guidelines outline the current understanding of how clinicians should use antiretroviral agents to treat adults and adolescents infected with HIV-1. They were developed by the Panel on Clinical Practices for Treatment of HIV (the Panel), convened by DHHS.

Basis for Recommendations. Recommendations are based upon expert opinion and scientific evidence. Each recommendation has a letter/Roman numeral rating (**Table 1**). The letter indicates the strength of the recommendation based on the expert opinion of the Panel. The Roman numeral indicates the quality of the scientific evidence to support the recommendation. When appropriate data are not available, inconclusive, or contradictory, the recommendation is based on "expert opinion." These recommendations are not intended to supersede the judgment of clinicians who are knowledgeable in the care of HIV infection.

Updating of Guidelines. These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. The guidelines are therefore updated frequently by the Panel, which meets monthly by teleconferencing to make ongoing revisions as necessary. All revisions are summarized and highlighted on the *AIDSinfo* Web site. Proposed revisions are posted for a public comment period, generally for 2 weeks, after which comments are reviewed by the Panel prior to finalization. Comments can be sent to **aidsinfowebmaster@aidsinfo.nih.gov**.

Other Guidelines. These guidelines focus on treatment for adults and adolescents. Separate guidelines outline how to use antiretroviral therapy for such populations as pregnant women, pediatric patients and health care workers with possible occupational exposure to HIV (see **http://aidsinfo.nih.gov/guidelines**). There is a brief discussion of the management of women in reproductive age and pregnant women in this document. However, for more detailed and up-to-date discussion on this and other special populations, the Panel defers to the designated expertise outlined by panels that have developed these guidelines.

Importance of HIV Expertise in Clinical Care. Multiple studies have demonstrated that better outcomes are achieved in patients cared for by a clinician with expertise *[1-6]*. This has been shown in terms of mortality, rate of hospitalizations, compliance with guidelines, cost of care, and adherence to medications. The definition of expertise in these studies has varied, but most rely on the number of patients actively managed. Based on this observation, the Panel recommends HIV primary care by a clinician with at least 20 HIV-infected patients and preferably at least 50 HIV-infected patients. Many authoritative groups have combined the recommendation based on active patients, along with fulfilling ongoing CME requirements on HIV-related topics.

BASIC EVALUATION

Pretreatment Evaluation

Each patient initially entering care should have a complete medical history, physical examination, and laboratory evaluation. The purpose is to confirm the presence of HIV infection, determine if HIV infection is acute (see **Acute HIV Infection**), determine the presence of co-infections, and assess overall health condition as recommended by the primary care guidelines for the management of HIV-infected patients *[7]*.

The following laboratory tests should be performed for each new patient during initial patient visits:

- HIV antibody testing (if laboratory confirmation not available) **(AI)**;
- CD4 cell count **(AI)**;
- Plasma HIV RNA **(AI)**;
- Complete blood count, chemistry profile, transaminase levels, BUN and creatinine, urinalysis, RPR or VDRL, tuberculin skin test (unless a history of prior tuberculosis or positive skin test), *Toxoplasma gondii* IgG, Hepatitis A, B, and C serologies, and PAP smear in women **(AIII)**;
- Fasting blood glucose and serum lipids if considered at risk for cardiovascular disease and for baseline evaluation prior to initiation of combination antiretroviral therapy **(AIII)**.

In addition:

- Resistance testing in chronically infected patients prior to initiating antiretroviral therapy is optional **(CIII)**;
- A test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* is optional **(BII)** in order to identify high risk behavior and the need for STD therapy;
- Chest x-ray if clinically indicated **(BIII)**.

Patients living with HIV infection must often cope with multiple social, psychiatric, and medical issues. Thus, the evaluation should also include assessment of substance abuse, economic factors, social support, mental illness, co-morbidities, and other factors that are known to impair the ability to adhere to treatment and to alter outcomes. Once evaluated, these factors should be managed accordingly.

Initial Assessment and Monitoring for Therapeutic Response

Two surrogate markers are routinely used to determine indications for treatment and to monitor the efficacy of therapy: $CD4^+$ T-cell count and plasma HIV RNA (or viral load).

$CD4^+$ T-cell count. The $CD4^+$ T-cell count (or CD4 count) serves as the major clinical indicator of immunocompetence in patients with HIV infection. It is usually the most important consideration in decisions to initiate antiretroviral therapy. The most recent CD4 cell count is the strongest predictor of subsequent disease progression and survival, according to clinical trials and cohort studies data on patients receiving antiretroviral therapy. A significant change between two tests (2 standard deviations) is defined as approximately 30% change of the absolute count and 3 percentage point change in CD4 percentage.

- **Use of CD4 for Initial Assessment**. The CD4 count is usually the most important consideration in decisions to initiate antiretroviral therapy. All patients should have a baseline CD4 cell count at entry into care **(AI)**; many authorities recommend two baseline measurements before decisions are made to initiate antiretroviral therapy due to wide variations in results **(CIII)**. The test should be repeated yet a third time if discordant results are seen **(AI)**. Recommendations for initiation of antiretroviral therapy based on CD4 cell count are found in the **When to Treat: Indications for Antiretroviral Therapy** section**.**
- **Use of CD4 Count for Monitoring Therapeutic Response**. Adequate viral suppression for most patients on therapy is defined as an increase in CD4 cell count that averages 100-150 cells/mm^3 per year with an accelerated response in the first three months. This is largely due to redistribution. Subsequent increases with good virologic control show an average increase of approximately 100 cells/mm^3 per year for the subsequent few years until a threshold is reached *[8]*.
- **Frequency of CD4 Count Monitoring.** In general, CD4 count should be determined every three to six months to (1) determine when to start antiretroviral in patients who do not meet the criteria for initiation; (2) assess immunologic response to antiretroviral therapy; and (3) assess the need for initiating chemoprophylaxis for opportunistic infections.

Viral Load. Plasma HIV RNA (viral load) may be a consideration in the decision to initiate therapy. In addition, viral load is critical for evaluating response to therapy **(AI)**. Three HIV viral load assays have been approved by the Food and Drug Administration (FDA) for clinical use:

- HIV-1 reverse transcriptase polymerase chain reaction assay (Amplicor HIV-1 Monitor Test, version 1.5, Roche Diagnostic);
- Nucleic acid amplification test for HIV RNA (NucliSens HIV-1 QT, Organon Teknika); and
- Signal amplification nucleic acid probe assay (VERSANT HIV-1RNA 3.0 assay, Bayer).

Analysis of 18 trials with over 5,000 participants with viral load monitoring showed a significant association between a decrease in plasma viremia and improved clinical outcome. Thus, viral load testing serves as a surrogate marker for treatment response and may be useful in predicting clinical progression. The minimal change in viral load considered to be statistically

significant (2 standard deviations) is a threefold or a 0.5 $\log_{10}$ copies/mL change. One key goal of therapy is a viral load below the limits of detection (at <50 copies/mL for the Amplicor assay, <75 copies/mL for the VERSANT assay, and <80 copies/mL for the NucliSens assay). This goal should be achieved by 16-24 weeks **(AI)**. Recommendations for the frequency of viral load monitoring are summarized below and in **Table 2**.

- **At Initiation or Change in Therapy**. Plasma viral load should be measured immediately before treatment, and at 2-8 weeks after treatment initiation or treatment changes due to suboptimal viral suppression. In the latter measure, there should be a decrease of at least a 1.0 $\log_{10}$ copies/mL **(BI)**.
- **In Patients With Viral Suppression Where Changes are Motivated by Drug Toxicity or Regimen Simplification**. Some experts also recommend repeating viral load measurement within 2-8 weeks after changing therapy. The purpose of viral load monitoring at this point is to confirm potency of the new regimen.**(BII)**
- **In Patients on a Stable Antiretroviral Regimen** The viral load testing should be repeated every 3-4 months thereafter or if clinically indicated.**(BII)** The testing should be repeated every 3-4 months thereafter or if clinically indicated. (**Table 2**)

Monitoring in Patients With Suboptimal Response. In addition to viral load monitoring, a number of additional factors should be assessed, such as non-adherence, altered pharmacology, or drug interactions. Resistance testing may be helpful in identifying the presence of resistance mutations that may necessitate a change in therapy. **(AII)**

TREATMENT GOALS

Eradication of HIV infection cannot be achieved with available antiretroviral regimens. This is chiefly because the pool of latently infected $CD4^+$ T cells is established during the earliest stages of acute HIV infection *[9]* and persists with a long half-life, even with prolonged suppression of plasma viremia *[10-13]*. Therefore, once the decision is made to initiate therapy, the primary goals of antiretroviral therapy are to:

- reduce HIV-related morbidity and mortality,
- improve quality of life,
- restore and preserve immunologic function, and
- maximally and durably suppress viral load.

Adoption of treatment strategies recommended in these guidelines has resulted in substantial reductions in HIV-related morbidity and mortality *[14-16]*.

Plasma viremia is a strong prognostic indicator of HIV disease progression *[17]*. Reductions in plasma viremia achieved with antiretroviral therapy account for substantial clinical benefits *[18]*. Therefore, suppression of plasma viremia as much as possible for as long as possible is a critical goal of antiretroviral therapy (see **Basic Evaluation: Initial Assessment and Monitoring for Therapeutic Response**). This goal, however, must be balanced against the need to preserve effective treatment options in patients who do not achieve undetectable viral load due to extensive viral resistance or persistent medication non-adherence.

Viral load reduction to below limits of assay detection in a treatment-naïve patient usually occurs within the first 16-24 weeks of therapy. However, maintenance of excellent treatment response is highly variable. Predictors of long-term virologic success include:

- potency of antiretroviral regimen,
- adherence to treatment regimen *[19, 20]*,
- low baseline viremia,
- higher baseline $CD4^+$ cell count *[19, 20]*, and
- rapid (i.e. $\geq$1 $\log_{10}$ in 1-4 months) reduction of viremia in response to treatment *[20]*.

Successful outcomes have not been observed across all patient populations, however. Studies have shown that approximately 70% of patients in urban clinic settings achieve the goal of no detectable virus compared to 80-90% in many clinical trials *[21]*.

Strategies to Achieve Treatment Goals

Achieving treatment goals requires a balance of sometimes competing considerations, outlined below. Providers and patients must work together to define priorities and determine treatment goals and options.

Selection of Combination Regimen. Several preferred and alternative antiretroviral regimens are recommended for use (see **What to Start With: Initial Combination Regimens for the Antiretroviral-Naïve Patient**). They vary in efficacy, pill burden, and potential side effects. A regimen tailored to the patient may be more successful in fully suppressing the virus with fewer side effects. Individual tailoring is based on such considerations as lifestyle, co-morbidities, and interactions with other medications.

Preservation of Future Treatment Options. Multiple changes in antiretroviral regimens, prompted by virologic failure due to drug resistant virus or patient non-adherence, can rapidly exhaust treatment options. While these are valid reasons to prompt a change in therapy, they should be considered carefully (see **Managing the Treatment Experienced Patient: Assessment of Antiretroviral Treatment Failure and Changing Therapy**).

Drug Sequencing. Appropriate sequencing of drugs for use in initial and subsequent salvage therapy preserves future treatment options and is another tool to maximize benefit from antiretroviral therapy. Currently recommended strategies spare at least two classes of drugs for later use and potentially avoid or delay certain class-specific side effects.

Improving Adherence. The reasons for variability in response to antiretrovirals are complex but may include inadequate adherence due to multiple social issues that confront patients *[22-24]*. Patient factors clearly associated with the risk of decreased adherence—such as active substance abuse, depression, and lack of social support—need to be addressed with patients before initiation of antiretroviral therapy *[25, 26]*. Strategies to improve medication adherence can improve outcomes.

WHEN TO TREAT: Indications for Antiretroviral Therapy

Panel's Recommendations (Table 4):

- ***Antiretroviral therapy is recommended for all patients with history of an AIDS-defining illness or severe symptoms of HIV infection regardless of CD4$^+$ T cell count. (AI)***
- ***Antiretroviral therapy is also recommended for asymptomatic patients with <200 CD4$^+$ T cells/mm^3 (AI)***
- ***Asymptomatic patients with CD4$^+$ T cell counts of 201–350 cells/mm^3 should be offered treatment. (BII)***
- ***For asymptomatic patients with CD4$^+$ T cell of >350 cells/mm^3 and plasma HIV RNA >100,000 copies/ml most experienced clinicians defer therapy but some clinicians may consider initiating treatment. (CII)***
- ***Therapy should be deferred for patients with CD4$^+$ T cell counts of >350 cells /mm^3 and plasma HIV RNA <100,000 copies/mL. (DII)***

The decision to begin therapy for the asymptomatic patient is complex and must be made in the setting of careful patient counseling and education.

Considerations of initiating antiretroviral therapy should be primarily based on the prognosis of disease-free survival as determined by baseline CD4$^+$ T cell count *[27-29]* (**Figure A**; and **Table 3a**, **3b**). Also important are baseline viral load *[27-29]*, readiness of the patient to begin therapy; and assessment of potential benefits and risks of initiating therapy for asymptomatic persons, including short-and long-term adverse drug effects; the likelihood, after counseling and education, of adherence to the prescribed treatment regimen.

Recommendations vary according to the CD4 count and viral load of the patient, as follows.

<200 CD4$^+$ T cell count, with AIDS-defining illness, or symptomatic. Randomized clinical trials provide strong evidence of improved survival and reduced disease progression by treating symptomatic patients and patients with <200 CD4$^+$ T cells/mm^3 *[30-33]*. Observational cohorts indicate a strong relationship between lower CD4$^+$ T cell counts and higher plasma HIV RNA levels in terms of risk for progression to AIDS for untreated persons and antiretroviral naïve patients beginning treatment. These data provide strong support for the conclusion that therapy should be initiated in patients with CD4$^+$ T cell count <200 cells/mm^3 (**Figure A** and **Table 3a**) **(AI)** *[27, 28]*.

200-350 CD4$^+$ T cell count, patient asymptomatic. The optimal time to initiate antiretroviral therapy among asymptomatic patients with CD4$^+$ T cell counts >200 cells/mm^3 is unknown. For these patients, the strength of the recommendation for therapy must balance other considerations, such as patient readiness for treatment and potential drug toxicities.

After considering available data in terms of the relative risk for progression to AIDS at certain CD4$^+$ T cell counts and viral loads, and the potential risks and benefits associated with initiating therapy, most specialists in this area believe that the evidence supports initiating therapy in asymptomatic HIV-infected persons with a CD4$^+$ T cell count of 200-350 cells/mm^3 **(BII)**.

There is a paucity of data from randomized, controlled trials concerning clinical endpoints (e.g., the development of AIDS-defining illnesses or death) for asymptomatic persons with >200 CD4$^+$ T cells/mm^3 to guide decisions on when to initiate therapy. Observational data from cohorts of HIV-infected persons provide some guidance to assist in risk assessment for disease progression.

One source of observational data comes from cohorts of untreated individuals with regular measurements of $CD4^+$ T cell counts and HIV RNA levels. **Table 3b** is taken from a report by the CASCADE Collaboration, composed of 20 cohorts in Europe and Australia *[29]*. The information in this table provides an estimate of the short-term (6-month) risk of AIDS progression according to $CD4^+$ T cell count, HIV RNA level, and age. These estimates can be considered in making the decision about whether to start antiretroviral therapy before the next clinic visit.

Another source of observational data is from cohorts that follow patients after the initiation of antiretroviral treatment. A pooled analysis of 13 cohorts from Europe and North America provide the most precise information on prognosis following the initiation of treatment *[28]*. These data indicate that $CD4^+$ T-cell count is a much more important prognostic indicator than viral load for those initiating therapy. In this study, risk of progression was also greater for those with a viral load >100,000, older patients, those infected through injecting drug use, and those with a previous diagnosis of AIDS. The following chart shows the risk of progression to AIDS or death after 3 years, according to $CD4^+$ T-cell count and HIV RNA level at the time antiretroviral therapy was initiated. These data are from a large subset of patients less than 50 years old and without a history of an AIDS-defining illness or injection drug use:

$CD4^+$ T cell count	3 yr-probability	
	VL $<10^5$	VL $>10^5$
0 - 49 cells/mm^3	16 %	20%
50 - 99 cells/mm^3	12 %	16%
100 - 199 cells/mm^3	9.3 %	12%
200 - 349 cells/mm^3	4.7 %	6.1%
$\geq$350 cells/mm^3	3.4 %	4.4%

These data provide strong support for the recommendation, based on observational cohort , that therapy should be initiated before the $CD4^+$ T cell count declines to <200 cells/mm^3. However, differences in risk for those with $CD4^+$ T cell counts between 200–350 and >350 cells/mm^3 are based on too few events, and too short a follow-up period, to make reliable statements about when treatment should be started.

While there are clear strengths to these observational data, there are also important limitations. Uncontrolled confounding factors could impact estimates in both studies. Furthermore, neither study provides direct evidence on the optimum $CD4^+$ T cell count to begin therapy. Such data will have to come from studies that follow patients who start therapy at different $CD4^+$ T-cell counts above 200 cells/mm^3 and compare them with a similar group of patients (e.g., with similar $CD4^+$ T cell count and HIV RNA level) who defer treatment. To completely balance the benefits and risks of therapy, follow-up will have to examine progression to AIDS, major toxicities, and death.

>350 $CD4^+$ T cell count, patient asymptomatic. There is little evidence on the benefit of initiating therapy in asymptomatic patients with $CD4^+$ T cell count > 350 cells/mm^3. Most clinicians would defer therapy.

- The deferred treatment approach is based on the recognition that robust immune reconstitution still occurs in the majority of patients who initiate treatment while $CD4^+$ T cell counts are in the 200–350 cells/mm^3range. Also, toxicity risks and adherence challenges generally outweigh the benefits of initiating therapy at $CD4^+$ T cell counts >350 cells/mm^3. In the deferred treatment approach, increased levels of plasma HIV RNA (i.e., >100,000 copies/mL) are an indication for monitoring of $CD4^+$ T cell counts and plasma HIV RNA levels at least every three months, but not necessarily for initiation of therapy. For patients with HIV RNA <100,000 copies/mL, therapy should be deferred **(DII)**.
- In the early treatment approach, asymptomatic patients with $CD4^+$ T cell counts >350 cells/mm^3 and levels of plasma HIV RNA >100,000 copies/mL would be treated because of the risk for immunologic deterioration and disease progression **(CII)**.

An estimate of the short term risk of AIDS progression may be useful in guiding clinicians and patients as they weigh the risks and benefits of initiating versus deferring therapy in this CD4 cell range. As cited above, **Table 3b** provides an analysis of data from the CASCADE Collaboration, demonstrating the risk of AIDS progression within 6 months for different strata of $CD4^+$ T cell count, viral load, and age. As seen in **Table 3b**, a 55 year old with a $CD4^+$ T cell count of 350 and a HIV viral load of 300,000 copies/ml has a 5% chance of progression to an AIDS-defining diagnosis in 6 months, compared with a 1.2% chance for a similar patient with a viral load of 3,000 copies/mL.

Benefits and Risks of Treatment

In addition to the risks of disease progression, the decision to initiate antiretroviral therapy also is influenced by an assessment of other potential risks and benefits associated with treatment. Potential benefits and risks of early ($CD4^+$ T cell counts >350

cells/mm^3) or deferred (CD4$^+$ T cell count 200-350 cells/mm^3) therapy initiation for the asymptomatic patient should be considered by the clinician and patient.

Potential Benefits of Deferred Therapy include:

- avoidance of treatment-related negative effects on quality of life and drug-related toxicities;
- preservation of treatment options;
- delay in development of drug resistance if there is incomplete viral suppression;
- more time for the patient to have a greater understanding of treatment demands;
- decreased total time on medication with reduced chance of treatment fatigue; and
- more time for the development of more potent, less toxic, and better studied combinations of antiretrovirals.

Potential Risks of Deferred Therapy include:

- the possibility that damage to the immune system, which might otherwise be salvaged by earlier therapy, is irreversible;
- the increased possibility of progression to AIDS; and
- the increased risk for HIV transmission to others during a longer untreated period.

Gender Differences. The recommendation of when to start antiretroviral therapy is the same for HIV-infected adult male and female patients. Data regarding sex-specific differences in viral load and CD4$^+$ T cell counts are conflicting. Certain studies *[34-40]*, although not others *[41-44]*, have concluded that after adjustment for CD4$^+$ T cell counts, levels of HIV RNA are lower in women than in men. Although viral load is lower in women at seroconversion, the differences decrease with time, and the median viral load in women and men become similar within 5–6 years after seroconversion *[35, 36, 40]*. Importantly, rates of disease progression do not differ by gender *[38, 40, 45, 46]*. These data demonstrate that sex-based differences in viral load occur predominantly during a window of time when the CD4$^+$ T cell count is relatively preserved, when treatment is recommended only in the setting of increased levels of plasma HIV RNA.

Adherence Considerations. Concern about adherence to therapy is a major determinant for timing of initiation of therapy, with patient readiness to start treatment being a key factor in future adherence *[47]*. Depression and substance abuse may negatively impact adherence and response to therapy, therefore, should be addressed, whenever possible, prior to initiating therapy. However, no patient should automatically be excluded from consideration for antiretroviral therapy simply because he or she exhibits a behavior or other characteristic judged by the clinician to lend itself to non-adherence. Rather, the likelihood of patient adherence to a long-term drug regimen should be discussed and determined by the patient and clinician before therapy is initiated. To achieve the level of adherence necessary for effective therapy, providers are encouraged to use strategies for assessing and assisting adherence. (see **Adherence** section).

WHAT TO START WITH: Initial Combination Regimens for the Antiretroviral-Naïve Patient

Much progress has been made since zidovudine monotherapy demonstrated survival benefits in advanced HIV patients in the late 1980s *[48]*. As of October 2003, there were 20 approved antiretroviral agents, belonging to four classes, with which to design combination regimens containing at least three drugs. These four classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), and fusion inhibitors (FI).

Summary of Recommended Regimens. Since the introduction in 1995 of PI and potent combination antiretroviral therapy (previously referred to as "highly active antiretroviral therapy" or "HAART"), a substantial body of clinical data has been amassed to guide the selection of initial therapy for the previously untreated patient. To date, most clinical experience with use of combination therapy in treatment-naïve individuals has been based on three different types of combination regimens, namely: NNRTI-based (1 NNRTI + 2 NRTI), PI-based (1-2 PI + 2 NRTI), and triple NRTI-based regimens. Recommendations are, accordingly, organized by these categories.

A list of Panel-recommended regimens for initial therapy in treatment naïve patients can be found in **Table 5**. In addition to notations in **Table 5**, **Criteria for Recommended Combination Antiretroviral Regimens** (below) outlines the rationale of the Panel's recommendations.

Potential advantages and disadvantages for each regimen recommended for initial therapy for treatment of naïve patients are listed in **Table 6** to guide prescribers in choosing the regimen best suited for an individual patient.

Criteria for Recommended Combination Antiretroviral Regimens

Data Used for Making Recommendations. In its deliberations for the guidelines, the Panel reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for FDA review. In selected cases, data presented in abstract format in major scientific meetings are also reviewed. The first criterion for selection is data from a randomized, prospective clinical trial with an adequate sample size, demonstrating potency as measured by durable viral suppression and immunologic enhancement (as evidenced by increased $CD4^+$ T-cell count). Few of these trials have enough follow-up data to include clinical endpoints (such as development of AIDS-defining illness or death). Thus, assessment of regimen efficacy and potency are mostly based on surrogate marker endpoints. A summary of selected prospective comparative trials for initial therapy with at least 48-week data can be seen in **Table 7**. Given the paucity of head-to-head trials that make comparisons among numerous potential antiretroviral combinations, the Panel reviewed data across numerous clinical trials in arriving at "preferred" versus "alternative" ratings in **Table 5**.

Regimens are designated as "preferred" for use in treatment-naïve patients when clinical trial data have demonstrated optimal efficacy and durability with acceptable tolerability and ease of use. "Alternative" regimens refer to regimens for which clinical trial data show efficacy but are considered alternative due to disadvantages compared to preferred regimens in terms of antiviral activity, durability, tolerability, or ease of use. In some cases, based on individual patient characteristics and needs, a regimen listed as an alternative regimen may actually be the preferred regimen in that patient. The designation of regimens as "preferred" or "alternative" may change over time as new safety and efficacy data emerge, which, in the opinion of the Panel, warrant reassignment of categories. Revisions will be updated on an ongoing basis and clearly noted on the website version of these guidelines.

The most extensive clinical trial data are available for the three types of regimens shown in **Table 5**. Data regarding "backbone" NRTI pairs have emerged that have led to the NRTI recommendations in **Table 5**. With the ever-increasing choices of more effective and more convenient regimens, some of the agents or combinations which were previously recommended by the Panel as alternative initial treatment options have been removed from the list.

Factors to Consider When Selecting an Initial Regimen. The Panel affirms that regimen selection should be individualized, taking into consideration a number of factors including:

- co-morbidity or conditions such as tuberculosis, liver disease, depression or mental illness, cardiovascular disease, chemical dependency, or pregnancy;
- adherence potential;
- dosing convenience regarding pill burden, dosing frequency, and food and fluid considerations;
- potential adverse drug effects;
- potential drug interactions with other medications;
- pre-treatment $CD4^+$ T cell count;
- gender; and
- pregnancy potential.

Considerations for Therapies. A listing of characteristics (dosing, pharmacokinetics, and common adverse effects) of individual antiretroviral agents can be found in **Tables 10-13**. Additionally, **Table 14** provides clinicians with dosing recommendations of these agents in patients with renal or hepatic insufficiency.

Insufficient Data for Recommendation. Current data are insufficient to recommend a number of other combinations that are under investigation, such as triple or quadruple class regimens (i.e., NRTI + NNRTI + PI or NRTI + NNRTI + PI + FI combinations); NRTI-sparing regimens such as two drug combinations containing only dual full-dose PIs or PI + NNRTI combinations; regimens containing FI as part of initial therapy; 4-NRTI regimens; regimens containing five or more active agents; and other novel strategies in treatment-naïve patients.

Not Recommended Therapies. A list of agents or components not recommended for initial treatment can be found in **Table 8**. Some agents or components not generally recommended for use, due to lack of potency or potential serious safety concerns, are listed in **Table 9**.

NNRTI–Based Regimens (1-NNRTI + 2-NRTIs)

Panel's Recommendations:

- ***Preferred NNRTI-Based Regimens:***
  - ***Efavirenz + (zidovudine or tenofovir) + (lamivudine or emtricitabine) (except during first trimester of pregnancy or in women with high pregnancy potential*) (AII)***
- ***Alternative NNRTI-Based Regimens:***
  - ***Efavirenz + (didanosine or abacavir or stavudine) + (lamivudine or emtricitabine) (except during pregnancy, particularly the first trimester, or in women with high pregnancy potential*) (BII) or***
  - ***Nevirapine-based regimens may be used as an alternative in adult females with CD4$^+$ T cell counts ≤250 cells/mm^3 and adult males with CD4$^+$ T cell counts ≤400 cells/mm^3 (BII).***

The Panel does not recommend the following NNRTIs as initial therapy:

- ***Delavirdine – due to inferior antiretroviral potency and three times daily dosing (DII)***
- ***Nevirapine for adult females with CD4$^+$ T cell counts >250 cells/mm^3 and adult males with CD4$^+$ T cell counts >400 cells/mm^3 unless the benefit clearly outweighs the risk (DI)***

**** Women with high pregnancy potential are those who are trying to conceive or who are not using effective and consistent contraception.***

Summary: NNRTI-based Regimens

Three NNRTIs (namely, delavirdine, efavirenz, and nevirapine) are currently marketed for use.

NNRTI-based regimens are commonly prescribed as initial therapy for treatment-naïve patients. In general, these regimens have the advantage of lower pill burden as compared to most of the PI-based regimens. Use of NNRTI-based regimens as initial therapy can preserve the PIs for later use, reducing or delaying patient exposure to some of the adverse effects more commonly associated with PIs. The major disadvantage of currently available NNRTIs is their low genetic barrier for development of resistance. These agents only require a single mutation to confer resistance, and cross resistance often develops across the entire class. As a result, patients who fail this initial regimen may lose the utility of other NNRTIs and/or may transmit NNRTI-resistant virus to others.

Based on clinical trial results and safety data, the Panel recommends the use of efavirenz as the preferred NNRTI as part of initial antiretroviral therapy **(AII)**. The exception is during pregnancy (especially during the first trimester) or in women who are planning to conceive or women who are not using effective and consistent contraception.

Nevirapine may be used as an alternative to efavirenz for the initial NNRTI-based regimen in adult females with pre-treatment CD4$^+$ T cell counts ≤250 cells/mm^3 or adult males with pre-treatment CD4$^+$ T cell counts ≤400 cells/mm^3. **(BII)** Symptomatic, sometimes serious or life-threatening hepatic events were observed with much higher frequency in women with pre-treatment CD4$^+$ T cell counts >250/mm^3 and men with pre-treatment CD4$^+$ T cell counts >400/mm^3; nevirapine should be used in these patients only if the benefit clearly outweighs the risk. Close monitoring for elevated liver enzymes and skin rash should be undertaken for all patients during the first 18 weeks of nevirapine therapy.

Among these three agents, delavirdine appears to have the least potent antiviral activity. As such, it is not recommended as part of an initial regimen. **(DII)**

Following is a more detailed discussion of recommendations for preferred and alternate NNRTI-based regimens for initial therapy.

Efavirenz as Preferred NNRTI (AII). Randomized, controlled trials and cohort studies in treatment-naïve patients have all demonstrated superior or similar viral suppression in the efavirenz-treated patients compared to other regimens. Specifically, these studies compared efavirenz + 2 NRTIs with various PI-based *[49-51]*. nevirapine-based *[52, 53]*, or triple NRTI-based *[54, 55]* regimens in treatment-naïve patients. The 2NN trial was the first randomized controlled trial comparing efavirenz and nevirapine. Although not statistically significant, the results showed less treatment failure (as defined by virologic failure, disease progression or death, or therapy change) in the efavirenz arm when compared to the nevirapine arm *[52]*.

Two major limitations of efavirenz are its common central nervous system side effects (which usually resolve over a few weeks) and its potential teratogenic effect on the unborn fetus. In animal reproductive studies, efavirenz was found to cause major central nervous system congenital anomalies in non-human primates at drug exposure levels similar to those achieved in humans *[56]*. At least four cases of neural tube defects in human newborns, where mothers were exposed to efavirenz during first trimester of pregnancy have been identified *[57, 58]*.The relative risk of teratogenicity of efavirenz in humans is unclear.

The most experience with efavirenz, demonstrating good virologic responses, has been shown in combination with 2-NRTI backbones of lamivudine plus zidovudine, tenofovir, stavudine, abacavir, or didanosine. Emtricitabine can be used in place of lamivudine in any of these regimens.

Nevirapine as Alternative NNRTI (BII). In the 2NN trial, the proportion of patients with virologic suppression (defined as HIV-RNA <50 copies/mL) was not significantly different between the efavirenz and nevirapine twice daily arms (70% and 65.4% respectively) *[52]*. However, two deaths were attributed to nevirapine use. One was due to fulminant hepatitis, and one was due to staphylococcal sepsis as a complication of Stevens-Johnson Syndrome.

Symptomatic, serious, and even fatal hepatic events associated with nevirapine use have been observed in clinical trials and post-marketing reports. These events generally occur within the first few weeks of treatment. In addition to elevated serum transaminases, approximately half of the patients also develop skin rash, with or without fever or flu-like symptoms. Women with higher $CD4^+$ T cell counts appear to be at highest risk. In a recent analysis, a 12-fold higher incidence of symptomatic hepatic events was seen in women (including pregnant women) with $CD4^+$ T cell counts of >250 cells/mm^3 at the time of nevirapine initiation when compared to women with $CD4^+$ T cell counts $\leq$250 cells/mm^3 (11.0% vs. 0.9%). An increased risk was also seen in men with pre-nevirapine $CD4^+$ T cell counts >400 cells/mm^3 when compared to men with pre-nevirapine $CD4^+$ T cell counts $\leq$400 cells/mm^3 (6.3% vs. 1.2%). Most of these patients had no identifiable underlying hepatic abnormalities. In some cases, hepatic injuries continued to progress despite discontinuation of nevirapine *[59, 60]*. Symptomatic hepatic events have not been reported with single doses of nevirapine given to mothers or infants for prevention of perinatal HIV infection.

Based on the safety data described, the Panel recommends that nevirapine may be used as an alternative to efavirenz in adult female patients with pre-treatment $CD4^+$ T cell counts $\leq$250 cells/mm^3 or adult male patients with $CD4^+$ T cell counts $\leq$400 cells/mm^3. **(BII)** In female patients with $CD4^+$ T cell counts >250 cells/mm^3 or male patients with $CD4^+$ T cell counts >400 cells/mm^3, nevirapine should not be initiated unless the benefit clearly outweighs the risk. **(DI)**

When starting nevirapine, a 14-day lead-in period at a dose of 200mg once daily should be prescribed before increasing to the maintenance dose of 200mg twice daily. Serum transaminases should be obtained at baseline, prior to and two weeks after dose escalation, then monthly for the first 18 weeks. Clinical and laboratory parameters should be assessed at each visit. More detailed recommendations on the management of nevirapine-associated hepatic events can be found in **Table 16a**.

PI-Based Regimens (1 or 2 PIs + 2 NRTIs)

Panel's Recommendations:

Preferred PI-based regimens

- ***Lopinavir/ritonavir + zidovudine + (lamivudine or emtricitabine) as preferred PI-based regimens (AII).***

Alternative PI-based regimens may include:

- ***Atazanavir* (BII), fosamprenavir(BII), ritonavir-boosted** fosamprenavir(BII), ritonavir-boosted** indinavir (BII), nelfinavir(CII), or ritonavir-boosted** saquinavir (BII) – all used in combination with (zidovudine or stavudine or tenofovir* or abacavir or didanosine) + (lamivudine or emtricitabine)***
- ***Lopinavir/ritonavir + (abacavir or stavudine or tenofovir or didanosine) + (lamivudine or emtricitabine) (BII)***

The Panel does not recommend the following PIs as initial therapy (DIII):

- *Amprenavir (boosted or unboosted) – due to high pill burden*
- *Unboosted indinavir – due to inconvenient three times daily dosing and need to take on an empty stomach or a light meal*
- *Ritonavir as sole PI – due to high incidence of gastrointestinal intolerance*
- *Unboosted saquinavir (hard gel or soft gel capsule) – due to poor oral bioavailability, three times daily dosing, and high pill burden*

* *ritonavir 100mg per day is recommended when tenofovir is used with atazanavir.*

** *ritonavir at daily doses of 100-400mg used as a pharmacokinetic-booster*

Summary: PI-Based Regimens

PI-based regimens (1or 2 PIs + 2 NRTIs) revolutionized the treatment of HIV infection, leading to sustained viral suppression, improved immunologic function, and prolonged patient survival. Since their inception in the mid-1990s, much has been learned about their efficacy as well as some short term and long term adverse effects.

To date, eight PIs have been approved for use in the United States. Each agent has its own unique characteristics based on its clinical efficacy, adverse effect profile, and pharmacokinetic properties. The characteristics, advantages, and disadvantages of each PI can be found in **Tables 6** & **12**. In selecting a PI-based regimen for a treatment-naïve patient, factors such as dosing frequency, food and fluid requirements, pill burden, drug interaction potential, baseline hepatic function, and toxicity profile should be taken into consideration. A number of metabolic abnormalities,

including dyslipidemia, fat maldistribution, and insulin resistance, have been associated with PI use. The eight PIs differ in their propensity to cause these metabolic complications. At this time, the extent to which these complications may result in adverse long term consequences, such as increased cardiac events in chronically-infected patients, is unknown.

The potent inhibitory effect of ritonavir on the cytochrome P450 3A4 isoenzyme has allowed the addition of low dose ritonavir to other PIs as a "pharmacokinetic booster" to increase drug exposure and prolong serum half-lives of the active PIs. This allows for reduced dosing frequency and pill burden, and in the case of indinavir, the addition of low dose ritonavir eliminates the need for food restrictions. All these advantages may improve overall adherence to the regimen. The increased trough concentration (C_{min}) may improve the antiretroviral activity of the active PIs, which is most beneficial in cases where the patient harbors HIV-1 strains with reduced susceptibility to the PI *[61-63]*. The major drawbacks associated with this strategy are the potential for increased risk of hyperlipidemia and a greater potential of drug-drug interactions from the addition of ritonavir.

The Panel considers lopinavir/ritonavir as the preferred PI for the treatment-naive patient **(AII)**. Discussed below, this recommendation is based on clinical trial data for virologic potency, barrier for virologic resistance, and patient tolerance. However, there are limited data on the comparative efficacy of lopinavir/ritonavir with other ritonavir-boosted regimens. Alternative PIs are listed in **Table 5** and discussed below in greater detail and may include atazanavir **(BII)**, fosamprenavir **(BII)**, or nelfinavir **(CII)** as sole PI, or ritonavir-boosted fosamprenavir **(BII)**, indinavir **(BII)**, or saquinavir **(BII)**.

Lopinavir/ritonavir (co-formulated) as Preferred PI (AII). In various clinical trials, regimens containing ritonavir-boosted lopinavir with 2-NRTIs have been found to have potent virologic activities in treatment-naïve patients and in some patients who experienced treatment failure. In a randomized, placebo-controlled trial comparing lopinavir/ritonavir to nelfinavir (each with stavudine and lamivudine) in 653 patients, lopinavir/ritonavir was superior to nelfinavir in maintaining a viral load <400 copies/mL through 48 weeks (84% versus 66% with persistent virologic response through 48 weeks; hazard ratio = 2.0; 95% CI: 1.5 to 2.7) *[64]*. Overall adverse event rates and study discontinuation rates due to adverse events were similar in the two groups. No evidence of genotypic or phenotypic resistance to PIs was detected in the 51 lopinavir/ritonavir-treated patients with >400 copies/mL at up to 48 weeks follow-up. In contrast, D30N and/or L90M mutations were detected in 43 of 96 (45%) of nelfinavir-treated patients *[65]*. A five-year follow-up study of lopinavir-ritonavir showed sustained virologic suppression in patients who were maintained on the original assigned regimen *[66]*. The major adverse effects of lopinavir/ritonavir are gastrointestinal intolerance (particularly diarrhea) and hyperlipidemia, especially hypertriglyceridemia, necessitating pharmacologic management in some patients.

In a pilot study, it was noted that lopinavir serum concentrations may be significantly reduced during the third trimester of pregnancy *[67]*. The implication of this pharmacokinetic change on virologic outcome in the mother, and the risk of perinatal HIV transmission, remains unknown. Further studies are underway to examine the pharmacologic and clinical efficacy of increased dosing of lopinavir/ritonavir in this population.

Alternative PI-based regimens (in alphabetical order)

Atazanavir (BII). Atazanavir is an azapeptide PI with the advantages of once daily dosing and less adverse effect on lipid profiles than other available PIs. Three pre-marketing trials compared atazanavir-based combination regimens to either nelfinavir- or efavirenz-based regimens. These studies established similar virologic efficacy of atazanavir 400 mg once daily and both comparator treatment groups in antiretroviral-naïve patients after 48 weeks of therapy *[51, 68, 69]*. The main adverse effect associated with atazanavir use is indirect hyperbilirubinemia with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Atazanavir may be chosen as initial therapy for patients where a once daily regimen is desired and in patients with underlying risk factors where hyperlipidemia may be undesirable. Although ritonavir-boosted atazanavir has been used in patients who failed other PI-based regimens, its long term efficacy and safety in treatment-naïve patients has not been established. Until clinical trial results in treatment-naïve patients are available, there is currently no recommendation for use of a ritonavir-boosted atazanavir regimen in these patients. The exception is for patients who receive concomitant therapy with tenofovir or efavirenz, where ritonavir-boosting is recommended to overcome the pharmacokinetic interactions between atazanavir and these two agents.

Fosamprenavir and Ritonavir-boosted Fosamprenavir (BII). Fosamprenavir, a prodrug of amprenavir, allows for reduced pill burden, when compared to amprenavir, when used either as a sole PI or in conjunction with ritonavir. The addition of ritonavir to fosamprenavir prolongs its half-life, making once daily dosing possible in treatment-naïve patients. Two pre-marketing trials compared fosamprenavir or ritonavir-boosted fosamprenavir to nelfinavir *[70, 71]*. In the first trial, more patients randomized to fosamprenavir achieved viral suppression at 48 weeks than those assigned to nelfinavir, with greater differences seen in those patients with pre-treatment viral load >100,000 copies/mL *[70]*.

Ritonavir-boosted Indinavir (BII). The inhibitory effect of ritonavir prolongs the half-life and increases the C_{min} of indinavir *[72]*. This combination allows for twice daily dosing and eliminates the meal restrictions required when using unboosted indinavir. Despite its potent antiviral activities, adherence to indinavir when used as a sole PI is hindered by its inconvenient dosing schedule of three times daily dosing and required administration on an empty stomach or with light meal. Ritonavir-boosted indinavir has been shown to have comparable virologic response when compared to indinavir used as a sole PI *[73]*. The higher concentration of indinavir in the presence of ritonavir may predispose some patients to a higher frequency of crystalluria and/or nephrolithiasis *[74]*. Hence, patients should be advised to maintain adequate oral hydration (at least 1.5 liter of non-caffeinated fluid per day) when taking the ritonavir-boosted indinavir regimen.

Nelfinavir (CII). Nelfinavir is generally well tolerated except for diarrhea, which occurs in 30-40% of patients. Clinical trials have found nelfinavir to have a virologic effect similar to atazanavir *[68]* and ritonavir-boosted fosamprenavir *[72]*, but inferior to lopinavir/ritonavir *[64]*, fosamprenavir *[70]*, and efavirenz *[50]* in terms of virologic suppression at 48 weeks. Genotypic resistance with the selection of the D30N mutation is often seen in patients with virologic rebound *[65, 75]*. The presence of D30N mutation alone does not confer resistance to other PIs. A smaller percentage of patients may select the multiple PI resistant L90M mutation upon virologic rebound, which may limit the choice of PIs as future options *[65, 75]*. Of note, among the currently marketed PIs, nelfinavir has the most safety and pharmacokinetic data in pregnant women. The approved dose of 1,250mg twice daily produces similar pharmacokinetic profiles during the third trimester of pregnancy as compared to non-pregnant state *[76]*. Thus no dosage adjustment is deemed necessary when nelfinavir is used during pregnancy.

Ritonavir-boosted Saquinavir (BII). The low oral bioavailability of both saquinavir hard gel and soft gel capsules makes them less desirable when used as a sole PI. Ritonavir inhibits CYP 3A4 isoenzymes in both the intestine and the liver. Adding low dose ritonavir to saquinavir results in a significant increase in oral bioavailability and delay in saquinavir clearance. This leads to a higher peak saquinavir concentration, longer elimination half-life, and higher pre-dose concentration. In a comparative study where a substantial number of patients were PI-naïve, low dose ritonavir (100 mg twice daily) boosted saquinavir (1,000 mg twice daily) was found to have a similar virologic response, but better toleration, than the ritonavir/indinavir combination *[61]*. In the presence of low dose ritonavir, the overall drug exposure of saquinavir is similar regardless of whether the soft gel or hard gel capsule formulation is used. The hard gel capsule, however, appears to have much better gastrointestinal tolerance than the soft gel preparation, and is preferred by some clinicians and patients *[77, 78]*.

Triple NRTI Regimens

Panel's Recommendations:

- ***A 3-NRTI regimen consisting of abacavir + zidovudine + lamivudine should only be used when a preferred or alternative NNRTI-based or PI-based regimen cannot or should not be used as first-line therapy (e.g. for important drug-drug interactions) in the treatment-naïve patient. (CII).***

The Panel DOES NOT RECOMMEND the use of the following 3-NRTI regimens as sole antiretroviral combination at any time:

- ***abacavir + tenofovir + lamivudine (EII)***
- ***didanosine + tenofovir + lamivudine (EII)***

Summary: Triple NRTI Regimens

A 3-NRTI combination regimen has multiple advantages: fewer drug-drug interactions, low pill burden, availability of a fixed dose combination (zidovudine + lamivudine + abacavir combined as Trizivir®), and sparing patients from potential side effects seen with PIs and NNRTIs. However, several clinical trials have shown that studied 3-NRTI regimens have less potent virologic activity than comparator NNRTI- or PI-based regimens. More importantly, several randomized and pilot studies of

different 3-NRTI regimens have reported virologic failure or early virologic non-response which led to early termination of the trials.

The Panel recommends that a triple NRTI regimen consisting of zidovudine + lamivudine + abacavir should only be used when a preferred or an alternative NNRTI-based or a PI-based regimen may be less desirable due to concerns over toxicities, drug interactions, or regimen complexity **(CII)**. Moreover, a 3-NRTI combination containing tenofovir + abacavir + lamivudine or tenofovir + didanosine + lamivudine should not be used as a triple NRTI regimen at any time **(EII**).

Following is discussion of 3-NRTI regimens studied in clinical trials.

Zidovudine + Lamivudine + Abacavir as alternative to the recommended PI or NNRTI regimens (CII). Zidovudine + lamivudine + abacavir is the only 3-NRTI combination where randomized, controlled trials showed favorable virologic outcomes, when compared to PI regimens. Comparisons, however, were not favorable to NNRTI-based regimens.

Two trials compared zidovudine + lamivudine + abacavir to zidovudine + lamivudine + indinavir *[79, 80]* in treatment-naïve patients. In the CNAAB3005 study, the overall virologic responses at 48 weeks for the 3-NRTI-based and PI-based regimens were equivalent (51% of patients with HIV-RNA <400 copies/mL in each group; and 40% of patients in the abacavir arm versus 46% in the indinavir arm had HIV-RNA <50 copies/mL). However, patients randomized to the abacavir arm who had high baseline plasma HIV-RNA >100,000 copies/mL were found to have significantly inferior virological response than patients in the indinavir arm (31% versus 45% with HIV-RNA <50 copies/mL; 95% CI: -27% to 0%) *[79]*.

In another study, the 3-NRTI arm compared unfavorably to two efavirenz-based arms. ACTG A5095 was a randomized, double-blinded, placebo-controlled trial comparing three PI-sparing regimens in treatment-naïve patients (zidovudine + lamivudine + abacavir versus zidovudine + lamivudine + efavirenz versus zidovudine + lamivudine + abacavir + efavirenz). Virologic failure (defined as a confirmed HIV-RNA value >200 copies/mL at least four months after starting treatment) was seen in 21% of patients in the 3-NRTI arm compared to 10% in the pooled efavirenz arms after 32 weeks of therapy ($p<0.001$). Through week 48, the proportion of patients with HIV RNA <200 copies/mL by intent-to-treat analysis was 74% (95% CI 65-83%) in the zidovudine + lamivudine + abacavir arm versus 89% (95% CI 84-92%) in the combined efavirenz arms. These differences were evident regardless of whether the baseline HIV-RNA levels were greater than or less than 100,000 copies/mL. These results led to the premature closure of the 3-NRTI arm of the study. Efavirenz-based therapy was also superior in patients who achieved virologic suppression (i.e., defined in this study as <200 copies/mL at least once) and in patients who reported 100% adherence to their regimen *[54]*.

Other 3-NRTI Trials Demonstrating Inferior or Poor Viral Responses. Three other studies compared 3-NRTI regimens to PI- or NNRTI-based regimens. They included stavudine + didanosine + lamivudine *[81]*, stavudine + lamivudine + abacavir *[82]*, and didanosine + stavudine + abacavir *[83]*. The 3-NRTI based regimens were all found to have inferior virologic responses than their comparators.

Two recent studies of different 3-NRTI regimens reported poor virologic responses and selection of major NRTI-resistant mutations. In one randomized trial, a once daily 3-NRTI combination of tenofovir abacavir + lamivudine was compared to an NNRTI-based regimen containing efavirenz + abacavir + lamivudine. A substantially higher rate of early virologic non-response was observed in the 3-NRTI arm. Early virologic non-response was defined as either a 1-log increase of HIV-RNA above nadir or failure to achieve a 2-log decline from baseline at week 8. For subjects who received >12 weeks of therapy, 49% in the 3-NRTI arm versus 5% in the efavirenz arm met the definition of viral non-responders. Genotypic analysis of HIV isolates from 14 non-responders in the 3-NRTI arm revealed the presence of a M184V mutation in all 14 isolates. Eight of the 14 isolates had K65R mutation, which may result in reduced susceptibility to tenofovir, abacavir, lamivudine, or emtricitabine. These findings led to the termination of this study *[55]*. In a single-center pilot study using a once daily regimen consisting of tenofovir + didanosine + lamivudine, 91% of the patients were considered to have virologic failure (defined as <2 log reduction of HIV-RNA by week 12). The M184I/V mutations were detected in 20 of 21 (95%) of the patients, and 50% of these patients also had K65R mutation, which confers resistance to tenofovir *[84]*.

Selection of Dual Nucleoside "Backbone" as Part of Initial Combination Therapy

Panel's Recommendations:

- ***(Zidovudine or tenofovir) + (lamivudine or emtricitabine) as the 2-NRTI backbone of choice as part of some combination regimens.*** *(see* ***Table 5****)* ***(AII)***
- ***(Stavudine or didanosine or abacavir) + (lamivudine or emtricitabine) may be used as alternative 2-NRTI backbone combinations.(BII)***

Eight nucleoside/nucleotide HIV-1 reverse transcriptase inhibitors (NRTIs) are currently available in the U.S. Dual nucleoside combinations are by far the most commonly utilized "backbone" of combination antiretroviral regimens upon which the addition of a PI(s) and/or NNRTI confers potency for long-term efficacy. The choice of the specific 2 NRTIs is made on the basis of potency and durability, short-and long-term toxicities, drug-drug interaction potential, the propensity to select for resistance mutations, and dosing convenience.

Highest regimen simplicity is possible with once-daily drugs (currently including abacavir, didanosine, emtricitabine, lamivudine, and tenofovir) or with fixed dosage combination products (such as zidovudine + lamivudine, abacavir + lamivudine, or tenofovir + emtricitabine). Until recently, most dual nucleoside regimens included one thymidine-based drug, specifically zidovudine or stavudine. Both of these drugs, when used along with lamivudine as 2-NRTI backbones of potent combination regimens, have documented durable virologic potency for over five years *[66, 85]*. It may be necessary to prescribe alternative NRTIs for some patients because of side effects of these agents, such as bone marrow suppression with zidovudine and the increasingly reported toxicities including lipoatrophy and symptomatic lactic acidosis with stavudine *[86, 87]*. More recent trials have shown promising results with dual NRTI backbones that include tenofovir *[88]*, didanosine *[89]*, or abacavir *[82, 90]* along with a second drug, usually lamivudine. Lamivudine is a common second agent in these combinations given its near-absent toxicity and the capacity of maintenance of susceptibility to thymidine analogs despite high-level resistance following a single M184V mutation *[91]*.

Zidovudine + lamivudine versus didanosine + stavudine. The ACTG 384 study examined the virologic efficacy and safety of two different NRTI backbones, namely, zidovudine + lamivudine versus didanosine + stavudine when used in combination with either efavirenz or nelfinavir alone or in combination. Overall, in this study, an initial regimen consisting of efavirenz + zidovudine + lamivudine resulted in best virologic response. In evaluating the toxicity data, the time to severe or dose-modifying toxicities was shorter in those patients randomized to didanosine + stavudine than those randomized to receive zidovudine + lamivudine *[50]*.

Tenofovir + lamivudine versus stavudine + lamivudine. Both the tenofovir + lamivudine combination and stavudine + lamivudine combination are highly and durably effective when used in combination with efavirenz, with data up to 144 weeks *[88]*. In this study, patients randomized to the stavudine + lamivudine arm experienced more adverse effects including peripheral neuropathy and hyperlipidemia.

Abacavir + lamivudine versus zidovudine + lamivudine. In a comparative trial of abacavir + lamivudine versus zidovudine + lamivudine (both combined with efavirenz), patients from both arms achieved similar virologic responses and higher $CD4^+$ T lymphocyte response at 48 weeks *[90]*. However, the potential for systemic hypersensitivity reaction (5-8%) does not warrant placing abacavir + lamivudine as a preferred 2-NRTI backbone at this time. The recent approval of the fixed dose combination of once daily abacavir + lamivudine therapy further simplify a regimen containing this combination. Of note, in the CNA 30021 study, comparing once versus twice daily dosing of abacavir in treatment-naïve patients, the incidence of severe hypersensitivity reaction was reported to be significantly higher in the once daily arm as compared to the twice daily arm (5% versus 2%) *[92]*.

Emtricitabine. Emtricitabine is a fluorinated analog of lamivudine with a long intracellular half-life allowing for once daily dosing. Like lamivudine, the M184V mutation is commonly seen after initiation of therapy with emtricitabine. It appears to have similar efficacy as lamivudine when used as part of a backbone NRTI *[93]*.

Zalcitabine. An early nucleoside analog, zalcitabine, is less convenient (given three times daily) and more toxic and should rarely if ever be used.

NRTIs and Hepatitis B. Three of the current NRTIs, emtricitabine, lamivudine, and tenofovir, all have potent activities against hepatitis B virus. Lamivudine is currently approved as a treatment for hepatitis B

infection. It is important to note that patients with hepatitis B and HIV co-infection may be at risk of acute exacerbation of hepatitis upon discontinuation of these drugs *[94, 95]*. Thus, patients with hepatitis B co-infection should be monitored closely for clinical or chemical hepatitis if these drugs are to be discontinued.

NRTIs that should not be used in combination. Certain members of this drug class should not be used in combination. These combinations are discussed in "**Antiretroviral Regimens or Components That Should Not Be Offered at Any Time**."

WHAT NOT TO USE: Antiretrovirals that Should Not Be Offered At Any Time (Table 9)

Some antiretroviral regimens or components are not recommended for HIV-1 infected patients due to suboptimal antiviral potency, unacceptable toxicity, or pharmacological concerns. These are summarized below.

Antiretroviral Regimens Not Recommended

Monotherapy (EII). Single antiretroviral drug therapy does not demonstrate potent and sustained antiviral activity and should not be used.

The rare exception, though controversial, is the use of zidovudine monotherapy to prevent perinatal HIV-1 transmission in a woman who does not meet clinical, immunologic, or virologic criteria for initiation of therapy and who has an HIV RNA <1,000 copies/mL *[96, 97]* **(DIII)**. Most clinicians, however, prefer to use a combination regimen in the pregnant woman for the management of both the mother's HIV infection and in the prevention of perinatal transmission.

The efficacy of zidovudine monotherapy during pregnancy to reduce perinatal transmission was identified in the PACTG 076 study. The goal of therapy in this case is solely to prevent perinatal HIV-1 transmission. Zidovudine monotherapy should be discontinued immediately after delivery. Combination antiretroviral therapy should be initiated post-partum if indicated. More information regarding management of the pregnant HIV patients can be found in "**Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States**" at **http://aidsinfo.nih.gov**.

Dual nucleoside regimens (DII). These regimens are not recommended because they have not demonstrated potent and sustained antiviral activity as compared to three-drug combination regimens *[98]*. For patients previously initiated on this treatment who have achieved sustained viral suppression, it is reasonable to continue on this therapy or to add a PI or NNRTI to this regimen **(DIII)**. If the patient is to stay on a 2-NRTI regimen, the plan should be to change to a three or more drug combination if viral rebound occurs. (See **Managing the Treatment Experienced Patient: Assessment of Antiretroviral Treatment Failure and Changing Therapy**.)

3-NRTI regimen of abacavir + tenofovir + lamivudine (or emtricitabine) (EII). In a randomized trial for treatment naïve patients, those randomized to a regimen consisting of abacavir + tenofovir + lamivudine had a significantly higher rate of "early virologic non-response" when compared to patients treated with efavirenz + abacavir + lamivudine *[55]*. This combination should not be used as a 3-NRTI regimen in any patient.

3-NRTI regimen of didanosine + tenofovir + lamivudine (or emtricitabine) (EII). In a small pilot study, a high rate (91%) of virologic failure (defined as <2 log reduction of HIV-RNA by week 12) was seen in treatment-naïve patients initiated on this 3-NRTI regimen *[84]*. This combination should not be used as a 3-NRTI regimen in any patient.

Antiretroviral Components Not Recommended *(in alphabetical order)*

Amprenavir oral solution in pregnant women; children <4 years of age; patients with renal or hepatic failure; and patients treated with metronidazole or disulfiram (EII). Due to the large amount of propylene glycol used as an excipient, which may be toxic to high risk patients.

Amprenavir + fosamprenavir (EIII). Fosamprenavir is the prodrug of amprenavir. There is no additional benefit, and potential additive toxicities, when using these agents together.

Amprenavir oral solution + ritonavir oral solution (EIII). The large amount of propylene glycol used as a vehicle in amprenavir oral solution may compete with the ethanol (vehicle of oral ritonavir solution) for the same metabolic pathway for elimination. This may lead to accumulation of either one of the vehicles.

Atazanavir + indinavir (EIII). Both of these PIs can cause grade 3 to 4 hyperbilirubinemia and jaundice. Additive or worsening of these adverse effects may be possible when these agents are used concomitantly.

Didanosine + stavudine (EII). The combined use of didanosine and stavudine as a 2-NRTI backbone can result in a high incidence of toxicities, particularly peripheral neuropathy, pancreatitis, and lactic acidosis *[50, 87, 99]*.This combination has been implicated in several deaths in HIV-1 infected pregnant women secondary to severe lactic acidosis with or without hepatic steatosis and pancreatitis *[100]*. In general, a combination containing didanosine and stavudine should be avoided unless other 2-NRTI combinations have failed or have caused unacceptable toxicities, and where potential benefits outweigh the risks of toxicities **(DIII)**.

Didanosine + zalcitabine or stavudine + zalcitabine (EII). These combinations are contraindicated due to increased rates and severity of peripheral neuropathy *[101, 102]*.

Efavirenz in first trimester of pregnancy and women with significant childbearing potential (EIII). Efavirenz use was associated with significant teratogenic effects in primates at drug exposures similar to those representing human exposure. Several cases of congenital anomalies have been reported after early human gestational exposure to efavirenz *[57, 58]*. Efavirenz should be avoided in pregnancy, particularly during the first trimester, and in women who are trying to conceive or who are not using effective and consistent contraception. If no other antiretroviral options are available in the woman who is pregnant or at risk for becoming pregnant, consultation should be obtained with a clinician who has expertise in both HIV and pregnancy.

Emtricitabine + lamivudine (EIII). Both of these drugs have similar resistance profiles and have minimal additive antiviral activity.

Lamivudine + zalcitabine (EII). *In vitro* data showed that these two agents may inhibit intracellular phosphorylation of one another, resulting in decreased triphosphate concentration and antiretroviral activities.

Initiation of nevirapine – for women with CD4$^+$ T cell counts >250 cells/mm^3 or men with CD4$^+$ T cell counts >400 cells/mm^3 (DI) Higher risk of symptomatic, including serious and life-threatening, hepatic events have been observed in these patient groups. Nevirapine should be initiated only if the benefit clearly outweighs the risk.

Saquinavir hard gel capsule (Invirase®) as a single PI (EII). The hard gel formulation of saquinavir is contraindicated as a single PI due to poor bioavailability that averages only 4% even with a concurrent high-fat meal.

Stavudine + zidovudine (EII). Combination regimens containing these two NRTIs should be avoided due to the demonstration of antagonism *in vitro [103]* and *in vivo [104]*.

LIMITATIONS TO TREATMENT SAFETY AND EFFICACY

A number of factors may influence the safety and efficacy of antiretroviral therapy in individual patients. Examples include, but are not limited to: non-adherence to therapy, adverse drug reactions, drug-drug interactions, and development of drug resistance. Each is discussed below. Drug resistance, which has become a major reason for treatment failure, is discussed in greater detail in the section, **Management of the Treatment-Experienced Patient**.

Adherence to Antiretroviral Therapy

HIV viral suppression, reduced rates of resistance *[105, 106]*, and improved survival *[107]* have been correlated with high rates of adherence to antiretroviral therapy. According to recommendations in these guidelines, many patients will be initiating, or have initiated therapy, when asymptomatic. This treatment must be maintained for a lifetime, which is an even greater challenge, given that the efficacy of therapy has increased life expectancy for people living with HIV. A commitment to lifelong therapy requires a commitment of both the patient and the health care team.

Measurement of adherence is imperfect and currently lacks established standards. While patient self-reporting of complete adherence has been an unreliable predictor of adherence, a patient's estimate of suboptimal adherence is a strong predictor and should be taken seriously *[108, 109]*. The clinician's estimate of the likelihood of a patient's adherence has also been proven to be an unreliable predictor of patient adherence *[110]*.

Regimen complexity and pill burden were the most common reasons for non-adherence when combination therapy was first introduced. A number of advances over the past several years have dramatically simplified many of the regimens. These guidelines note regimen simplicity as well as potency in their recommendations.

Adherence to HIV medications has been well studied. However, the determinants, measurements, and interventions to improve adherence to antiretroviral therapies are insufficiently characterized and understood. Additional research in this topic continues to be needed. Various strategies can be used and have been associated with improvements in adherence. These strategies are listed in **Table 15**.

Clinicians seeking additional information are referred to the **http://www.aidsinfo.nih.gov/guidelines/adherence/AH_102904.html** Web site.

Assessing and Monitoring Adherence. The first principle to success is to negotiate an understandable treatment plan to which the patient can commit *[111, 112]*. Trusting relationships between the patient, clinician, and health care team (including case managers, social workers, pharmacists, and others) are essential for optimal adherence. Therefore, establishing a trusting relationship over time is critical to good communication that will facilitate quality treatment outcomes. This often requires several office visits and the patience of clinicians, before therapy can be started.

Prior to writing the first prescriptions, clinicians need to assess the patient's readiness to take medication.

Patients need to understand that the first regimen is the best chance for long-term success *[113]*. Resources need to be identified to assist in success. Interventions can also assist with identifying adherence education needs and strategies for each patient. Examples include adherence support groups, adherence counselors, behavioral interventions *[114]*, using community-based case managers and peer educators.

Lastly, and most importantly, adherence counseling and assessment should be done at each clinical encounter. Early detection of non-adherence and prompt intervention can greatly reduce the chance of virologic failure and development viral resistance.

Adverse Effects of Antiretroviral Agents

Adverse effects have been reported with virtually all antiretroviral drugs and are among the most common reasons for switching or discontinuation of therapy and for medication non-adherence *[115]*. In a review of over 1,000 patients in a Swiss HIV cohort that received combination antiretroviral therapy, 47% and 27% of the patients were reported to have clinical and laboratory adverse events, respectively *[116]*. Whereas some common adverse effects were identified during pre-marketing clinical trials, some less frequent toxicities (such as lactic acidosis with hepatic steatosis and progressive ascending neuromuscular weakness syndrome) and some long term complications (such as dyslipidemia and fat maldistribution) were not recognized until after the drugs had been used in a larger population for a longer duration. In rare cases, some events may result in significant morbidity and even mortality.

Several factors may predispose individuals to certain antiretroviral-associated adverse events. For example, female patients seem to have a higher propensity of developing Stevens-Johnson Syndrome and symptomatic hepatic events from nevirapine *[60, 117, 118]* or lactic acidosis from NRTIs *[119]*. Other factors may also contribute to the development of adverse events, such as: use of concomitant medications with overlapping and additive toxicities; co-morbid conditions that may increase risk of or exacerbate adverse effects (e.g. alcoholism *[120]*, or hepatitis B or hepatitis C co-infection may increase risk of hepatotoxicity *[121-123]*); or drug-drug interactions that may lead to an increase in dose-related toxicities (e.g., concomitant use of hydroxyurea *[124, 125]* or ribavirin *[126-128]* with didanosine, increasing didanosine-associated toxicities).

While the therapeutic goals of antiretroviral therapy include achieving and maintaining viral suppression and improving patient immune function, one of the secondary goals should be to select a safe and effective regimen, taking into account individual patient underlying conditions, concomitant medications, and history of drug intolerance.

Information on adverse events is outlined in multiple tables in the guidelines:

1. **Tables 10-13** summarize common adverse effects of individual antiretroviral agents;
2. **Tables 16a-c** provide clinicians with a list of antiretroviral-associated adverse events, along with their common causative agents, estimated frequency of occurrence, symptom onset and clinical manifestations, potential preventive measures, and suggested management strategies. Adverse events of antiretroviral drugs are classified in these tables in the following categories, based on the acuity and severity of the presenting signs and symptoms:
   - Potentially life-threatening and serious toxicities;
   - Adverse effects that may lead to long-term consequences; and
   - Adverse effects presenting as clinical symptoms that may affect overall quality of life and/or may impact on overall medication adherence.
3. **Table 17** includes a list of overlapping toxicities of antiretroviral agents and other drugs commonly used in HIV patients.
4. **Table 18** lists "Black Box Warnings" found in the product labeling of antiretroviral drugs.

Drug Interactions

Potential drug-drug and/or drug-food interactions should be taken into consideration when selecting an antiretroviral regimen. A thorough review of current medications can help in designing a regimen that minimizes undesirable interactions. Moreover, review of drug interaction potential should be undertaken when any new drug, including over-the-counter agents, is added to an existing antiretroviral combination. **Tables 19-21b** list significant drug interactions with different antiretroviral agents and suggested recommendations on contraindication, dose modification, and alternative agents.

PI and NNRTI Drug Interactions. Most drug interactions with antiretrovirals are mediated through inhibition or induction of hepatic drug metabolism *[63]*. All PIs and NNRTIs are metabolized in the liver by the cytochrome P450 (CYP) system, particularly by the CYP3A4 isoenzyme. The list of drugs that may have significant interactions with PIs and/or NNRTIs is extensive and continuously expanding. Some examples of these drugs include medications that are commonly prescribed for HIV patients for non-HIV medical conditions, such as lipid-lowering agents (the "statins"), benzodiazepines, calcium channel blockers, immunosuppressants (such as cyclosporine, and tacrolimus), anticonvulsants, rifamycins, erectile dysfunction agents (such as sildenafil), ergot derivatives, azole antifungals, macrolides, oral contraceptive, and methadone. Unapproved therapies, such as St. John's Wort, can also cause negative interactions.

All PIs are substrates and inhibitors of CYP3A4, with ritonavir having the most pronounced, and saquinavir having the least, potent inhibitory effect. Some PIs are also inducers of certain CYP isoenzymes (e.g. amprenavir and ritonavir). The NNRTIs are also substrates of CYP3A4 and can act as an inducer (nevirapine), an inhibitor (delavirdine), or a mixed inducer and inhibitor (efavirenz). Thus, these antiretroviral agents can interact with each other in multiple ways and with other drugs commonly prescribed for other concomitant diseases.

For example, the use of a CYP3A4 substrate that has a narrow margin of safety in the presence of a potent CYP3A4 inhibitor may lead to markedly prolonged elimination half-life ($t_{1/2}$) and toxic drug accumulation. Avoidance of concomitant use or dose reduction of the affected drug, with close monitoring for dose-related toxicities, may be warranted.

The inhibitory effect of ritonavir (or delavirdine), however, can be beneficial when added to a PI, such as amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, or saquinavir *[129]*. Lower than therapeutic doses of ritonavir are commonly used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration (C_{min}) and prolong the $t_{1/2}$ of the active PIs *[130]*. The higher C_{min} allows for a greater C_{min}: IC50 ratio, reducing the chance for development of drug resistance as a result of suboptimal drug exposure; the longer $t_{1/2}$ allows for less frequent dosing, which may enhance medication adherence.

Co-administration of PIs or NNRTIs with a potent CYP3A4 inducer, on the other hand, may lead to suboptimal drug concentrations and reduced therapeutic effects of the antiretroviral agents. These drug combinations should be avoided. If this is not possible, close monitoring of plasma HIV-RNA, with or without antiretroviral dosage adjustment and/or therapeutic drug monitoring, may be warranted. For example, the rifamycins (rifampin, and, to a lesser extent rifabutin) are CYP3A4 inducers that can significantly reduce plasma concentrations of most PIs and NNRTIs *[131, 132]*. As rifabutin is a less potent inducer, it is generally considered a reasonable alternative to rifampin for the treatment of tuberculosis when it is used with a PI- or NNRTI-based regimen, despite wider experience with rifampin use *[133]*. **Table 20** lists dosage recommendations for concomitant use of rifamycins and other CYP3A4 inducers and PIs and NNRTIs.

NRTI Drug Interactions. Unlike PIs and NNRTIs, NRTIs do not undergo hepatic transformation through the CYP metabolic pathway. Some, however, do have other routes of hepatic metabolism. Significant pharmacodynamic interactions of NRTIs and other drugs have been reported. They include: increases in intracellular drug levels and toxicities when didanosine is used in combination with hydroxyurea *[134, 135]* or ribavirin *[128]*; additive bone marrow suppressive effects of zidovudine and ganciclovir *[136]*; and antagonism of intracellular phosphorylation with the combination of zidovudine and stavudine *[103]*. Pharmacokinetic interactions have also been reported. However, the mechanisms of some of these interactions are still unclear. Some such interactions include increases of didanosine concentrations in the presence of oral ganciclovir or tenofovir *[137, 138]*, and decreases in atazanavir concentration when it is co-administered with tenofovir *[139, 140]*. **Table 20** lists significant interactions with NRTIs.

Fusion Inhibitor Drug Interaction. The fusion inhibitor enfuvirtide is a 36 amino-acid peptide that does not enter human cells. It is expected to undergo

catabolism to its constituent amino acids with subsequent recycling of the amino acids in the body pool. No clinically significant drug-drug interaction has been identified with enfuvirtide to date.

UTILIZATION OF DRUG RESISTANCE TESTING IN CLINICAL PRACTICE

Panel's Recommendations:

- ***HIV drug resistance testing should be performed to assist in selecting active drugs when changing antiretroviral regimens in cases of virologic failure (BII).***
- ***Drug resistance testing should also be considered when managing suboptimal viral load reduction (BIII).***
- ***Drug resistance testing in the setting of virologic failure should be performed while the patient is taking his/her antiretroviral drugs, or immediately (i.e., within 4 weeks) after discontinuing therapy (BII).***
- ***If the decision is made to initiate therapy in a person with acute HIV infection, it is likely that resistance testing at baseline will optimize virologic response; this strategy should be considered (BIII).***
- ***Drug resistance testing at baseline in antiretroviral-naïve, chronically infected patients is an untested strategy. However, it may be reasonable to consider resistance testing when there is a significant probability that the patient was infected with a drug-resistance virus, i.e., if the patient is thought to have been infected by a person who was receiving antiretroviral drugs (CIII).***
- ***Drug resistance testing is not advised for persons with viral load <1,000 copies/mL, since amplification of the virus is unreliable (DIII).***

Genotypic and Phenotypic Resistance Assays

There are two types of resistance assays for use in assessing viral strains and selecting treatment strategies: genotypic and phenotypic assays.

Genotypic Assays. Genotyping assays detect drug resistance mutations that are present in the relevant viral genes. Certain genotyping assays involve sequencing of the entire reverse transcriptase and protease genes, whereas others use probes to detect selected mutations that are known to confer drug resistance. Genotypic assays can be performed rapidly, and results can be reported within 1-2 weeks of sample collection. Interpretation of test results requires knowledge of the mutations that are selected for by different antiretroviral drugs and of the potential for cross-resistance to other drugs conferred by certain mutations. The International AIDS Society-USA (IAS-USA) maintains a list of significant resistance-associated mutations in the reverse transcriptase, protease, and envelope genes (see **http://www.iasusa.org/resistance_mutations**). (Note that current commercially available tests do not detect resistance-associated mutations in the envelope gene.) Various techniques such as rules-based algorithms and *Virtual Phenotype* are now available to assist the provider in interpreting genotyping test results *[141-144]*. The benefit of consultation with specialists in HIV drug resistance has been demonstrated in clinical trials *[145]*. Clinicians are encouraged to consult a specialist in order to facilitate interpretation of genotyping results to help design an optimal new regimen.

Phenotypic Assays. Phenotyping assays measure a virus's ability to grow in different concentrations of antiretroviral drugs. Automated, recombinant phenotyping assays are commercially available with results available in 2-3 weeks. However, phenotyping assays are more costly to perform than genotyping assays. Recombinant phenotyping assays involve insertion of the reverse transcriptase and protease gene sequences derived from patient plasma HIV RNA into the backbone of a laboratory clone of HIV either by cloning or by *in vitro* recombination. Replication of the recombinant virus at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. Drug concentrations that inhibit 50% and 90% of viral replication (i.e., the median inhibitory concentration [IC] IC_{50} and IC_{90}) are calculated, and the ratio of the IC_{50} of test and reference viruses is reported as the fold increase in IC_{50} (i.e., fold resistance). Interpretation of phenotyping assay results is complicated by the paucity of data regarding the specific resistance level (i.e., fold increase in IC_{50}) that is associated with drug failure, although clinically significant fold increase cutoffs are now available for some drugs *[146-148]*. Again, consultation with a specialist can be helpful for interpreting test results.

Further limitations of both genotyping and phenotyping assays include the lack of uniform quality assurance for all available assays, relatively high cost, and insensitivity for minor viral species. If drug-resistant viruses are present but constitute <10%-20% of the circulating virus population, they probably will not be detected by available assays. This limitation is important because, after drugs exerting selective pressure on drug resistant populations are discontinued, a re-emergence of wild type virus as the predominant plasma population is often

observed, with the result that the proportion of resistant virus may decrease to below these thresholds *[149-151]*. This reversion to predominantly wild type virus often occurs in the first 4-6 weeks after drugs are stopped. Prospective clinical studies have shown that, despite this plasma reversion, reinstitution of the same antiretroviral agents (or those sharing similar resistance pathways) is usually associated with early drug failure, in which it can be demonstrated that the virus present at failure is derived from previously archived resistant virus *[152]*. Therefore, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued **(BII)**. Since detectable resistant virus may persist in the plasma of some patients for longer periods of time, resistance testing beyond 4-6 weeks post-discontinuation may provide valuable information. Yet, the absence of detectable resistance in such patients must be interpreted with caution in designing subsequent antiretroviral regimens.

Using Resistance Assays in Clinical Practice

No definitive prospective data exist to support using one type of resistance assay over another (i.e., genotyping versus phenotyping) in different clinical situations. Therefore, one type of assay is recommended per sample. However, for patients with a complex treatment history, results derived from both assays might provide critical and complementary information to guide regimen changes.

Drug resistance testing is not advised for persons with viral load <1,000 copies/mL, since amplification of the virus is unreliable, and unnecessary charges may be incurred for testing **(DIII)**.

Use of Resistance Assays in Virologic Failure. Resistance assays are useful in guiding decisions for patients experiencing virologic failure while on antiretroviral therapy (**Table 22**). Prospective data supporting drug-resistance testing in clinical practice are derived from trials in which test utility was assessed for cases of virologic failure. These studies involved genotyping assays, phenotyping assays, or both *[141, 145, 153-158]*. In general, these studies indicated that the virologic response to therapy was increased when results of resistance testing were available, compared to responses observed when changes in therapy were guided by clinical judgment only. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in cases of virologic failure, as measured by the early virologic response to the salvage regimen **(BII)**. (See **Management of Treatment-experienced Patients**.)

Resistance testing can also help guide treatment decisions for patients with suboptimal viral load reduction **(BIII)**. Virologic failure in the setting of combination antiretroviral therapy is, for certain patients, associated with resistance to one component of the regimen only *[159, 160]*. In that situation, substituting individual drugs in a failing regimen might be possible, although this concept will require clinical validation. (See **Management of Treatment-experienced Patients**.)

Use of Resistance Assays in Determining Initial Treatment. Transmission of drug-resistant HIV strains has been documented and has been associated with suboptimal virologic response to initial antiretroviral therapy *[161]*. If the decision is made to initiate therapy in a person with acute HIV infection, it is likely that resistance testing at baseline will optimize virologic response, although this strategy has not been tested in prospective clinical trials **(BIII)**. Because of its more rapid turnaround time, using a genotyping assay might be preferred in this situation. Since some resistance-associated mutations are known to persist in the absence of drug pressure, it may be reasonable to extend this strategy for 1-3 years post-seroconversion. **(CIII)**

Using resistance testing before initiation of antiretroviral therapy in patients with chronic HIV infection is less straightforward. Available resistance assays might fail to detect drug-resistant species that were transmitted when infection occurred but, with the passage of time, have become a minor species in the absence of selective drug pressure. As with acute HIV infection, prospective evaluation of "baseline" resistance testing in this setting has not been performed. It may be reasonable to consider such testing, however, when there is a significant possibility that the patient was infected with a drug-resistance virus (i.e., if the patient is thought to have been infected by a person who was receiving antiretroviral drugs) **(CIII)**. One study suggested that baseline testing may be cost-effective when the prevalence of drug resistance in the relevant drug-naïve population is ≥5% *[162]*. However, such population data are infrequently available.

Use of Resistance Assays in Pregnant Patients. In pregnant women, the purpose of antiretroviral therapy is to reduce plasma HIV RNA to below the limit of detection, for the benefit of both mother and child. In this regard, recommendations for resistance testing during pregnancy are the same as for non-pregnant persons.

MANAGEMENT OF THE TREATMENT – EXPERIENCED PATIENT

Panel's Recommendations:

- ***Although most patients experience benefits from taking antiretroviral regimens, adherence, intolerance/toxicity and pharmacokinetic issues may complicate therapy and virologic failure or treatment-limiting toxicity occur commonly.***
- ***Evaluation of antiretroviral treatment failure should include assessing the severity of HIV disease of the patient; the antiretroviral treatment history, including the duration, drugs used, antiretroviral potency, adherence history, and drug intolerance/toxicity; and the results of current and prior drug resistance testing.***
- ***Virologic failure on treatment can be defined as a confirmed HIV RNA level >400 copies/mL after 24 weeks, >50 copies/mL after 48 weeks, or a repeated HIV RNA level >400 copies/mL after prior suppression of viremia to <400 copies/ml.***
- ***In managing virologic failure, the provider should make a distinction between limited, intermediate, and extensive prior treatment exposure and resistance.***
- ***The goal of treatment with limited or intermediate prior drug exposure and drug resistance is to re-establish maximal virologic suppression.***
- ***The goal of treatment with extensive prior drug exposure and drug resistance where viral suppression is difficult or impossible to achieve with currently available drugs is preservation of immune function and prevention of clinical progression.***
- ***Assessing and managing a patient with extensive prior antiretroviral experience and drug resistance who is experiencing treatment failure is complex and expert advice is critical.***

The Treatment-Experienced Patient

Most treatment-experienced patients experience benefits from antiretroviral therapy regimens. In clinical trials of combination regimens, a majority of study subjects maintained virologic suppression for 3-6 years *[85, 163, 164]*. In clinic patients, higher virologic failure rates have been reported *[23, 165]*, but are decreasing *[21, 28]*. In a patient on antiretroviral therapy with virologic suppression, adherence to antiretroviral drugs should be assessed on an ongoing basis (see **Adherence** section). Antiretroviral treatment failure is common and increases the risk of HIV disease progression and should be addressed aggressively.

Definitions and Causes of Antiretroviral Treatment Failure

Antiretroviral treatment failure can be defined as a suboptimal response to therapy. Any of a number of factors may be the cause, including regimen complexity that hinders adherence, medication intolerance and toxicity, suboptimal pharmacokinetics, inadequate antiviral potency, drug resistance, etc. Treatment failure is often associated with virologic failure, immunologic failure, and/or clinical progression (see below).

Many factors increase the likelihood of treatment failure, including:

- baseline patient factors such as: earlier calendar year of starting therapy, higher pretreatment or baseline HIV RNA level (depending on the specific regimen used), lower pretreatment or nadir CD4 cell count, prior AIDS diagnosis, co-morbidities (e.g. depression, active substance use), presence of drug resistant virus, prior treatment failure with development of drug resistance or cross resistance;
- incomplete medication adherence and missed clinic appointments;
- drug side effects and toxicity;
- suboptimal pharmacokinetics (variable absorption, metabolism, and/or penetration into reservoirs, food/fasting requirements, adverse drug-drug interactions with concomitant medications);
- suboptimal potency of the antiretroviral regimen; and/or
- other, unknown reasons.

Some patient cohorts suggest that suboptimal adherence and toxicity accounted for 28%-40% of treatment failure and regimen discontinuation *[166, 167]*. Multiple reasons for treatment failure can occur in one patient. Some factors which have not been associated with treatment failure include: gender, race, pregnancy, history of past substance use.

Virologic Failure can be defined as incomplete or lack of HIV RNA response to antiretroviral therapy:

- ***Incomplete virologic response***: This can be defined as repeated HIV RNA >400 copies/mL after 24 weeks or >50 copies/mL by 48 weeks in a treatment-naïve patient initiating therapy. Baseline HIV RNA may impact the time course of response and some patients will take longer than others to suppress HIV RNA levels. The timing, pattern, and/or slope of HIV RNA decrease may predict ultimate virologic response *[168]*. For example, most patients with an adequate virologic response at 24 weeks had at least a 1 $\log_{10}$ copies/mL HIV RNA decrease at 1-4 weeks after starting therapy *[169-171]*.

- ***Virologic rebound***: After virologic suppression, repeated detection of HIV RNA.

Immunologic Failure can be defined as failure to increase the CD4 cell count by 25-50 cells/mm^3 above the baseline count over the first year of therapy, or a decrease to below the baseline CD4 cell count on therapy. Mean increases in CD4 cell counts in treatment-naïve patients with initial antiretroviral regimens are approximately 150 cells/mm^3 over the first year *[172]*. A lower baseline CD4 cell count may be associated with less of a response to therapy. For reasons not fully understood, some patients may have initial CD4 cell increases, but then minimal subsequent increases.

Immunologic failure (i.e., return to baseline CD4 cell count) occurred an average of 3 years following virologic failure in patients remaining on the same antiretroviral regimen *[168]*.

Clinical Progression can be defined as the occurrence or recurrence of HIV-related events (after at least 3 months on an antiretroviral regimen), excluding immune reconstitution syndromes *[173]*. In one study, clinical progression (a new AIDS event or death) occurred in 7% of treated patients with virologic suppression, 9% of treated patients with virologic rebound, and 20% of treated patients who never achieved virologic suppression over 2.5 years *[165]*.

Relationship Across Virologic Failure, Immunologic Failure, and Clinical Progression. Some patients demonstrate discordant responses in virologic, immunologic and clinical parameters *[174]*. In addition, virologic failure, immunologic failure, and clinical progression have distinct time courses and may occur independently or simultaneously. In general, virologic failure occurs first, followed by immunologic failure, and finally by clinical progression. These events may be separated by months to years.

Although heterogeneous, patients who experience treatment failure may be divided into those with

- limited prior treatment and drug resistance who have adequate treatment options;
- an intermediate amount of prior treatment and drug resistance with some available treatment options; and
- extensive prior treatment and drug resistance who have few or no adequate treatment options. The assessment, goals of therapy and approach to managing treatment failure differs for each of these three groups.

Assessment of Antiretroviral Treatment Failure and Changing Therapy

In general, the cause of treatment failure should be explored by reviewing the medical history and performing a physical examination to assess for signs of clinical progression. Important elements of the medical history include: change in HIV RNA and CD4 cell count over time; occurrence of HIV-related clinical events; antiretroviral treatment history and results of prior resistance testing (if any); medication-taking behavior, including adherence to recommended drug doses, dosing frequency and food/fasting requirements; tolerance of the medications; concomitant medications (with consideration for adverse drug-drug interactions); and co-morbidities (including substance use). In many cases the cause(s) of treatment failure will be readily apparent. In some cases, no obvious cause may be identified.

For more information about the approach to treatment failure, see **Tables 23–25**.

Initial Assessment of Treatment Failure. In conducting the assessment of treatment failure, it is important to distinguish among the reasons for treatment failure because the approaches to subsequent treatment will differ. The following assessments should be initially undertaken:

- **Adherence.** Assess the patient's adherence to the regimen. For incomplete adherence, identify and address the underlying cause(s) for non-adherence (e.g. access to medications, depression, active substance use), and simplify the regimen if possible (e.g., decrease pill count or dosing frequency) **(AIII)** (see **Adherence** section).
- **Medication Intolerance.** Assess the patient's side effects. Address and review the likely duration of side effects (e.g., the limited duration of gastrointestinal symptoms with some regimens). Management strategies for intolerance may include:
  - use symptomatic treatment (e.g. antiemetics, antidiarrheals);
  - change one drug to another within the same drug class, if needed (e.g. change to stavudine or tenofovir for zidovudine-related gastrointestinal symptoms or anemia; change to nevirapine for efavirenz-related central nervous system symptoms**) (AII)**;
  - change drug classes (e.g., from a PI to an NNRTI) if necessary **(AII)**.
- **Pharmacokinetic Issues.** Review food/fasting requirements for each medication. Review recent history of gastrointestinal symptoms (such as vomiting or diarrhea) to assess the likelihood of short-term malabsorption. Review concomitant

medications and dietary supplements for possible adverse drug-drug interactions and make appropriate substitutions for antiretroviral agents and/or concomitant medications, if possible **(AIII)**. (See also **Therapeutic Drug Monitoring**)

- **Suspected Drug Resistance.** Obtain resistance testing while the patient is taking the failing regimen or within 4 weeks after regimen discontinuation (see **Utilization of Drug Resistance in Clinical Practice**).

Subsequent Assessment of Treatment Failure. When adherence, tolerability, and pharmacokinetic causes of treatment failure have been considered and addressed, make an assessment for virologic failure, immunologic failure, and clinical progression.

1. **Virologic Failure.** There is no consensus on the optimal time to change therapy for virologic failure. The most aggressive approach would be to change for any repeated, detectable viremia (e.g., two consecutive HIV RNA >400 copies/mL after suppression to <400 copies/mL in a patient taking the regimen). Other approaches allow detectable viremia up to an arbitrary level (e.g., 1,000-5,000 copies/mL). However, ongoing viral replication in the presence of antiretroviral drugs promotes the selection of drug resistance mutations *[175]* and may limit future treatment options. Isolated episodes of viremia ("blips", e.g. single levels of 50-1,000 copies/mL) usually are not associated with subsequent virologic failure, but rebound to higher viral load levels or more frequent episodes of viremia increase the risk of failure *[176, 177]*.

   When assessing virologic failure, distinguish between limited, intermediate and extensive drug resistance, taking into account prior treatment history and prior resistance test results. Drug resistance tends to be cumulative for a given individual and thus all prior treatment history and resistance test results should be taken into account. **Table 23** provides potential management strategies in different clinical scenarios.

   - ***Prior Treatment With No Resistance Identified.*** Consider the timing of the drug resistance test (e.g., was the patient off antiretroviral medications?) and/or non-adherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., in 2–4 weeks) to determine if a resistant virus becomes evident **(CIII)**.
   - ***Limited Prior Treatment and Drug Resistance.*** The goal in this situation is to re-suppress HIV RNA levels maximally and prevent further selection of resistance mutations. With virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. Change at least 2 drugs in the regimen to active agents **(BII)**. A single drug substitution (made on the basis of resistance testing) can be considered, but is unproven in this setting **(CIII)**.
   - ***Intermediate Prior Treatment and Drug Resistance.*** The goal in this situation usually is to re-suppress HIV RNA levels maximally and prevent further selection of resistance mutations. Change at least 2 drugs in the regimen to active agents (**BII**).
   - ***Extensive Prior Treatment and Drug Resistance*** (**Tables 23–25**): Viral suppression is often difficult to achieve in this population. Thus, the goal is to preserve immunologic function and prevent clinical progression (even with ongoing viremia). Even partial virologic suppression of HIV RNA >0.5 log10 copies/mL from baseline correlates with clinical benefits *[178]*; however, this must be balanced with the ongoing risk of accumulating additional resistance mutations. It is reasonable to observe a patient on the same regimen, rather than changing the regimen (depending on the stage of HIV disease), if there are few or no treatment options (**BII**). There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 cell increases, decreases the risk of disease progression *[150]*. In a patient with a lower CD4 cell count (e.g. <100 cells/mm^3), a change in therapy may be critical to prevent further immunologic decline and clinical progression and is therefore indicated (**BIII**). A patient with a higher CD4 cell count may not be at significant risk for clinical progression, so a change in therapy is optional (**CIII**). Discontinuing or briefly interrupting therapy (even with ongoing viremia) may lead to a rapid increase in HIV RNA, a decrease in CD4 cell count, and increases the risk for clinical progression *[179, 180]* and therefore is not recommended (**DIII**).

2. **Immunologic Failure.** Immunologic failure may not warrant a change in therapy in the setting of suppressed viremia. Assessment should include an evaluation for other possible causes of immunosuppression (e.g. HIV-2, HTLV-1, HTLV-2, drug toxicity). Although some clinicians have explored the use of intensification with additional

antiretroviral drugs *[181]* or immune-based therapies (e.g., interleukin-2) to improve immunologic responses *[182]*, such therapies remain unproven and generally should not be offered in the setting of immunologic failure **(DII)**.

3. **Clinical Progression.** Consider the possibility of immune reconstitution syndromes *[173]* that typically occur within the first 3 months after starting effective antiretroviral therapy and that may respond to anti-inflammatory treatment(s) rather than changing antiretroviral therapy. Clinical progression may not warrant a change in therapy in the setting of suppressed viremia (**BIII**).

Changing an Antiretroviral Therapy Regimen for Virologic Failure

Panel's Recommendations:

- ***For the patient with virologic failure, perform resistance testing while the patient still is taking the drug regimen or within 4 weeks after regimen discontinuation (AII).***
- ***Use the treatment history and past and current resistance test results to identify active agents (preferably 3 or more) to design a new regimen (AII).***
- ***If three active agents cannot be identified, consider pharmacokinetic enhancement of protease inhibitors (with the exception of nelfinavir) with ritonavir (BII) and/or re-using other prior antiretroviral agents (CIII).***
- ***Adding a drug with a new mechanism of action (e.g. HIV entry inhibitor) to an optimized background antiretroviral regimen can add significant antiretroviral activity (BII).***
- ***In general, one active drug should not be added to a failing regimen because drug resistance is likely to develop quickly (DII). However, in patients with advanced HIV disease (e.g. CD4 <100) and higher risk of clinical progression, adding one active agent (with an optimized background regimen) may provide clinical benefits and should be considered (CIII).***

General Approach (see **Tables 23–25**). Ideally, one should design a regimen with three or more active drugs (on the basis of resistance testing or new mechanistic class) **(BII)** *[154]*. Note that using "new" drugs that the patient has not yet taken may not be sufficient because of cross-resistance within drug classes that reduces drug activity. As such, drug potency is more important than the number of drugs prescribed.

Early studies of treatment-experienced patients identified factors associated with better virologic responses to subsequent regimens *[183, 184]*. They include: lower HIV RNA at the time of therapy change, using a new (i.e. not yet taken) class of drugs (e.g. NNRTI, HIV entry inhibitors), and using ritonavir-boosted PIs in PI-experienced patients.

Sequencing and Cross Resistance. The order of use of some antiretroviral agents may be important. Cross-resistance among NRTIs is common but varies by drug. Most, if not all, NNRTI-associated resistance mutations confer resistance to the entire NNRTI class of drugs. Novel early mutations to some protease inhibitors (e.g., amprenavir, atazanavir, nelfinavir, saquinavir) that do not confer cross-resistance to other PIs may occur initially, but then subsequent accumulation of additional mutations confers broad cross-resistance to the entire protease inhibitor class.

New Agents. Investigational agents in existing drug classes currently are under investigation in clinical trials. Some of these agents demonstrate distinct resistance patterns and activity against drug-resistant viruses.

Drugs with newer mechanisms of action (e.g. HIV entry inhibitors) should demonstrate antiretroviral activity, even in patients with resistance to the reverse transcriptase inhibitors and PIs. The first approved HIV entry inhibitor is enfuvirtide (T-20), a drug that must be given by subcutaneous injection twice daily. With its novel mechanism of action, enfuvirtide demonstrated potent antiretroviral activity, even in heavily treatment-experienced patients *[185-187]*. Enfuvirtide has not been well studied in patients at earlier stages of HIV infection.

Current Approach. Two clinical trials illustrate effective therapeutic strategies for heavily treatment-experienced patients *[185, 186]*. In these studies, patients received an antiretroviral regimen optimized on the basis of resistance testing and then were randomized to receive enfuvirtide (T-20) or placebo. With more active drugs (including enfuvirtide) in the regimen, the enfuvirtide group had a better virologic response than the placebo group and these results persisted through 48 weeks of follow-up *[187]*.

These studies illustrate and support the strategy of conducting resistance testing while a treatment-experienced patient is taking their failing regimen, designing a new regimen based on the treatment history and resistance testing results, and selecting active antiretroviral drugs for the new treatment regimen.

In general, using a single active antiretroviral drug in a new regimen is not recommended because of the risk of rapidly developing resistance to that drug. However, in patients with advanced HIV disease with a high likelihood of clinical progression (e.g., a CD4 cell count less than 100/mm^3), adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits. Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., antiretroviral activity) of using a single active drug in the heavily treatment-experienced patient is complicated, and consultation with an expert is advised.

Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents

Therapeutic drug monitoring (TDM) is a strategy applied to certain antiarrhythmics, anticonvulsants, and antibiotics to utilize drug concentrations to design regimens that are safe and will achieve a desired therapeutic outcome. The key characteristic of a drug that is a candidate for TDM is knowledge of a therapeutic range of concentrations. The therapeutic range is a probabilistic concept. It is a range of concentrations established through clinical investigations that are associated with achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

Current antiretroviral agents meet most of the characteristics of agents that can be considered candidates for a TDM strategy *[188]*. The rationale for TDM in managing antiretroviral therapy arises because of:

- data showing that considerable inter-patient variability in drug concentrations among patients who take the same dose, and
- data indicating relationships between the concentration of drug in the body and anti-HIV effect—and, in some cases, toxicities.

TDM With PIs and NNRTIs. Data describing relationships between antiretroviral agents and treatment response have been reviewed in various publications *[189-192]*. While there are limitations and unanswered questions in these data, the consensus of U.S. and European clinical pharmacologists is that the data provide a framework for the potential implementation of TDM for PIs and NNRTIs. This is because concentration-response data exist for PIs and NNRTIs. Information on relationships between concentrations and drug-associated toxicities are sparse. Clinicians using TDM as a strategy to manage these toxicities should consult the most current literature for specific concentration recommendations.

TDM with NRTIs. Relationships between plasma concentrations of NRTIs and their intracellular pharmacologically active moieties have not yet been established. Therefore, monitoring of plasma NRTI concentrations largely remains a research tool.

Scenarios for Use of TDM. There are multiple scenarios in which both data and expert opinion indicate that information on the concentration of an antiretroviral agent may be useful in patient management. Consultation with an expert clinical pharmacologist may be advisable. These scenarios include:

- **clinically significant drug-drug or drug-food interactions** that may result in reduced efficacy or increased dose-related toxicities;
- **changes in pathophysiologic states** that may impair gastrointestinal, hepatic, or renal function, thereby potentially altering drug absorption, distribution, metabolism, or elimination;
- **persons such as pregnant women** who may be at risk for virologic failure as a result of their pharmacokinetic characteristics that result in plasma concentrations lower than those achieved in the typical patient;
- **in treatment-experienced persons** who may have viral isolates with reduced susceptibility to antiretroviral agents;
- **use of alternative dosing regimens** whose safety and efficacy have not been established in clinical trials;
- **concentration-dependent toxicities**; and
- **lack of expected virologic resp**onse in a treatment-naïve person.

Use of TDM to Monitor Drug Concentrations. There are several challenges and scientific gaps to the implementation of TDM in the clinical setting (see Limitations to Conducting TDM). Use of TDM to monitor drug concentration in a patient requires multiple steps:

- quantification of the concentration of the drug, usually in plasma or serum;
- determination of the patient's pharmacokinetic characteristics;
- interpretation of the concentrations; and
- adjustment of the drug dose to achieve concentrations within the therapeutic range if necessary.

Guidelines for the collection of blood samples and other practical suggestions can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee *[189]* (see : **http://www.hivpharmacology.com**) *[193]*.

Limitations to Using TDM in Patient Management. There are multiple factors that limit the use of TDM in the clinical setting. They include the following:

- Lack of prospective studies demonstrating that TDM improves clinical outcome. This is the most important limiting factor for the implementation of TDM at present.
- Lack of established therapeutic range of concentrations associated with achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions; and
- Lack of widespread availability of laboratories that perform quantitation of antiretroviral drug concentrations under rigorous quality assurance/quality control standards and the lack of experts in the interpretation of antiretroviral concentration data and application of such data to revise patients' dosing regimens.

TDM in Different Patient Populations

- **Patients with wild type virus**. **Table 26** presents a synthesis of recommendations *[189-191, 193]* for minimum target trough PI and NNRTI concentrations in persons with wild-type virus.
- **Treatment-experienced patients**. Fewer data are available to formulate suggestions for minimum target trough concentration in treatment-experienced patients who have viral isolates with reduced susceptibility to these agents. It is likely that use of these agents in the setting of reduced viral susceptibility may require higher trough concentrations than those for wild-type virus.

A final caveat to the use of measured drug concentration in patient management is a general one: drug concentration information cannot be used alone; it must be integrated with other clinical and patient information. In addition, as knowledge of associations between antiretroviral concentrations and virologic response continues to accumulate, clinicians employing a TDM strategy for patient management should consult the most current literature.

Discontinuation or Interruption of Antiretroviral Therapy

Treatment interruption may become necessary (due to serious drug toxicity, intervening illness that precludes oral therapy, or non-availability) or it may be planned for various reasons. The principles of discontinuation of antiretroviral drugs are generally the same regardless of the reason – all components should be stopped simultaneously (**AIII**); a possible exception is planned interruption with efavirenz or nevirapine as noted below. Planned interruption of on-going antiviral therapy has been considered in several situations, which differ by indications and rationale. The safety and efficacy of treatment interruption in these settings has not been clearly established. Potential risks of disease progression and potential benefits of reduction of drug toxicities and/or preservation of future treatment options may vary dependent upon a number of factors, including the clinical and immunologic status of the patients, and the presence or absence of resistant HIV at the time of interruption. Research is ongoing in several of the scenarios listed below and it is hoped that these results will provide the basis and guidance for clearer recommendations. Thus, none of these approaches can be recommended at this time outside of controlled clinical trials. Some of these aforementioned scenarios include:

- In patients who initiated therapy during acute HIV infection and achieved virologic suppression.
- In patients with chronic HIV infection with viral suppression who either may have started antiretroviral therapy at and have maintained a CD4 cell count above those currently recommended for initiating therapy; or in patients who may have started antiretroviral therapy at a CD4 count currently recommended for initiating therapy and also have maintained a CD4 count above those currently recommended for initiating therapy. (see discussion to follow)
- In pregnant women who initiated antiretroviral therapy during pregnancy primarily for the purpose of preventing mother-to-child HIV transmission, who otherwise do not meet CD4 criteria for starting treatment, and desire to stop therapy after delivery. (see **Discontinuation of Antiretroviral Therapy Post Partum**)
- In patients who have had exposure to multiple antiretroviral agents, have antiretroviral treatment failure, and have few treatment options available due to extensive resistance mutations. Several clinical trials have been conducted to better understand the role of treatment interruption in these patients, yielding conflicting results.*[180, 194-196]*. The Panel notes that

partial virologic suppression from combination therapy has been associated with clinical benefits, thus interruption is generally not recommended unless it is done in a clinical trial setting.

If therapy has to be discontinued, the patient should be counseled regarding the lack of controlled clinical trial data to support this approach, the need for close clinical and laboratory evaluation, and depending on the CD4+ T cell count, the need for chemoprophylaxis against opportunistic infections. There should also be a plan of when to restart therapy.

Prior to treatment interruption, a number of antiretroviral-specific issues should be taken into consideration. These include:

- **Discontinuation of efavirenz or nevirapine.** Pharmacokinetic data demonstrate that detectable drug levels may persist for 21 days or longer after discontinuation of nevirapine or efavirenz *[197-199]*. Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTIs due to their longer half-lives when compared to the other agents. More importantly, this may increase the risk of selection of NNRTI-resistant mutations. This is further complicated by evidence that certain genetic polymorphisms may result in slower rate of clearance. Such polymorphism may be more common among some ethnic groups, such as in African Americans and in Hispanics *[200, 201]*. Some experts recommend stopping the NNRTI first before the other antiretroviral drugs (i.e. NRTI-backbone or PI). The optimal interval between stopping NNRTI and other antiretroviral drugs is not known. An alternative strategy is to substitute the NNRTI with PI prior to interruption of all antiretroviral drugs. If this strategy is to be used, the goal is to assure that the PI use also achieve complete viral suppression during this interval. Further research to determine the best approach to discontinuing NNRTIs is needed.
- **Discontinuation and restarting nevirapine**. In a patient who has interrupted treatment with nevirapine for more than two weeks and is to be restarted at a later time point, nevirapine should be reintroduced with a dose escalation period consisting of 200mg once daily for 14 days, then increased to a 200mg twice daily regimen **(AII)**.
- **Discontinuation of emtricitabine, lamivudine, or tenofovir in patients with hepatitis B co-infection**. Patients with hepatitis B co-infection (hepatitis B surface antigen and/or HBe antigen positive) and receiving one or a combination of the above NRTIs may experience an exacerbation of their hepatitis upon discontinuation of these drugs *[94, 95]*. If any of the above agents is to be discontinued, the patients should be closely monitored for exacerbation of hepatitis or hepatic flare (**AII**). Some experts suggest initiating adefovir for the treatment of hepatitis B in selected patients (**CIII**).

Treatment Interruption and Reinstitution Based on CD4 Cell Count (CD4-guided Therapy)

In patients with HIV infection on antiviral therapy with viral suppression who have maintained CD4 levels above those currently recommended for initiating therapy, some relevant, but not definitive, data exist on stopping antiretroviral therapy. The rationale is that it is safe and appropriate to temporarily discontinue therapy when immune competence has been reestablished and is stable. Suggestions for the CD4 threshold to discontinue therapy are variable, but usually 500-800/mm^3 and the suggested CD4 threshold to re-initiate combination antiretroviral therapy is also arbitrary in this situation, but usually around 350-400 cells/mm^3.

No prospective clinical trials have been conducted to address the long term safety of this strategy. However, several small prospective trials with short term follow-up and several retrospective analyses of a single episode of treatment interruption support this strategy. That support is based on safety when treatment is stopped and good virologic response when treatment is re-initiated with minimal or no risk of resistance *[202-204]*. These studies have shown that the rapidity and magnitude of $CD4^+$ cell count decline after treatment discontinuation correlates with the nadir pretreatment $CD4^+$ cell count. The best results are seen in patients who initiated therapy when the $CD4^+$ cell count was over 350 cells/mm^3, a group which would not merit therapy by the current guidelines. These studies appear to consistently show short term safety and efficacy with little risk of increased resistance for a single episode of treatment interruption. Additionally, the nadir CD4 count and the $CD4^+$ cell count at discontinuation appear to be important factors. In general, both CD4 rebound and return to viral suppression can be achieved after restarting therapy.

This option may be offered to patients with immune reconstitution, although participation in a controlled trial would be preferred. The long term safety and efficacy of this approach are not known. Patients who opt to interrupt therapy need to be warned that the HIV viral load will increase, usually to the pre-treatment level and this will be accompanied by an increased risk of

transmission to others. Patients and clinicians who care for these patients must also recognize that careful monitoring of CD4 levels will be required and re-initiation of antiviral therapy be strongly advised when the CD4 count reaches the level of current recommendation for initiation of therapy. It is important to note that no data exist on the safety and efficacy of sequential or multiple treatment interruptions in patients who started therapy at or have maintained CD4 levels above those currently recommended for initiating therapy. While a strategy of sequential periods of antiviral therapy guided to maintain CD4 levels above a certain minimum might be an attractive option to minimize treatment-related toxicities, the safety of this approach has not been established.

CONSIDERATIONS FOR ANTIRETROVIRAL USE IN SPECIAL PATIENT POPULATIONS

Acute HIV Infection

Panel's Recommendations:

- ***Whether treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown; treatment should be considered optional at this time (CIII).***
- ***Therapy should also be considered optional for patients in whom HIV seroconversion has occurred within the previous 6 months (CIII).***
- ***If the clinician and patient elect to treat acute HIV infection with antiretroviral therapy, treatment should be implemented with the goal of suppressing plasma HIV RNA levels to below detectable levels (AIII).***
- ***For patients with acute HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels and $CD4^+$ T cell count and toxicity monitoring should be performed as described for patients with established, chronic HIV infection (AII).***
- ***If the decision is made to initiate therapy in a person with acute HIV infection, it is likely that resistance testing at baseline will optimize virologic response; this strategy should be considered (BIII).***

An estimated 40%-90% of patients acutely infected with HIV will experience symptoms of acute retroviral syndrome (Table 27) *[205-208]*. However, acute HIV infection is often not recognized by primary care clinicians because of the similarity of the symptoms to those of influenza, infectious mononucleosis or other illnesses. Additionally, acute infection can occur asymptomatically.

Diagnosis of Acute HIV Infection. Health care providers should consider a diagnosis of acute HIV infection for patients who experience a compatible clinical syndrome (Table 27) and who report recent high risk behavior. In these situations, tests for plasma HIV RNA and HIV antibody should be obtained (**BII**). Acute HIV infection is defined by detectable HIV RNA in plasma by using sensitive PCR or bDNA assays in the setting of a negative or indeterminate HIV antibody test. A low-positive HIV RNA level (<10,000 copies/mL) may represent a false-positive test, since values in acute infection are generally very high (>100,000 copies/mL).

Patients with HIV infection diagnosed by HIV RNA testing should have confirmatory serologic testing performed at a subsequent time point **(AI)** (Table 2).

Treatment for Acute HIV Infection. Clinical trials information regarding treatment of acute HIV infection is limited. Ongoing trials are addressing the question of the long-term benefit of potent treatment regimens initiated during acute infection. Potential benefits and risks of treating acute infection are as follows:

- **Potential Benefits of Treating Acute Infection**. Preliminary data indicate that treatment of acute HIV infection with combination antiretroviral therapy has a beneficial effect on laboratory markers of disease progression *[209-213]*.Theoretically, early intervention could decrease the severity of acute disease; alter the initial viral setpoint, which can affect disease-progression rates; reduce the rate of viral mutation as a result of suppression of viral replication; preserve immune function; and reduce the risk for viral transmission.
- **Potential Risks of Treating Acute HIV Infection**. The potential disadvantages of initiating therapy include exposure to antiretroviral therapy without a known clinical benefit, which could result in drug toxicities, development of antiretroviral drug resistance, the need for continuous therapy, and adverse effect on quality of life.

The above risk and benefit considerations are similar to those for initiating therapy in the chronically infected asymptomatic patient. The health care provider and the patient should be fully aware that the rationale for therapy for acute HIV infection is based on theoretical considerations, and the potential benefits should be weighed against the potential risks. For these reasons, treatment of acute HIV infection should be considered optional at this time (**CIII**).

Treatment of Recent But Non-Acute HIV Infection or Infection of Undetermined Duration. Besides patients with acute HIV infection, experienced clinicians also recommend consideration of therapy for patients in whom seroconversion has occurred within the previous 6 months **(CIII)**. Although the initial burst of viremia among infected adults usually resolves in 2 months, rationale for treatment during the 2 to 6-month period after infection is based on the probability that virus replication in lymphoid tissue is still not maximally contained by the immune system during this time *[214]*.

Decisions regarding therapy for patients who test antibody-positive and who believe the infection is recent, but for whom the time of infection cannot be documented, should be made as discussed in **When to Treat: Indications for Antiretroviral Therapy (CIII)**.

Treatment Regimen. If the clinician and patient have made the decision to use antiretroviral therapy for acute or recent HIV infection, treatment should be implemented in an attempt to suppress plasma HIV RNA levels to below detectable levels **(AIII)**. Data are insufficient to draw firm conclusions regarding specific drug recommendations to use in acute HIV infection. Therefore, potential combinations of agents should be those used in established infection (**Table 5**).

Patient Follow-up. Testing for plasma HIV RNA levels and $CD4^+$ T cell count and toxicity monitoring should be performed as described in **Initial Assessment and Monitoring for Therapeutic Response** (i.e., HIV-RNA on initiation of therapy, after 2-8 weeks, and every 3-4 months thereafter) **(AII)**.

Duration of Therapy for Acute HIV Infection. The optimal duration of therapy for patients with acute HIV infection is unknown, but ongoing clinical trials may provide relevant data regarding these concerns. Difficulties inherent in determining the optimal duration and therapy composition for acute infection should be considered when first counseling the patient regarding therapy.

HIV-Infected Adolescents

Older children and adolescents now make up the largest percentage of HIV-infected children cared for at U.S. sites. The CDC estimates that at least one half of the 40,000 yearly new HIV-infected cases in the U.S. are in people 13 to 24 years of age *[215]*. HIV-infected adolescents represent a heterogeneous group in terms of sociodemographics, mode of HIV infection, sexual and substance abuse history, clinical and immunologic status, psychosocial development and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start and what antiretroviral medications should be used.

Most adolescents have been infected during their teenage years and are in an early stage of infection, making them ideal candidates for early intervention, such as prevention counseling. A limited but increasing number of HIV-infected adolescents are long-term survivors of HIV infection acquired perinatally or through blood products as infants. Such adolescents may have a unique clinical course that differs from that of adolescents infected later in life *[216]*.

Antiretroviral Therapy Considerations in Adolescents. Adult guidelines for antiretroviral therapy are usually appropriate for post pubertal adolescents because HIV-infected adolescents who were infected sexually or through injecting-drug use during adolescence follow a clinical course that is more similar to that of adults than to that of children.

Dosage for medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty and not on the basis of age *[217, 218]*. Adolescents in early puberty (i.e., Tanner Stage I and II) should be administered doses using pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult dosing schedules. Because puberty may be delayed in perinatally-HIV-infected children *[219]*, continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than usual adult doses. Since data are not available to predict optimal medication doses for each antiretroviral medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition from pediatric to adult doses. Youth who are in their growth spurt (i.e., Tanner Stage III in females and Tanner Stage IV in males) using adult or pediatric dosing guidelines and those adolescents whose doses have been transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity.

Adherence Concerns in Adolescents. HIV-infected adolescents have specific adherence problems. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who are frequently inexperienced with health-care systems. Many HIV-infected

adolescents face challenges in adhering to medical regimens for reasons that include:

- denial and fear of their HIV infection;
- misinformation;
- distrust of the medical establishment;
- fear and lack of belief in the effectiveness of medications;
- low self-esteem;
- unstructured and chaotic lifestyles; and
- lack of familial and social support.

Treatment regimens for adolescents must balance the goal of prescribing a maximally potent antiretroviral regimen with realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (beepers, timers, and pill boxes) that are stylish and do not call attention to themselves. It is important to make medication adherence as user friendly and as little stigmatizing as possible for the older child or adolescent. The concrete thought processes of adolescents make it difficult for them to take medications when they are asymptomatic, particularly if the medications have side effects. Adherence with complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers Direct observed therapy, while considered impractical for all adolescents, might be important for selected adolescents infected with HIV *[220, 221]*. For a more detailed discussion on specific issues on therapy and adherence for HIV-infected adolescents the reader can link to **Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection** *[222]*.

Developmental issues make caring for adolescents unique. The adolescent's approach to illness is often different from that of an adult. The adolescent also faces difficulties in changing caretakers; graduating from a pediatrician to an adolescent care provider and then to an internist.

Special Considerations in Adolescent Females. Gynecological care is especially difficult to provide for the HIV infected female adolescent but is a critical part of their care. Because many adolescents with HIV infection are sexually active, contraception and prevention of HIV transmission should be discussed with the adolescent, including the interaction of specific antiretroviral drugs on birth control pills. The potential for pregnancy may also alter choices of antiretroviral therapy. As an example, efavirenz should be used with caution in females of child bearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring including periodic pregnancy testing and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see **HIV-Infected Women of Reproductive Age and Pregnant Women** *[97]*.

Given the lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need to support this appropriate transition in care for HIV infected infants through adolescents.

Injection Drug Users

Challenges of Treating IDUs Infected With HIV. Injection drug use represents the second most common route of transmission of HIV in the United States. Although treatment of HIV disease in this population can be successful, injection drug users with HIV disease present special treatment challenges. These include the existence of an array of complicating co-morbid conditions, limited access to HIV care, inadequate adherence to therapy, medication side effects and toxicities, need for substance abuse treatment, and the presence of treatment complicating drug interactions *[223-225]*.

Underlying health problems among this population result in increased morbidity and mortality, either independent of or accentuated by HIV disease. Many of these problems are the consequence of prior poverty-related infectious disease exposures and the added effects of non-sterile needle and syringe use. These include tuberculosis, skin and soft tissue infections, recurrent bacterial pneumonia, endocarditis, hepatitis B and C, and neurologic and renal disease. Furthermore, the high prevalence of underlying mental illness in this population, antedating and/or exacerbated by substance use, results in both morbidity and difficulties in provision of clinical care and treatment *[223-225]*. Successful HIV therapy for injection drug users often rests upon acquiring familiarity with and providing care for these co-morbid conditions**.**

Injection drug users often have decreased access to HIV care and are less likely to receive antiretroviral therapy than other populations *[226, 227]*. Factors associated with lack of use of antiretroviral therapy among drug users have included active drug use, younger age, female gender, suboptimal health care, not being in a drug treatment program, recent

incarceration, and lack of health care provider expertise *[226, 227]*. The chaotic lifestyle of many drug users, the powerful pull of addictive substances and a series of beliefs about the dangers of antiretroviral therapy among this population impact on and blunt the benefit of antiretroviral therapy and contribute to decreased adherence to antiretroviral therapy *[228]*. The chronic and relapsing nature of substance abuse and lack of appreciation of substance abuse as a biologic and medical disease, compounded by the high rate of co-existing mental illness, further complicates the relationship between health care workers and injection drug users.

Efficacy of HIV Treatment in IDUs. Although underrepresented in clinical trials of HIV therapies, available data indicate that, when not actively using drugs, efficacy of antiretroviral therapies among injection drug users is similar to other populations. Further, therapeutic failure in this population is generally the degree to which drug use results in disruption of organized daily activities, rather than drug use *per se*. While many drug users can control their drug use sufficiently and over sustained periods of time to engage in care successfully, treatment of substance abuse is often a prerequisite for successful antiretroviral therapy. Close collaboration with substance abuse treatment programs, and proper support and attention to the special needs of this population, is often a critical component of successful treatment for HIV disease. Essential to this end, as well, are flexible community based HIV care sites characterized by familiarity with, and non-judgmental expertise in, managing the wide array of needs of substance abusers, and the development and use of effective strategies for promoting medication adherence *[224, 225]*. Foremost among these is the provision of substance abuse treatment. In addition, other support mechanisms for adherence are of value and the use of drug treatment and community based outreach sites for modified directly observed therapy has shown promise in this population *[229]*.

IDU/HIV Drug Toxicities and Interactions.
Injection drug users are more likely to experience an increased frequency of side effects and toxicities of antiretroviral therapies. Although not systematically studied, this is likely due to the high prevalence of underlying hepatic, renal, neurologic, psychiatric, gastrointestinal and hematologic disease among injection drug users. The selection of initial and continuing antiretroviral agents in this population should be made based upon the presence of these conditions and risks.

Methadone and Antiretroviral Therapy.
Methadone, an orally administered long-acting opiate agonist, is the most common pharmacologic treatment for opiate addiction. Its use is associated with decreased heroin use, improved quality of life, and decreased needle sharing. Methadone exists in two racemic forms, R (active) and S (inactive). As a consequence of its opiate induced effects on gastric emptying and metabolism by cytochrome P450 isoenzymes 3A4 and 2D6, pharmacologic effects and interactions with antiretrovirals may commonly occur *[230]*. These may diminish the effectiveness of either or both therapies by causing opiate withdrawal or overdose and/or increase in toxicity or decrease in efficacy of antiretrovirals.

- **Methadone and NRTIs**. Most of the currently available antiretrovirals have been examined in terms of potential pharmacokinetic interactions of significance with methadone (See **Table 20**.) Among the NRTIs, none appear to have a clinically significant effect on methadone metabolism. Conversely, important effects of methadone on NRTIs have been well documented. Methadone is known to increase the area under the curve of zidovudine by 40% *[230]*, with possible increase in zidovudine related side effects. Levels of stavudine and the buffered tablet formulation of didanosine are decreased, respectively, 18% and 63% by methadone *[231]*. This marked reduction in didanosine levels is not observed with the EC formulation. Recent data indicate lack of significant interaction between abacavir and tenofovir and methadone.
- **Methadone and NNRTIs**. Pharmacokinetic interactions between NNRTIs and methadone are well known and clinically problematic *[232]*. Both efavirenz and nevirapine, potent inducers of p450 enzymes, have been associated with significant decreases in methadone levels. Methadone levels are decreased by 43% and 46% in those receiving efavirenz and nevirapine, respectively, with corresponding clinical opiate withdrawal. It is necessary to inform patients and substance abuse treatment facilities of the likelihood of occurrence of this interaction if either drug is prescribed to those receiving methadone. The clinical effect is usually seen after seven days of co-administration and is treated with increase in methadone dosage, usually at 5-10 mg daily until the patient is comfortable. Delavirdine, an inhibitor of p450 isoenzymes, increases methadone levels moderately and without clinical significance.
- **Methadone and PIs**. Limited information indicates that PI levels are generally not affected by methadone, except for amprenavir, which appears to

be reduced by 30%. However, a number of PI have significant effects on methadone metabolism. Saquinavir does not affect free unbound methadone levels. However, amprenavir, nelfinavir and lopinavir administration results in a significant decrease in methadone levels *[233, 234]*. Whereas amprenavir may result in mild opiate withdrawal, decrease in methadone concentration from nelfinavir was not associated with opiate withdrawal. This is likely because of lack of effect on free rather than total methadone levels. Lopinavir/ritonavir combination has been associated with significant reductions in methadone levels and opiate withdrawal symptoms. This is due to the lopinavir and not ritonavir component *[235]*. Finally, another study indicates a lack of pharmacokinetic interaction between atazanavir and methadone *[236]*.

Buprenorphine. Buprenorphine, a partial μ-opiate agonist, is increasingly being used for opiate abuse treatment. Its decreased risk of respiratory depression and overdose enables use in physician's offices for the treatment of opioid dependence. This flexible treatment setting could be of significant value to drug abusing opiate addicted HIV infected patients requiring antiretroviral therapy as it would enable one physician or program to provide needed medical and substance abuse services.

Only limited information is currently available about interactions between buprenorphine and antiretroviral agents. In contrast to methadone, buprenorphine does not appear to raise zidovudine levels. Pilot data indicate that buprenorphine levels do not appear to be reduced and opiate withdrawal does not occur during co-administration with efavirenz.

Summary

Provision of successful antiretroviral therapy for injection drug users is possible. It is enhanced by supportive clinical care sites and provision of drug treatment, awareness of interactions with methadone and the increased risk of side effects and toxicities and the need for simple regimens to enhance medication adherence. These are important considerations in selection of regimens and providing appropriate patient monitoring in this population. Preference should be given to antiretroviral agents with lower risk for hepatic and neuropsychiatric side effects, simple dosing schedules and lack of interaction with methadone.

HIV-Infected Women of Reproductive Age and Pregnant Women

Panel's Recommendations:

- ***When initiating antiretroviral therapy for women of reproductive age, the indications for initiation of therapy and the goals of treatment are the same as for other adults and adolescents (AI).***
- ***Efavirenz should be avoided for the woman who desires to become pregnant or who does not use effective and consistent contraception. (AIII)***
- ***For the woman who is pregnant, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of viral suppression to <1,000 copies/mL to reduce the risk of transmission of HIV to the fetus and newborn (AI).***
- ***Selection of an antiretroviral combination should take into account known safety, efficacy, and pharmacokinetic data of each agent during pregnancy (AIII).***
- ***Clinicians should consult the most current PHS guidelines when designing a regimen for a pregnant patient (AIII).***

This section provides a brief discussion of some unique considerations when caring for HIV-1 infected women of reproductive age and pregnant women. For more up-to-date and in-depth discussion regarding the management of these patients, the clinicians should consult the latest guidelines of the ***Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States***, which can be found in the **http://www.aidsinfo.nih.gov** website *[97]*.

Women of Reproductive Age. In women of reproductive age, antiretroviral regimen selection should account for the possibility of planned or unplanned pregnancy. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans and use of effective contraception should be discussed with the patient. As part of the evaluation for initiating therapy, women should be counseled about the potential teratogenic risk of efavirenz-containing regimens should pregnancy occur. These regimens should be avoided in women who are trying to conceive or are not using effective and consistent contraception. Various PIs and NNRTIs are known to interact with oral contraceptives, resulting in possible

decreases in ethinyl estradiol or increases in estradiol or norethindrone levels (see **Table 20**). These changes may decrease the effectiveness of the oral contraceptives or potentially increase risk of estrogen- or progestin-related side effects. Providers should be aware of these drug interactions and an alternative or additional contraceptive method should be considered. Amprenavir (and probably fosamprenavir) not only increases blood levels of both estrogen and progestin components, but oral contraceptives decrease amprenavir levels as well; these drugs should not be co-administered. There is minimal information about drug interactions with use of newer hormonal contraceptive methods (e.g., patch, vaginal ring). Counseling should be provided on an ongoing basis. Women who express a desire to become pregnant should be referred for pre-conception counseling and care, including discussion of special considerations with antiretroviral therapy use during pregnancy.

Pregnant Women. Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of mother-to-child transmission (PMTCT) and to maternal and fetal safety, timing of initiation of treatment and selection of regimens may be different from non-pregnant adults or adolescents.

PMTCT. Antiretroviral therapy is recommended in all pregnant women, regardless of virologic, immunologic, or clinical parameters, for the purpose of PMTCT.**(AI)** Reduction of HIV-RNA levels to below 1,000 copies/mL and use of antiretroviral therapy appear to have an independent effect on reduction of perinatal transmission *[96, 237, 238]*.

The decision to use any antiretroviral drug during pregnancy should be made by the woman after discussion with her clinician regarding the benefits versus risks to her and her fetus. Long-term follow-up is recommended for all infants born to women who have received antiretroviral drugs during pregnancy, regardless of the infants' HIV status.

Regimen Considerations. Recommendations regarding the choice of antiretroviral drugs for treatment of infected women are subject to unique considerations including:

- potential changes in pharmacokinetics and thus dosing requirements resulting from physiologic changes associated with pregnancy,
- potential adverse effects of antiretroviral drugs on a pregnant woman,
- effect on the risk for perinatal HIV transmission, and
- potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, all of which are not known for many antiretroviral drugs (see **Table 28**).

Based on available data, recommendations related to drug choices have been developed by the US Public Health Service Task Force and can be found in **Table 29**.

Current pharmacokinetic studies in pregnancy, although not completed for all agents, suggest no need for dosage modification for NRTIs and nevirapine. Nelfinavir, given as 1,250mg twice daily achieves optimal blood levels, but 750mg three times daily dosing does not, thus, the 1,250mg twice daily dosing should be used in all pregnant women *[76]*. Serum concentrations for unboosted indinavir and saquinavir may result in lower than optimal levels during pregnancy, thus ritonavir boosting will be necessary to achieve more optimal concentrations. Preliminary data suggest lower than optimal concentration of lopinavir is seen with the currently recommended adult dose of lopinavir/ritonavir, this agent should be used with close monitoring of virologic response *[67]*.

Some agents may cause harm to the mother and/or the fetus, and are advised to be avoided or used with extreme caution. These agents include:

1. Efavirenz-containing regimens should be avoided in pregnancy (particularly during the first trimester) because significant teratogenic effects were seen in primate studies at drug exposures similar to those achieved during human exposure. In addition, several cases of neural tube defects have now been reported after early human gestational exposure to efavirenz *[57]*.
2. The combination of ddI and d4T should be avoided during pregnancy because of several reports of fatal and non-fatal but serious lactic acidosis with hepatic steatosis and/or pancreatitis after prolonged use of regimens containing these two nucleoside analogues in combination *[100]*. This combination should be used during pregnancy only when other NRTI drug combinations have failed or have caused unacceptable toxicity or side effects.
3. Nevirapine has been associated with a 12-fold increased risk of symptomatic hepatotoxicity in women with pre-nevirapine $CD4^+$ T cell counts >250 cells/mm^3. A majority of the cases occurred within the first 18 weeks of therapy. Hepatic failure and death have been reported among a small number of pregnant patients *[239]*. Pregnant patients on chronic nevirapine prior to pregnancy are probably at a much lower risk for this toxicity. In nevirapine-naïve pregnant women

with CD4$^+$ T cell counts >250 cells/mm^3, nevirapine should not be initiated as a component of a combination regimen unless the benefit clearly outweighs the risk. If nevirapine is used, close clinical and laboratory monitoring, especially during the first 18 weeks of treatment, is strongly advised.

4. The oral liquid formulation of amprenavir contains high level of propylene glycol and should not be used in pregnant women.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to antiretroviral drugs (either administered alone or in combinations) to the **Antiretroviral Pregnancy Registry** (**Telephone: 910–251–9087** or **1–800–258–4263**). The registry collects observational, non-experimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of antiretroviral therapy during pregnancy, please refer to ***Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*** *[97]*

Lastly, the women should be counseled regarding the avoidance of breastfeeding. Continued clinical, immunologic, and virologic follow-up should be done as recommended for non-pregnant adults and adolescents.

Discontinuation of Antiretroviral Therapy Post-Partum. Pregnant women who are started on antiretroviral therapy during therapy for the sole purpose of PMTCT and who do not meet criteria for starting treatment for their own health may choose to stop antiretroviral therapy after delivery. However, if therapy includes nevirapine, stopping all regimen components simultaneously may result in functional monotherapy because of its long half-life and subsequent increased risk for resistance. Nevirapine resistance mutations have been identified postpartum in women taking nevirapine-containing combination regimens only for prevention of mother-to-child transmission. In one study nevirapine resistance was identified in 16% of women despite continuation of the nucleoside backbone for 5 days after stopping nevirapine *[240]*. Further research is needed to assess appropriate strategies for stopping nevirapine-containing combination regimens after delivery in situations where ongoing maternal treatment is not indicated.

Antiretroviral Considerations in Patients with Co-Infections

Hepatitis B (HBV)/HIV Co-Infection

HIV-infected patients with chronic HBV co-infection have a higher frequency of HBe antigenemia, higher levels of HBV DNA and higher rates of HBV-associated liver diseases *[241-245]*. It is unclear if chronic HBV-infection increases HIV disease progression, but it does increase the frequency of antiretroviral-associated hepatotoxicity *[122, 246]*.

Assessment of HBV/HIV Co-infection. Patients with HIV/HBV should be advised to avoid or limit alcohol consumption and use appropriate precautions to prevent transmission of both viruses. They should receive hepatitis A virus (HAV) vaccine if found to be susceptible, as determined by the absence of HAV antibody.

All patients with HBV should be considered for HBV therapy. Antiviral therapy is recommended for those patients with active HBV replication, defined as HBeAg positive or HBV DNA level >10^5 c/mL and necroinflammation in the liver [a serum alanine transferase (ALT) at least 2 x upper limit of normal (ULN) or histologic evidence of moderate disease activity or fibrosis] *[247]*. Response to HBV therapy is generally poor in patients with baseline ALT levels <2 x ULN.

Treatment of HBV/HIV Co-Infection. There are two forms of therapy for HBV infection, and neither is "preferred":

- Interferon alfa 2a or 2b given subcutaneously in doses of 5 MU per day or 10 MU three times weekly for 16-24 weeks (for HBeAg positive individuals) or ≥48 weeks (for HBeAg negative individuals) *[247, 248]*. Recommendations for duration and efficacy of interferon therapy are less clear for HIV co-infected patients due to a paucity of published experience *[249-251]*.
- As an alternative to interferon, nucleoside or nucleotide analog may be used. Lamivudine, emtricitabine, and tenofovir are active against both HIV and HBV. All of these drugs have the potential for serious hepatotoxicity due to a flare in hepatitis B when they are discontinued *[252]*.

Lamivudine. This drug is highly active against HBV based on evidence of improved liver histology and decrease in HBV DNA levels *[253, 254]*. However, rates of resistance to lamivudine have been noted to be

significantly higher with HIV co-infection—about 50% at 2 years and 90% at 4 years *[253-256]*.

Adefovir. This drug is highly active against HBV, including lamivudine-resistant strains *[253, 257]*. Rates of HBV resistance in HIV seronegative patients at follow-up of >124 weeks is about 2% *[258]*. This drug has no appreciable HIV activity at doses used for treatment of HBV and limited data suggest little risk of generating HIV resistance to this class *[258, 259]*. More data are needed to confirm this observation.

Tenofovir. This drug is highly active against HBV with an average 4 $\log_{10}$ copies/mL decrease in HBV DNA levels, including infections with lamivudine-resistant strains *[260-262]*. Short term follow-up (24 weeks) shows levels of HBV resistance rates are very low *[260-262]*.

Emtricitabine. Experience is limited but this drug appears to be very similar to lamivudine in its activity against HBV, including the rapid evolution of resistance. Emtricitabine-resistant isolates show cross resistance to lamivudine, but not to tenofovir or adefovir *[263, 264]*.

Scenarios for Treating HBV/HIV Co-Infection. The above data have led to the following recommendations for therapy of HBV/HIV co-infection:

- **Need to treat HIV and not HBV**: Consider withholding tenofovir, emtricitabine and lamivudine for future use if necessary. Avoid using lamivudine or tenofovir as the single drug with anti-HBV activity in this setting.
- **Need to treat HIV & HBV**: Consider using tenofovir, lamivudine, or emtricitabine. Due to high rates of HBV resistance to lamivudine or emtricitabine, some authorities recommend combining either of these drugs with tenofovir.
- **Need to treat HBV and not HIV**: Consider adefovir or interferon-alpha (pegylated preferred). Avoid lamivudine, emtricitabine, and tenofovir since these drugs should only be used as components of a fully suppressive combination antiretroviral regimen, unless HIV resistance to these specific agents has been previously documented.
- **Need to discontinue lamivudine, tenofovir or emtricitabine**: Monitor clinical course and liver function tests carefully and consider use of adefovir to prevent flares especially in patients who have marginal hepatic reserve *[94, 95]*.

Hepatitis C (HCV)/HIV Co-Infection

Long-term studies of patients with chronic HCV infection show that between 2-20% develop cirrhosis in 20 years *[265]*. This rate of progression increases with older age, alcoholism, and HIV infection *[265-267]*. A meta-analysis demonstrated that the rate of progression to cirrhosis with HIV/HCV co-infection was about 3-fold higher when compared to patients who are seronegative for HIV *[266]*. This accelerated rate is magnified in patients with low CD4 cell counts. Chronic HCV infection also complicates HIV treatment by the increased frequency of antiretroviral-associated hepatotoxicity *[122]*. Multiple studies show poor prognosis for HCV/HIV co-infection in the era of combination antiretroviral therapy. It is unclear if HCV adversely affects the rate of HIV progression *[268, 269]* or if this primarily reflects the impact of injection drug use (see **Injection Drug Use** section), which is strongly linked to HCV infection *[269-271]*. It is also unclear if antiretroviral therapy improves the attributable morbidity and mortality for untreated HCV.

Assessment of HCV/HIV Co-Infection. Patients with HIV/HCV infection should be advised to avoid or limit alcohol consumption, use appropriate precautions to prevent transmission of both viruses to others, and should be given hepatitis A and B vaccine if found to be susceptible. All patients with HCV, including those with HIV co-infection, should be evaluated for HCV therapy.

Standard indications for HCV therapy in the absence of HIV infection are detectable plasma HCV RNA and a liver biopsy showing bridging or portal fibrosis. ALT levels may be elevated in association with HCV infection. However, ALT levels do not accurately reflect the severity of HIV-associated liver disease. Liver biopsy is important for HCV therapeutic decision making but is indicated only if the patient is considered a treatment candidate based on multiple other variables including severity and stability of HIV disease, other co-morbidities, probability of adherence, and if there are contraindications to interferon-alpha, one of the drugs available for treatment of HCV.

Clinical trials in patients with HCV/HIV co-infection using pegylated interferon plus ribavirin for 48 weeks show sustained virologic response (SVR) rates of 60-70% for HCV genotype 2/3 but only 15-28% for genotype 1 *[272, 273]*. These data are based on experience almost exclusively in carefully selected patients with CD4 cell counts over 200/mm^3 *[273-275]*.

Treatment of HCV/HIV Co-infection. Based on these observations, treatment of HCV is recommended according to standard guidelines *[276] with* preference

for those with higher CD4 cell counts (>200 cells/mm^3). For some patients with lower CD4 counts, it may be preferable to initiate antiretroviral therapy and delay HCV therapy. Concurrent treatment is feasible, but may be complicated by pill burden, drug toxicities and drug interactions.

Scenarios for Treating HCV/HIV Co-Infection . Differences in HCV therapy management in the presence of HIV co-infection include:

- Ribavirin should not be given with didanosine due to the potential for drug-drug interactions leading to pancreatitis and lactic acidosis *[103]*;
- Some NRTIs and all NNRTIs and PIs are potentially hepatotoxic so that monitoring of serum transaminase levels is particularly important *[246]*;
- Zidovudine combined with ribavirin is associated with higher rates of anemia suggesting this combination be avoided when possible;
- Growth factors to manage interferon-associated neutropenia and ribavirin-associated anemia may be required.

Mycobacterium Tuberculosis (TB/HIV Co-infection)

Panel's Recommendations:

- ***The treatment of tuberculosis in patients with HIV infection should follow the same principles for persons without HIV infection. (AI)***
- ***Presence of active tuberculosis requires immediate initiation of treatment. (AI)***
- ***In antiretroviral-naïve patients, delay of antiretroviral therapy for 4-8 weeks after initiation of tuberculosis treatment permits a better definition of causes of adverse reactions and paradoxical reactions. (BIII)***
- ***Directly observed therapy is strongly recommended for HIV/TB co-infected patients.(AII)***
- ***Rifampin/rifabutin-based regimens should be given at least three times weekly in patients with CD4$^+$ T cell count <100 cells/mm^3. (AII)***
- ***Once weekly rifapentine is not recommended in HIV-infected patients. (EI)***
- ***Despite drug interactions, rifamycin should be included in patients receiving anti-retroviral therapy, with dosage adjustment as necessary.(AII)***
- ***Paradoxical reaction should be treated with continuation of treatment for tuberculosis and HIV, along with use of non-steroidal anti-inflammatory agents. (BIII)***
- ***In severe cases of paradoxical reaction, some suggest use of high dose prednisone. (CIII)***

HIV infection increases the risk of progression from latent to active tuberculosis by approximately 100 fold *[277]*. The CD4$^+$ cell count influences both the frequency and clinical expression of active tuberculosis *[278, 279]*. Tuberculosis also negatively impacts HIV disease. It is associated with a higher HIV viral load and more rapid progression of HIV disease *[277, 278]*. Important issues with respect to the use of antiretroviral drugs in patients with tuberculosis co-infection are the sequencing of treatments, potential for significant drug interactions with rifamycins, high rates of hepatotoxicity with drugs used for both infections, and development of immune reconstitution tuberculosis ("paradoxical reactions").

Scenarios for Treating TB/HIV Co-infection. The treatment of tuberculosis should follow the general principles for tuberculosis in persons without HIV (**AI)**. Below are various scenarios:

- **Patients on Antiretroviral Therapy**. Patients receiving antiretroviral treatment at the time tuberculosis treatment is started will require assessment of the antiretroviral regimen with changes that will permit use of the optimal tuberculosis regimen with particular attention to rifamycins (discussed below).
- **Patients Not Currently on Antiretroviral Therapy**. For patients who have not received antiretroviral therapy, the simultaneous initiation of treatment of both conditions has been associated with a high rate of side effects and paradoxical reactions *[280, 281]*. Active tuberculosis always requires immediate initiation of treatment **(AI)**. A delay in antiretroviral therapy for 4-8 weeks permits better definition of causes of adverse drug reactions and paradoxical reactions. Thus, it is recommended that simultaneous initiation for tuberculosis and HIV should be avoided, with the possible exception of patients who have CD4$^+$ cell count < 50 cells/mm^3. The optimal time to delay initiation of antiretroviral therapy is not known, but many authorities suggest a delay of 4-8 weeks **(BIII)**.

Treatment of tuberculosis. Treatment of drug-susceptible tuberculosis should consist of the standard regimen outlined in treatment guidelines, which consist of isoniazid (INH), rifampin or rifabutin (RIF), pyrizinamide (PZA), and ethambutol (EMB) or streptomycin (SM) given two months followed by INH + RIF for 4-7 months *[282]* **(AI)**. Special attention should be given to the potential of drug-drug interactions with rifamycin as discussed below. In the case of single or multi-drug resistant tuberculosis, therapy should be prescribed based on susceptibility result and preferably in consultation with expert in tuberculosis.

Directly Observed Therapy (DOT). DOT is strongly recommended for patients with HIV/TB co-infection **(AII)**. Once or twice-weekly dosing has been associated with increased rates of rifamycin resistance in patients with advanced HIV *[283, 284]*. Thus, once-weekly rifapentine is not recommended **(EI)** and rifampin/rifabutin-based TB regimens should be given at least three times weekly for those with a CD4 cell count <100 cells/mm^3 *[282]* **(AII)**. In general, daily directly observed therapy (DOT) is recommended for the first two months and then three times weekly DOT for the continuation phase **(BII)**.

Anti-tuberculosis/Antiretroviral Drug Toxicities and Interactions. All antiretroviral drugs are associated with the potential for hepatotoxicity. INH, RIF and PZA may also cause drug-induced hepatitis. These first line anti-tuberculous drugs should be used if at all possible even with co-administration of other hepatotoxic drug or baseline liver disease **(AIII)**. Patients receiving these drugs should have frequent monitoring for clinical symptoms of hepatitis and laboratory monitoring for hepatotoxicity, including serum aminotransferases, bilirubin, and alkaline phosphatase.

Rifamycins are essential drugs for the treatment of tuberculosis, but are also associated with frequent drug interactions with PIs and NNRTIs due to their effects as inducers of the hepatic cytochrome P-450 enzyme system. Despite these interactions, rifamycin should be included in the tuberculosis treatment regimen in patients receiving antiretroviral agents *[285]* **(AII)**. Among the rifamycins, rifampin is the most potent inducer. Unfortunately, of all available NNRTIs and PIs, rifampin may be used only with full dose ritonavir or with efavirenz (**Table 19**). Rifampin cannot be used safely with ritonavir-boosted PI regimens. Rifabutin is recommended when used in combination with appropriate dose adjustments, according to **Table 20** *[286]*.

Some patients treated for tuberculosis will develop a "paradoxical reaction" characterized by fever, new lymphadenopathy, worsening of pulmonary infiltrates and expanding pleural effusions. These reactions may occur in the absence of HIV infection or in the absence of antiretroviral therapy, but are more common with immune reconstitution due to antiretroviral treatment. If not severe, these reactions should be managed with continuation with drugs for tuberculosis and HIV with non-steroidal anti-inflammatory agents **(BIII)**. Occasional severe cases have been managed with high dose prednisone (1mg/kg for 1-2 weeks followed by tapering doses) *[280, 281]* **(CIII)**.

PREVENTION COUNSELING FOR THE HIV-INFECTED PATIENT

Prevention counseling is an essential component of management for HIV-infected persons. Each patient encounter provides an opportunity to reinforce HIV prevention messages. Therefore, each encounter should include assessment and documentation of:

- the patient's knowledge and understanding of HIV transmission; and
- the patient's HIV transmission behaviors since the last encounter with a member of the health-care team.

This should be followed by a discussion of strategies to prevent transmission that might be useful to the patient. Each member of the health care team can routinely provide this counseling. Partner notification is a key component of HIV detection and prevention and should be pursued with the patient by the provider or by referral services. Behavior changes among HIV infected persons have been observed during the era of combination antiretroviral therapy that impacts prevention, however, evidence exists that awareness of the potential benefits of antiretroviral therapy has contributed to relapse into high-risk activities. There is good evidence that the probability of HIV transmission correlates with inoculum size based on precedent in other viral infections and on the basis of the discordant couples study and studies of perinatal transmission. There is an assumption that risk of transmission is reduced with exposure by sex or needle-sharing with therapy to reduce viral load, although there are no clinical studies to support that claim and there are no viral load thresholds that could be considered safe. Further, there is the concern that this impression might lead or has led to high risk behavior which might more than nullify any potential benefit. Lastly, HIV-infected women may engage in unprotected sex while attempting to become pregnant. Providers should discuss patient plans/desires concerning childbearing at intervals throughout care and refer women who are interested in getting pregnant for preconception counseling and care.

The following link provides more information that providers can access to provide them with better understanding of the need for prevention and prevention counseling *[287]*.

CONCLUSION

The Panel has carefully reviewed recent results from clinical trials in HIV therapy and considered how they inform appropriate care guidelines. The Panel appreciates that HIV care is highly complex and rapidly evolving. Guidelines are never fixed and must always be individualized. Where possible, the Panel has based recommendations on the best evidence from prospective trials with defined endpoints. When such evidence does not yet exist, the panel attempted to reflect reasonable options in its conclusions.

HIV care requires, as always, partnerships and open communication. The provider can make recommendations most likely to lead to positive outcomes only if the patient's own point of view and social context is well known. Guidelines are only a starting point for medical decision-making. They can identify some of the boundaries of high care quality, but cannot substitute for sound judgment.

As further research is conducted and reported, guidelines will be modified. The Panel expects new drugs from current and newer classes to become available soon. These may well affect choices in initial and secondary drug regimens. The Panel also anticipates continued progress in the simplicity of regimens and in reduced toxicity. The Panel hopes the guidelines are useful and is committed to their continued adjustment and improvement.

- Information included in these guidelines may not represent FDA approval or approved labeling for the particular products or indications in question. Specifically, the terms “safe” and “effective” may not be synonymous with the FDA-defined legal standards for product approval.

Table 1. Rating Scheme for Clinical Practice Recommendations

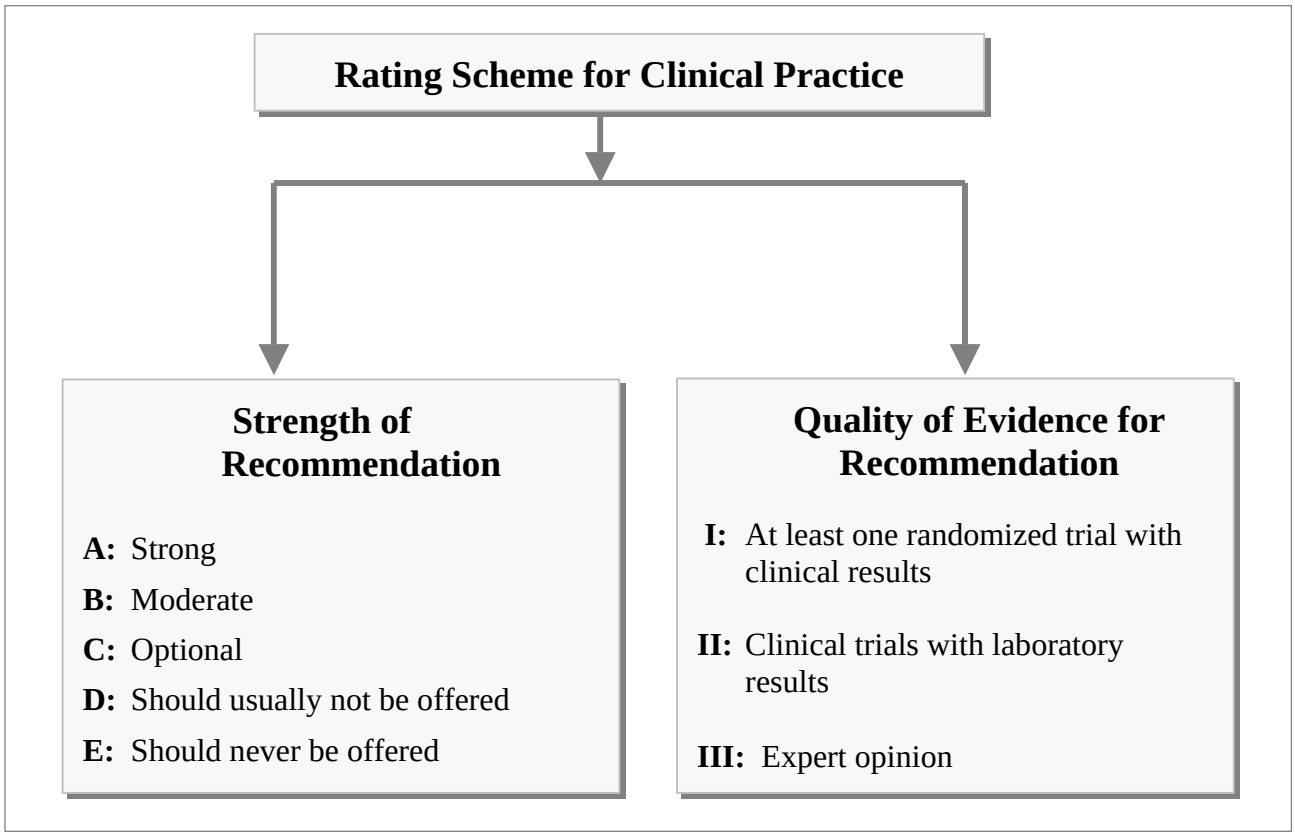

Table 2. Indications for Plasma HIV RNA Testing*

Clinical Indication	Information	Use
Syndrome consistent with acute HIV infection (see **Table 27**)	Establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis†
Initial evaluation of newly diagnosed HIV infection	Baseline viral load setpoint	Use in conjunction with $CD4^+$ T cell count for decision to start or defer therapy
Every 3–4 months in patients not on therapy	Changes in viral load	Use in conjunction with $CD4^+$ T cell count for decision to start therapy
2–8 weeks after initiation of or change in antiretroviral therapy	Initial assessment of drug efficacy	Decision to continue or change therapy
3–4 months after start of therapy	Assessment of virologic effect of therapy	Decision to continue or change therapy
Every 3–4 months in patients on therapy	Durability of antiretroviral effect	Decision to continue or change therapy
Clinical event or significant decline in $CD4^+$ T cells	Association with changing or stable viral load	Decision to continue, initiate, or change therapy

* Acute illness (e.g., bacterial pneumonia, tuberculosis, herpes simplex virus, *Pneumocystis jiroveci* pneumonia), and vaccinations can cause an increase in plasma HIV RNA for 2–4 weeks; viral load testing should not be performed during this time. Plasma HIV RNA results should usually be verified with a repeat determination before starting or making changes in therapy.

† Diagnosis of HIV infection made by HIV RNA testing should be confirmed by standard methods (i.e., ELISA and Western blot testing) performed 2–4 months after the initial indeterminate or negative test.

Table 3a: Probability of progressing to AIDS or death according to CD4 cell count, viral load, and sociodemographic factors

	CD4 cell count (cells/µL)									
	< 50		50–99		100–199		200–349		≥ 350	
	Viral load ≥ 5*	Viral load < 5*	Viral load ≥ 5*	Viral load < 5*	Viral load ≥ 5*	Viral load < 5*	Viral load ≥ 5*	Viral load < 5*	Viral load ≥ 5*	Viral load < 5*
CDC stage A/B and no history of IDU										
Age < 50 years										
Year 1	12 (11–14)	9.5 (8.0–11)	9.2 (7.7–11)	7.0 (5.8–8.5)	6.2 (5.2–7.3)	4.7 (4.0–5.6)	2.6 (2.1–3.2)	2.0 (1.6–2.5)	2.0 (1.6–2.5)	1.5 (1.2–1.9)
Year 2	17 (15–20)	13 (11–15)	13 (11–15)	10 (8.4–12)	9.5 (8.1–11)	7.3 (6.2–8.5)	4.5 (3.7–5.4)	3.3 (2.8–4.1)	3.3 (2.7–4.0)	2.5 (2.1–3.0)
Year 3	20 (18–23)	16 (13–19)	16 (14–19)	12 (10–15)	12 (10–14)	9.3 (7.9–11)	6.1 (5.0–7.4)	4.7 (3.9–5.6)	4.4 (3.6–5.4)	3.4 (2.8–4.1)
Age ≥ 50 years										
Year 1	17 (14–20)	13 (11–16)	12 (10–15)	9.6 (7.7–12)	8.5 (7.0–10)	6.5 (5.3–7.9)	3.6 (2.8–4.5)	2.7 (2.2–3.4)	2.8 (2.2–3.5)	2.1 (1.6–2.7)
Year 2	23 (19–27)	18 (15–21)	18 (15–21)	14 (11–17)	13 (10–15)	9.9 (8.2–12)	6.1 (5.0–7.6)	4.7 (3.8–5.8)	4.5 (3.6–5.7)	3.4 (2.8–4.3)
Year 3	27 (23–32)	21 (18–25)	22 (18–26)	17 (14–20)	16 (14–19)	13 (10–15)	8.3 (6.7–10)	6.4 (5.1–7.9)	6.0 (4.8–7.6)	4.6 (3.7–5.8)
CDC stage A/B and history of IDU										
Age < 50 years										
Year 1	17 (14–20)	13 (11–16)	12 (10–15)	9.5 (7.7–12)	8.4 (7.0–10)	6.5 (5.3–7.9)	3.6 (2.8–4.5)	2.7 (2.2–3.4)	2.7 (2.1–3.5)	2.1 (1.6–2.6)
Year 2	24 (21–28)	19 (16–23)	19 (16–22)	15 12–18)	14 (12–16)	11 (8.8–13)	6.6 (5.4–8.1)	5.0 (4.1–6.1)	4.9 (3.9–6.1)	3.7 (3.0–4.6)
Year 3	30 (26–35)	24 (20–28)	24 (20–28)	19 (15–23)	18 (15–22)	14 (12–17)	9.4 (7.6–11)	7.2 (5.8–8.8)	6.8 (5.4–8.6)	5.2 (4.2–6.5)
Age ≥ 50 years										
Year 1	22 (18–27)	17 (14–22)	17 (13–21)	13 (10–16)	11 (9.1–14)	8.8 (6.9–11)	4.9 (3.7–6.4)	3.7 (2.8–4.9)	3.8 (2.8–5.0)	2.9 (2.2–3.8)
Year 2	32 (26–38)	25 (20–31)	25 (20–31)	20 (15–25)	18 (15–23)	14 (11–18)	9.0 (7.0–11)	6.9 (5.4–8.8)	6.7 (5.1–8.7)	5.1 (3.9–6.6)
Year 3	39 (32–46)	31 (25–38)	33 (26–38)	25 (20–31)	24 (20–30)	19 (15–24)	13 (9.9–16)	9.8 (7.6–12)	9.3 (7.1–12)	7.1 (5.4–9.2)
CDC stage C and no history of IDU										
Age < 50 years										
Year 1	17 (15–19)	13 (11–15)	13 (11–15)	9.8 (8.1–12)	8.7 (7.2–10)	6.6 (5.5–8.1)	3.7 (2.9–4.7)	2.8 (2.2–3.5)	2.8 (2.2–3.6)	2.1 (1.7–2.7)
Year 2	23 (21–26)	18 (16–21)	18 (15–21)	14 (12–17)	13 (11–16)	10 (8.4–12)	6.3 (5.1–7.8)	4.8 (3.9–5.9)	4.6 (3.7–5.9)	3.5 (2.8–4.4)
Year 3	28 (25–31)	22 (19–25)	22 (19–26)	17 (14–21)	17 (14–20)	13 (11–15)	8.5 (6.9–11)	6.5 (5.2–8.1)	6.2 (4.9–7.9)	4.7 (3.7–6.0)
Age ≥ 50 years										
Year 1	23 (20–26)	18 (15–21)	17 (14–20)	13 (11–16)	12 (9.7–14)	9.1 (7.3–11)	5.1 (3.9–6.5)	3.8 (3.0–5.0)	3.9 (3.0–5.1)	3.0 (2.3–3.9)
Year 2	31 (27–35)	24 (20–28)	24 (20–28)	19 (15–23)	18 (15–21)	14 (11–17)	8.6 (6.8–11)	6.6 (5.2–8.3)	6.4 (4.9–8.2)	4.9 (3.8–6.2)
Year 3	36 (32–41)	29 (24–34)	29 (25–34)	23 (19–28)	22 (18–27)	17 (14–21)	12 (9.2–15)	8.9 (7.0–11)	8.5 (6.5–11)	6.5 (5.0–8.3)
CDC stage C and history of IDU										
Age < 50 years										
Year 1	23 (20–26)	18 (15–21)	17 (14–21)	13 (11–16)	12 (9.5–14)	9.0 (7.2–11)	5.0 (3.9–6.5)	3.8 (2.9–5.0)	3.9 (2.9–5.1)	2.9 (2.2–3.9)
Year 2	33 (29–37)	26 (22–30)	26 (22–30)	20 (16–24)	19 (15–23)	15 (12–18)	9.2 (7.3–12)	7.0 (5.6–8.9)	6.8 (5.3–8.8)	5.2 (4.1–6.7)
Year 3	40 (35–45)	32 (27–37)	32 (27–38)	25 (21–31)	25 (22–30)	19 (16–24)	13 (10–16)	10.0 (7.9–13)	9.5 (7.3–12)	7.3 (5.6–9.4)
Age ≥ 50 years										
Year 1	30 (25–36)	24 (19–29)	23 (18–28)	18 (14–23)	16 (12–20)	12 (9.5–16)	6.9 (5.1–9.2)	5.3 (3.9–7.1)	5.3 (3.9–7.2)	4.0 (3.0–5.5)
Year 2	42 (36–49)	34 (28–41)	34 (27–41)	27 (21–33)	25 (20–31)	20 (15–25)	12 (9.6–16)	9.6 (7.3–13)	9.3 (7.0–12)	7.1 (5.3–9.5)
Year 3	50 (43–58)	41 (34–49)	42 (34–50)	33 (27–41)	33 (26–40)	26 (20–32)	17 (13–23)	14 (10–18)	13 (9.6–17)	9.9 (7.4–13)

IDU=injection-drug use. *Log copies/mL

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Table 3b. Predicted 6-month risk of AIDS according to age and current CD4 cell count and viral load, based on a Poisson regression model.

Viral load (copies/mL)	Predicted risk (%) at current CD4 cell count (x 10^6 cells/l)[a]									
	50	100	150	200	250	300	350	400	450	500
Age 25 years										
3,000			2.3	1.6	1.1	0.8	0.6	0.5	0.4	0.3
10,000				2.3	1.6	1.2	0.9	0.7	0.5	0.4
30,000	13.3				2.2	1.6	1.2	0.9	0.7	0.6
100,000		10.6				2.4	1.8	1.4	1.1	0.8
300,000	25.1	14.5					2.5	1.9	1.5	1.2
Age 35 years										
3,000				2.0	1.4	1.0	0.8	0.6	0.5	0.4
10,000	12.1				2.0	1.5	1.1	0.9	0.7	0.5
30,000	16.6					2.1	1.6	1.2	0.9	0.7
100,000	23.1	13.2					2.3	1.7	1.3	1.1
300,000	30.8		11.7					2.4	1.9	1.5
Age 45 years										
3,000	10.7			2.5	1.8	1.3	1.0	0.7	0.6	0.5
10,000	15.1				2.6	1.9	1.4	1.1	0.8	0.7
30,000	20.6	11.7				2.6	2.0	1.5	1.2	0.9
100,000	28.4		10.6					2.2	1.7	1.3
300,000		22.4		10.1					2.4	1.9
Age 55 years										
3,000	13.4				2.3	1.7	1.2	0.9	0.7	0.6
10,000		10.7				2.4	1.8	1.4	1.1	0.8
30,000	25.4	14.6					2.5	1.9	1.5	1.2
100,000		20.5	13.3						2.2	1.7
300,000		27.5		12.6						2.4

[a] Shading distinguishes risk: <2%, no shading; 2–9.9%, light gray; 10–19.9%, mid-gray; ≥ 20%, darkest gray.

Reprint with permission from Lippincott, Williams & Wilkins [Phillips A; CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. *AIDS* 2004; 18 (1):51-8].

Table 4. Indications for Initiating Antiretroviral Therapy for the Chronically HIV-1 Infected Patient

The optimal time to initiate therapy is unknown among persons with asymptomatic disease and $CD4^+$ T cell count of >200 cells/mm^3. This table provides general guidance rather than absolute recommendations for an individual patient. All decisions regarding initiating therapy should be made on the basis of prognosis as determined by the $CD4^+$ T cell count and level of plasma HIV RNA indicated in table 3, the potential benefits and risks of therapy, and the willingness of the patient to accept therapy.

			Recommendation
			Treat
			Treat
			Treatment should be offered following full discussion of pros and cons with each patient (see text)

* AIDS-defining illness per Centers for Disease Control, 1993. Severe symptoms include unexplained fever or diarrhea > 2-4 weeks, oral candidiasis, or > 10% unexplained weight loss.

** Clinical benefit has been demonstrated in controlled trials only for patients with $CD4^+$ T cells < 200/mm^3, however, the majority of clinicians would offer therapy at a $CD4^+$ T cell threshold < 350/mm^3. A collaborative analysis of data from 13 cohort studies from Europe and North America found that lower CD4 count, higher HIV viral load, injection drug use, and age over 50 were all predictors of progression to AIDS or death in antiretroviral naïve patients beginning combination antiretroviral therapy. These data indicate that the prognosis is better for patients who initiate therapy at > 200 cells/mm^3, but risk after initiation of therapy does not vary considerably at > 200 cells/mm^3. (For additional information, see "**When to Treat - Indications for Antiretroviral Therapy**")

Table 5. Antiretroviral Regimens Recommended for Treatment of HIV-1 Infection in Antiretroviral Naïve Patients

Regimens should be individualized based on the advantages and disadvantages of each combination such as pill burden, dosing frequency, toxicities, drug-drug interaction potential, co-morbid conditions, and level of plasma HIV-RNA. Clinicians should refer to **Table 6** to review the pros and cons of different components of a regimen and to **Tables 10-12** for adverse effects and dosages of individual antiretroviral agents. Preferred regimens are in bold type; regimens are designated as "preferred" for use in treatment naïve patients when clinical trial data suggest optimal and durable efficacy with acceptable tolerability and ease of use. Alternative regimens are those where clinical trial data show efficacy, but it is considered alternative due to disadvantages compared to the preferred agent, such as antiviral activity, durability, tolerability, drug interaction potential, or ease of use. In some cases, based on individual patient characteristics, a regimen listed as alternative in this table may actually be the preferred regimen for a selected patient. Clinicians initiating antiretroviral regimens in the HIV-1-infected pregnant patient should refer to "*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*" at **http://aidsinfo.nih.gov/guidelines/**.

		No. of pills
Preferred Regimens NNRTI-based	**Efavirenz + (lamivudine or emtricitabine) + (zidovudine or tenofovir DF) (AII) –** [note: efavirenz is not recommended for use in 1st trimester of pregnancy or in women with high pregnancy potential*]	2-3
PI-based	**lopinavir/ritonavir (co-formulation) + (lamivudine or emtricitabine) + zidovudine (AII)**	8-9
Alternative Regimens NNRTI-based	**efavirenz** + (lamivudine or emtricitabine) + (abacavir or didanosine or stavudine) **(BII) –** [note: efavirenz is not recommended for use in 1st trimester of pregnancy or in women with high pregnancy potential*]	2-4
	nevirapine + (lamivudine or emtricitabine) + (zidovudine or stavudine or didanosine or abacavir or tenofovir) **(BII)** - [note: High incidence (11%) of symptomatic hepatic events was observed in women with pre-nevirapine $CD4^+$ T cell counts >250 cells/mm^3 and men with $CD4^+$ T cell counts >400 cells/mm^3 (6.3%). Nevirapine should not be initiated in these patients unless the benefit clearly outweighs the risk.]	3-6
PI-based	**atazanavir** + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or didanosine) or (tenofovir + ritonavir 100mg/d) **(BII)**	3-6
	fosamprenavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) **(BII)**	5-8
	fosamprenavir/ritonavir† + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) **(BII)**	5-8
	indinavir/ritonavir† + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) **(BII)**	7-12
	lopinavir/ritonavir + (lamivudine or emtricitabine) + (stavudine or abacavir or tenofovir or didanosine) **(BII)**	7-10
	nelfinavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) **(CII)**	5-8
	saquinavir (sgc, hgc, or tablets)ϕ **/ritonavir**† + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) **(BII)**	7-15
3 NRTI-based	**abacavir** + zidovudine + lamivudine **- only when a preferred or an alternative NNRTI- or a PI-based regimen cannot or should not be used (CII)**	2

* Women with child bearing potential implies women who want to conceive or those who are not using effective contraception

† Low-dose (100–400 mg) ritonavir per day

ϕ sgc = soft gel capsule; hgc = hard gel capsule

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Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

			Disadvantages
NNRTIs		**NNRTI Class Advantages:** • Less fat maldistribution and dyslipidemia than PI-based regimens • Save PI options for future use	**NNRTI Class Disadvantages:** • Low genetic barrier to resistance (single mutation confers resistance) • Cross-resistance among NNRTIs • Skin rash • Potential for CYP450 drug interactions (see **Tables 19-21b**)
	Efavirenz (preferred NNRTI)	• Potent antiretroviral activity • Low pill burden and frequency (1 tablet per day)	• Neuropsychiatric side effects • Teratogenic in nonhuman primates, contraindicated in 1st trimester of pregnancy and avoid use in women with pregnant potential
	Nevirapine	• No food effect • No evidence of increase adverse hepatic events in women who received single dose nevirapine for prevention of mother to child transmission (PMTCT)	• Higher incidence of rash than with other NNRTIs, including rare but serious hypersensitivity reactions (Stevens-Johnson Syndrome or toxic epidermal necrolysis) • Higher incidence of hepatotoxicity than with other NNRTIs, including serious and even fatal cases of hepatic necrosis • Female patients and patients with high pre-NVP $CD4^+$ T cell counts (>250 cells/mm^3 in females & >400 cells/mm^3 in males) are at a higher risk of symptomatic hepatic events. NVP is not recommended in these patients unless the benefit clearly outweighs the risk.
PIs		**PI Class Advantage:** • Save NNRTI for future use • Longest prospective study data including data on survival benefit	**PI Class Disadvantages:** • Metabolic complications - fat maldistribution, dyslipidemia, insulin resistance • CYP3A4 inhibitors & substrates – potential for drug interactions (more pronounced with ritonavir-based regimens) (see **Tables 19-21b**)
	Lopinavir/ ritonavir (preferred PI)	• Potent antiretroviral activity • Co-formulated as Kaletra®	• Gastrointestinal intolerance • Hyperlipidemia • Preliminary data show lower drug exposure in pregnant women • Food requirement
	Atazanavir	• Less adverse effect on lipids than other PIs • Once daily dosing • Low pill burden (2 pills per day)	• Indirect Hyperbilirubinemia • PR interval prolongation – generally inconsequential unless combined with another drug with similar effect • Reduced drug exposure when used with tenofovir and efavirenz – avoid concomitant use unless combined with RTV (ATV 300mg qd + RTV 100mg qd) • Absorption depends on food and low gastric pH
	Fosamprenavir	• Lower pill burden than amprenavir (4 vs. 16 cap per day) • No food effect	• Skin rash
	Fosamprenavir/ ritonavir	• Lower pill burden than amprenavir/ritonavir • Once daily regimen in patients with no history of PI failure • No food effect	• Skin rash
	Indinavir/ ritonavir	• RTV-boosting allows for twice-daily instead of 3-times-daily dosing • Eliminates food restriction of indinavir	• Potential for higher incidence of nephrolithiasis than with IDV alone • High fluid intake required (1.5–2 liters of fluid per day)
	Nelfinavir	• Favorable safety and pharmacokinetic profile for pregnant women when compared to other PIs	• Diarrhea • Higher rate of virologic failure when compared to other PIs (LPV/r & fosamprenavir) and efavirenz in clinical trials • Food requirement
	Saquinavir (hgc, sgc, or tablets) + ritonavir	• Low-dose ritonavir reduces saquinavir daily dose and frequency	• Gastrointestinal intolerance (hgc or tablets better tolerated than sgc)

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

			Disadvantages
NRTIs		• Established backbone of combination antiretroviral therapy	• Rare but serious cases of lactic acidosis with hepatic steatosis reported with most NRTIs
Triple NRTI regimen	Abacavir + zidovudine + lamivudine only	• Abacavir + zidovudine + lamivudine - Co-formulated as Trizivir® • Minimal drug-drug interactions • Low pill burden • Saves PI & NNRTI for future use	• Inferior virologic response when compared to efavirenz-based and indinavir-based regimens • Potential for abacavir hypersensitivity reaction
Dual NRTIs: backbone of three or more drug combination therapy	Zidovudine + lamivudine	• Most extensive and favorable virological experience • Co-formulated as Combivir®– ease of dosing • No food effect • Lamivudine – minimal side effects	• Bone marrow suppression with zidovudine • Gastrointestinal intolerance
	Stavudine + lamivudine	• No food effect	• Peripheral neuropathy, lipoatrophy, hyperlactatemia and lactic acidosis, reports of progressive ascending motor weakness, potential for hyperlipidemia with stavudine use • Stavudine - Higher incidence of mitochondrial toxicity than with other NRTIs
	Tenofovir + lamivudine	• Good virologic response when used with efavirenz • Once-daily dosing • No food effect	• Tenofovir – some reports of renal impairment • Interactions with: 1. atazanavir – tenofovir reduces atazanavir levels – need to add ritonavir); and 2. didanosine – tenofovir increases didanosine level – need to reduce dose of didanosine
	Abacavir + lamivudine	• No food effect • Study showing non-inferior to zidovudine + lamivudine as 2-NRTI backbone • Once daily dosing • Co-formulation (Epzicom®)	• Potential for abacavir systemic hypersensitivity reaction • Higher incidence of severe hypersensitivity reactions with once daily dosing as compared to twice daily dosing of Abacavir reported in one study
	Didanosine + lamivudine	• Once-daily dosing	• Peripheral neuropathy, pancreatitis – associated with didanosine • Food effect – needs to be taken on an empty stomach • Requires dosing separation from most PIs • Potential increase in toxicities when used with ribavirin, tenofovir, or hydroxyurea (lower dose of didanosine is recommended when used with tenofovir)
	NRTI + emtricitabine (in place of lamivudine)	• Long half-life than lamivudine • Once daily dosing • Co-formulation with tenofovir (Truvada®)	• Less experience than lamivudine

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Table 7. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

Three Class Comparison Studies
PI-based *vs.* NNRTI-based *vs.* 3-NRTI Regimens

ATLANTIC [1]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <500	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	d4T + ddI + IDV	100	417†	4.3 $\log_{10}$†	57	55	5	No difference among regimens except at 50 copy endpoint at which Arm C is inferior to Arms A and B (p=0.004)	The 3-NRTI regimen is less potent than either the IDV or NVP based regimen.
B	d4T + ddI + NVP	89	394†	4.3 $\log_{10}$†	58	54	7		
C	d4T + ddI + 3TC	109	396†	4.2 $\log_{10}$†	59	46	6		

CLASS (GSK)[2]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Statistical Significance	Comments & Conclusion
A	ABC/3TC + EFV	97	307	4.90 $\log_{10}$	81	72	2	No significant difference among the arms at 400 copy endpoint; NNRTI performed better at 50 copy endpoint.	NNRTI arm tended to perform better at lower viral copy cutoff.
B	ABC/3TC + r/AMP	96	306	4.85 $\log_{10}$	75	59	5		
C	ABC/3TC + d4T	98	296	4.81 $\log_{10}$	80	60	6		

* Values are means unless otherwise indicated by †; † Median value

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Table 7. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

Two Class Comparison Studies
PI-based *vs.* NNRTI-based Regimens

AACTG 384 [3, 4]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	Probability of not experiencing 1st regimen failure by 48 wks**	# of subjects with toxicity related failure of 1st regimen°	Premise	Comments & Conclusion
A	d4T + ddI + EFV	155	273†	5.0 $\log_{10}$†	62	20	Four drug regimens might be superior to sequential three drug regimens.	No significant benefit to the 4-drug regimens in this study over ZDV+3TC+EFV
B	d4T + ddI + NFV	155	264†	5.0 $\log_{10}$†	63	19		
C	ZDV+3TC+EFV	155	272†	4.9 $\log_{10}$†	89	11		
D	ZDV+3TC + NFV	155	307†	4.9 $\log_{10}$†	66	3	The way antiviral drugs are combined and sequenced is important.	Best first regimen appeared to be ZDV+3TC + EFV
E	d4T + ddI + NFV + EFV	178	274†	5.1 $\log_{10}$†	77	23		
F	ZDV+3TC + NFV + EFV	182	279†	4.9 $\log_{10}$†	84	12		The efficacy of ARVs depend on how they are combined.

** First regimen failure = virologic failure or toxicity related failure. Criteria for virologic failure: (1) decrease by < a factor of 10 in HIV-RNA by wk 8; or (2) increase by a factor of >10 above nadir measurement (and >2000 copies/mL within 24 wks); or (3) HIV-RNA level >200 copies/mL in a subject with two previous measurements of less than 200 copies/mL, or at any time after wk 24

° Any time during study follow-up

AI 424-034 Atazanavir Study (BMS) [5]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV/3TC + ATV	404	286	4.87 $\log_{10}$	70	32	NA	No significant difference between the two arms at either viral load endpoint.	ATV not inferior to EFV with a ZDV/3TC backbone. Uncharacteristically low response rates in both arms attributed by investigators by plasma collection technique.
B	ZDV/3TC + EFV	401	280	4.91 $\log_{10}$	64	37	NA		

COMBINE [6]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <200	% Subjects with plasma HIV RNA (ITT) <20	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV/3TC + NFV	70	347	5.21 $\log_{10}$	60	50	21	Virologic efficacy of regimens similar (no "p" values < 0.05).	NVP is at least as effective as NFV when combined with ZDV/3TC.
B	ZDV/3TC + NVP	72	396	5.07 $\log_{10}$	75	65	25		

Table 7. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

[**Two Class Comparison Studies (PI-based *vs*. NNRTI-based Regimens** (continued)]

DUPONT 006 [7]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV/3TC + EFV	154	350	4.77 $\log_{10}$	70	64	6	Arm A is superior to either of the other two arms.	EFV is superior to IDV with a ZDV/3TC nucleoside backbone.
B	ZDV/3TC + IDV	148	341	4.78 $\log_{10}$	48	43	20		
C	IDV + EFV	148	344	4.79 $\log_{10}$	53	47	6		

* Values are means unless otherwise indicated by †; † Median value

Two Class Comparison Studies
NNRTI-based *vs*. 3-NRTI Regimens

AACTG 5095 [8] (Interim analysis; Arms B and C pooled)

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <200	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %**	Statistical Significance	Comments & Conclusion
A	ZDV/3TC/ABC	382	234	4.85 $\log_{10}$	74	61	<1%	Virologic failure on Arm A significantly earlier than on the pooled EFV containing arms.	ZDV/3TC/ABC is inferior in a pooled analysis evaluating patients on either ZDV/3TC/ABC/EFV or ZDV/3TC/EFV
B C	Pooled Arm B (ZDV/3TC + EFV) and Arm C (ZDV/3TC/ABC + EFV)	765	242	4.86 $\log_{10}$	89	83	<1%		

****** <1% dropped out of the study for an adverse event, 5-8% made protocol-permitted drug substitutions (d4T for ZDV, ddI for ABC, NVP for EFV) for treatment-limiting toxicities.

* Values are means unless otherwise indicated by †; † Median value

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Table 7. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

Two Class Comparison Studies
PI-based *vs*. 3-NRTI Regimens

CNAAB3005 (GSK) [9]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV/3TC + ABC	282	359	4.85 $\log_{10}$†	51	40	17	Neither arm is inferior to the other.	Arm A is not inferior to Arm B, except for patients with baseline HIV-RNA > 100,000 copies/mL
B	ZDV/3TC + IDV	280	360	4.82 $\log_{10}$†	51	46	22		

CNA 3014 (GSK) [10]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV/3TC + ABC	169	331†	4.78 $\log_{10}$†	64	59	10	Arm A superior to Arm B at < 400 copy viral load cutoff ($p<0.002$). Difference not statistically significant at <50 cutoff.	ABC superior to IDV with ZDV/3TC backbone.
B	ZDV/3TC + IDV	173	299†	4.82 $\log_{10}$†	50	48	13		

* Values are means unless otherwise indicated by †; † Median value

Single Class Comparison Studies
Comparison of NNRTI-Based Regimens

2NN [11]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA <50 (ITT)	Adverse Effects Dropout %	Statistical Significance	Comments & Conclusion
A	d4T + 3TC + NVP (400 mg qd)	220	200	4.7 $\log_{10}$†	70	24	Only statistically inferior arm (Treatment failure) is Arm D.	No significant difference between NVP qd & bid, NVP+EFV inferior to EFV (but not different from NVP qd).
B	d4T + 3TC + NVP (200 mg bid)	387	170	4.7 $\log_{10}$†	65	21		
C	d4T + 3TC + EFV	400	190	4.7 $\log_{10}$†	70	16		NVP bid and EFV arms not significantly different but equivalence not clearly demonstrated. EFV+NVP not recommended due to adverse events.
D	d4T + 3TC + EFV + NVP	209	190	4.7 $\log_{10}$†	63	30		

* Values are means unless otherwise indicated by †; † Median value

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Table 7. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

Single Class Comparison Studies
Comparison of PI-Based Regimens

M98 863 (ABBOTT) [12]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	d4T + 3TC + LPV/r	326	260	5.01 $\log_{10}$	75	67	3.4	Arm A superior to Arm B at either viral load endpoint ($p<0.001$)	r/LOP superior to NFV with D4T + 3TC nucleoside backbone.
B	d4T + 3TC + NFV	327	258	4.98 $\log_{10}$	63	52	3.7		

NEAT - APV 30001 (GSK) [13]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ABC + 3TC + f APV (1400mg bid)	166	214†	4.82 $\log_{10}$†	66	58	6	Arm A virologically superior to Arm B ($P<0.001$)	fAPV superior to NFV with ABC/3TC backbone.
B	ABC + 3TC + NFV	83	212†	4.85 $\log_{10}$†	51	42	5		

SOLO - APV 30002 (GSK) [14]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Statistical Significance	Comments & Conclusion
A	ABC + 3TC + r/f-APV (200 mg/1400 mg qd)	322	166†	4.8 $\log_{10}$†	68	56	9	Arms A and B were not different in performance.	Daily r/f-APV is no worse than NFV in an ABC/3TC backbone.
B	ABC + 3TC + NFV	327	177†	4.8 $\log_{10}$†	65	52	6		

* Values are means unless otherwise indicated by †; † Median value

AI424–007 (BMS) [15]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	d4T + ddI + ATV	103	357	4.65 $\log_{10}$	64	36	6	No significant difference between the two arms at either viral load endpoint.	ATV not inferior to NFV in D4T/ddI backbone.
B	d4T + ddI + NFV	103	341	4.79 $\log_{10}$	56	39	7		

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Table 7. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

[Single Class Comparison Studies: Comparison of PI-Based Regimens (continued)**]**

AI424-008 (BMS) [16]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	d4T + 3TC + ATV	181	294	4.74 $\log_{10}$	67	33	1	Arm A was not inferior to Arm B at either viral load endpoint.	ATV and NLF were comparable with a d4T and 3TC backbone
B	d4T + 3TC + NFV	91	283	4.73 $\log_{10}$	59	38	3		

Nucleoside Backbone Comparison Studies

CNA 30024 (GSK) [17]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Statistical Significance	Comments & Conclusion
A	ZDV/3TC + EFV	325	258†	4.76 $\log_{10}$†	71	33	Arms not different at 48 weeks.	ZDV/3TC and ABC/3TC equivalent with EFV background therapy.
B	ABC/3TC + EFV	324	267†	4.81 $\log_{10}$†	74	23		

* Values are means unless otherwise indicated by †; † Median value

FTC 301A (Triangle/Gilead) [18]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	FTC +ddI + EFV	286	312	4.8 $\log_{10}$	81	78	7	FTC and d4T would be of equal efficacy in a background of ddI and EFV.	FTC superior to d4T in ddI + EFV background.
B	d4T + ddI + EFV	285	324	4.8 $\log_{10}$	68	59	13		

Gilead 903 [19]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	TDF + 3 TC + EFV	299	276	4.91 $\log_{10}$	80	76	6	TDF and d4T would be of equal efficacy in a background of 3TC and EFV.	TDF and d4T virologically equivalent. d4T associated with more toxicity.
B	d4T + 3TC + EFV	301	283	4.91 $\log_{10}$	84	80	6		

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Table 7. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

[**Nucleoside Backbone Comparison Studies** (continued)]

START I [20]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <500	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	d4T + 3 TC + IDV	101	424	4.57 $\log_{10}$	53	49	5	d4T and ZDV would be equivalent in suppression of viral load in a background of IDV and 3TC	Arm A is as potent as arm B
B	ZDV + 3TC + IDV	103	422	4.46 $\log_{10}$	52	47	6		

* Values are means unless otherwise indicated by †; † Median value

Antiretroviral Dosage Comparison Studies

AGOURON Study 542[21]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	d4T + 3TC + NFV (1250 mg bid)	323	279	5.0 $\log_{10}$	61	54	3.4	Arm A noninferior to Arm B	BID and TID dosing regimens of NFV had comparable efficacy and safety
B	d4T + 3TC + NFV (750 mg tid)	192	283	5.1 $\log_{10}$	58	51	3.7		

AI-454-148 (BMS) [22]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ddI (tablets-qd) + d4T + NFV	503	363	4.7 $\log_{10}$†	50	34	4	Arm A was inferior to Arm B.	once daily reduced mass ddI plus d4T was inferior to ZDV plus 3TC when used in combination with NFV
B	ZDV + 3TC + NFV	327	370	4.7 $\log_{10}$†	59	47	2		

AI454-152 (BMS)[23]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ddI (qd EC capsules) + d4T + NLF	258	410	4.76 $\log_{10}$	55	33	6	Arm A non-inferior to Arm B	Two nucleoside backbones showed comparable efficacy in combination with NFV
B	ZDV + 3TC + NFV	253	410	4.77 $\log_{10}$	56	33	7		

* Values are means unless otherwise indicated by †; † Median value

Table 7. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

[Antiretroviral Dosage Comparison Studies (continued)**]**

EPV20001 (GSK) [24]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV+ 3TC (bid) + EFV	278	399	4.57 $\log_{10}$	65	63	12	Arm B is non-inferior to Arm A	QD and BID dosing regimen of 3TC were comparable for efficacy
B	ZDV + 3TC (qd) + EFV	276	376	4.58 $\log_{10}$	67	61	6		

* Values are means unless otherwise indicated by †; † Median value

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Table 8. Antiretroviral Drugs and Components Not Recommended as Initial Therapy

	Reasons for not recommending as initial therapy
Amprenavir (Unboosted or ritonavir boosted) **(DIII)**	• High pill burden
Delavirdine **(DII)**	• Inferior virologic efficacy • Inconvenient dosing (three times daily)
Enfuvirtide **(DIII** as initial regimen**)**	• No clinical trial experience in treatment-naïve patients • Requires twice daily subcutaneous injections
Indinavir (Unboosted) **(DIII)**	• Inconvenient dosing (three times daily with meal restrictions)
Ritonavir as sole PI **(DIII)**	• High pill burden • Gastrointestinal intolerance
Saquinavir soft gel capsule (Unboosted) **(DII)**	• High pill burden • Inferior virologic efficacy
Zalcitabine + zidovudine **(DII)**	• Inferior virologic efficacy • Higher rate of adverse effects than other 2-NRTI alternatives

Table 9. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time

		Exception
Antiretroviral Regimens Not Recommended		
Monotherapy (EII)	• Rapid development of resistance • Inferior antiretroviral activity when compared to combination with three or more antiretrovirals	• Pregnant women with pretreatment HIV-RNA <1,000 copies/mL using ZDV monotherapy for prevention of perinatal HIV transmission and not for HIV treatment for the mother*; however, combination therapy is generally preferred.
2-NRTI regimens (EII)	• Rapid development of resistance • Inferior antiretroviral activity when compared to combination with three or more antiretrovirals	• For patients currently on this treatment some clinicians may continue if virologic goals are achieved **(DII)**
Abacavir + tenofovir + lamivudine (or emtricitabine) as a triple-NRTI regimen (EII)	• High rate of early virologic non-response seen when this triple NRTI combination was used as initial regimen in treatment-naïve patients	• No exception
Tenofovir + didanosine + lamivudine (or emtricitabine) combination as a triple-NRTI regimen (EII)	• High rate of early virologic non-response seen when this triple NRTI combination was used as initial regimen in treatment-naïve patients	• No exception
Antiretroviral Components Not Recommended As Part of Antiretroviral Regimen		
Amprenavir oral solution (EIII) in: • pregnant women; • children <4 yr old; • patients with renal or hepatic failure; and • patients on metronidazole or disulfiram	• Oral liquid contains large amount of the excipient propylene glycol, which may be toxic in the patients at risk	• No exception
Amprenavir + fosamprenavir (EII)	• Amprenavir is the active antiviral for both drugs, combined use have no benefit and may increase toxicities	• No exception
Amprenavir oral solution + ritonavir oral solution (EIII)	• The large amount of propylene glycol used as a vehicle in amprenavir oral solution may compete with ethanol (the vehicle in oral ritonavir solution) for the same metabolic pathway for elimination. This may lead to accumulation of either one of the vehicles.	• No exception
Atazanavir + indinavir (EIII)	• Potential additive hyperbilirubinemia	• No exception
Didanosine + stavudine (EIII)	• High incidence of toxicities – peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women*	• When no other antiretroviral options are available and potential benefits outweigh the risks* **(DIII)**
Didanosine + zalcitabine (EIII)	• Additive peripheral neuropathy	• No exception
Efavirenz in first trimester of pregnancy or in women with significant child-bearing potential* (EIII)	• Teratogenic in nonhuman primates	• When no other antiretroviral options are available and potential benefits outweigh the risks* **(DIII)**
Emtricitabine + lamivudine (EIII)	• Similar resistance profile • No potential benefit	• No exception
Lamivudine + Zalcitabine (EIII)	• In vitro antagonism	• No exception
Nevirapine initiation in women with CD4 >250 cells/mm^3 or men with CD4 >400 cells/mm^3 (DI)	Higher incidence of symptomatic (including serious and even fatal) hepatic events in these patient groups	Only if the benefit clearly outweighs the risk
Saquinavir hard gel capsule (Invirase®) as single protease inhibitor (EIII)	• Poor oral bioavailability (4%) • Inferior antiretroviral activity when compared to other protease inhibitors	• No exception
Stavudine + zalcitabine (EIII)	• Additive peripheral neuropathy	• No exception
Stavudine + zidovudine (EII)	• Antagonistic effect on HIV-1	• No exception

- When constructing an antiretroviral regimen for an HIV-infected pregnant woman, please consult "*Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*" in **http://www.aidsinfo.nih.gov/guidelines/**.

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Table 10. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

				-				**Adverse Events**
Abacavir (ABC) **Ziagen®** **Trizivir®** - w/ ZDV+3TC **Epzicom®** - w/ 3TC	Ziagen® 300 mg tablets or 20 mg/mL oral solution Trizivir® - ABC 300 mg + ZDV 300 mg + 3TC 150 mg Epzicom® - ABC 600 mg + 3TC 300 mg	300 mg two times/day; or 600mg once daily; or as Trizivir® - 1 tablet two times/day Epzicom® - 1 tablet once daily	Take without regard to meals; Alcohol increases abacavir levels 41%; abacavir has no effect on alcohol	83%	1.5 hours	12-26 hours	Metabolized by alcohol dehydrogenase and glucuronyl transferase. Renal excretion of metabolites 82% Trizivir® & Epzicom® not for patients with CrCl < 50 mL/min	Hypersensitivity reaction which can be fatal, symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath
Didanosine (ddI) **Videx®, Videx EC®, Generic didanosine enteric coated (dose same as Videx EC)**	Videx EC® 125, 200, 250, or 400 mg Videx® buffered tabs 25, 50, 100, 150, 200 mg Videx® buffered powders: 100, 167, 250 mg	Body weight ≥ **60kg:** 400 mg once daily (buffered tablets or EC capsule); or 200 mg two times/day (buffered tablets); with TDF: 250 mg/day **< 60 kg**: 250mg daily (buffered tablets or EC capsule); or 125mg two times/day (buffered tablets) with TDF: appropriate dose not established; probably < 250 mg/day	Levels decrease 55%; Take 1/2 hour before or 2 hours after meal	30–40%	1.5 hours	> 20 hours	Renal excretion 50% Dosage adjustment in renal insufficiency (see Table 14)	Pancreatitis; peripheral neuropathy; nausea; diarrhea Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with use of NRTIs.
Emtricitabine (FTC) **Emtriva™** **Truvada™** - w/ TDF	Emtriva™ - 200 mg hard gelatin capsule Truvada™ - FTC 200 mg + TDF 300 mg	Emtriva™ - 200 mg once daily Truvada™ - One tablet once daily	Take without regard to meals	93%	10 hours	> 20 hours	Renal excretion Dosage adjustment in renal insufficiency (see Table 14) Truvada™ - not for patients with CrCl < 30 mL/min	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs.)
Lamivudine (3TC) **Epivir®** **Combivir®** - w/ ZDV ; **Epizicom®** - w/ ABC **Trizivir®** - w/ ZDV+ABC ;	Epivir® 150 mg and 300 mg tablets or 10 mg/mL oral solution Combivir® - 3TC 150 mg + ZDV 300 mg Epizicom® - 3TC 300 mg + ABC 600 mg Trizivir® - 3TC 150 mg + ZDV 300 mg + ABC 300 mg	Epivir® 150 mg two times/day; or 300 mg daily Combivir® - 1 tablet two times/day Epizicom® - 1 tablet once daily Trizivir® - 1 tablet two times/day	Take without regard to meals	86%	5-7 hours	18 -22 hours	Renal excretion Dosage adjustment in renal insufficiency (see Table 14) Combivir®, Trizivir® & Epzicom® not for patients with CrCl < 50 mL/min	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)

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Table 10. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

								Adverse Events
Stavudine (d4T) **Zerit®**	Zerit® 15, 20, 30, 40 mg capsules or 1mg/mL for oral solution	Body weight >60 kg: 40 mg two times/day; Body weight <60 kg: 30 mg two times/day	Take without regard to meals	86%	1.0 hour	7.5 hours	Renal excretion 50% Dosage adjustment in renal insufficiency (see Table 14)	• Peripheral neuropathy; • Lipodystrophy • Rapidly progressive ascending neuromuscular weakness (rare) • Pancreatitis • Lactic acidosis with hepatic steatosis (higher incidence with d4T than with other NRTIs • Hyperlipidemia
Tenofovir Disoproxil Fumarate (TDF) **Viread®** **Truvada® -** w/ FTC	Viread® 300 mg tablet Truvada® - TDF 300 mg + FTC 200 mg	Viread® 1 tablet once daily Truvada® 1 tablet once daily	Take without regard to meals	25% in fasting state; 39% with high-fat meal	17 hours	>60 hours	Renal excretion Dosage adjustment in renal insufficiency (see Table 14) Truvada™ - not for patients with CrCl < 30 mL/min	Asthenia, headache, diarrhea, nausea, vomiting, and flatulence; renal insufficiency; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)
Zalcitabine (ddC) **Hivid®**	0.375, 0.75 mg tablets	0.75 mg three times/day	Take without regard to meals	85%	1.2 hours	N/A	Renal excretion 70% Dosage adjustment in renal insufficiency (see Table 14)	• Peripheral neuropathy; • Stomatitis; • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs); • Pancreatitis
Zidovudine (AZT, ZDV) **Retrovir®** **Combivir®-** w/ 3TC ; **Trizivir®- w/** 3TC+ABC **;**	**Retrovir®** 100 mg capsules, 300 mg tablets, 10 mg/mL intravenous solution, 10 mg/mL oral solution **Combivir®** 3TC 150 mg + ZDV 300 mg **Trizivir® -** 3TC 150 mg + ZDV 300 mg + ABC 300 mg	**Retrovir®** 300 mg two times/day or 200 mg three times/ day **Combivir® or Trizivir® -** 1 tablet two times/day	Take without regard to meals	60%	1.1 hours	7 hours	Metabolized to AZT glucuronide (GAZT). Renal excretion of GAZT Dosage adjustment in renal insufficiency (see Table 14) Combivir® & Trizivir® - not for patients with CrCl < 50 mL/min	• Bone marrow suppression: macrocytic anemia or neutropenia; • Gastrointestinal intolerance, headache, insomnia, asthenia; • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity associated with use of NRTIs.

Table 11. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

							Adverse Events
Delavirdine (DLV)/ Rescriptor®	100 mg tablets or 200 mg tablets	400 mg 3 times/day; four 100 mg tablets can be dispersed in ≥3 oz. of water to produce slurry; 200 mg tablets should be taken as intact tablets; separate dosing from buffered didanosine or antacids by 1 hour	Take without regard to meals	85%	5.8 hours	Metabolized by cytochrome P450 (3A inhibitor); 51% excreted in urine (<5% unchanged); 44% in feces	• Rash*; • Increased transaminase levels; • Headaches
Efavirenz (EFV)/ Sustiva®	50, 100, 200 mg capsules or 600 mg tablets	600 mg daily on an empty stomach, at or before bedtime	High-fat/high-caloric meals increase peak plasma concentrations of capsules by 39% and tablets by 79%; take on an empty stomach	Data not available	40–55 hours	Metabolized by cytochrome P450 (3A mixed inducer/ inhibitor); 14%–34% excreted in urine (glucuronidated metabolites, <1% unchanged); 16%–61% in feces.	• Rash*; • Central nervous system symptoms;† • Increased transaminase levels; • False-positive cannabinoid test; • Teratogenic in monkeys‡
Nevirapine (NVP)/ Viramune®	200 mg tablets or 50 mg/5 mL oral suspension	200 mg daily for 14 days; thereafter, 200 mg by mouth two times/day	Take without regard to meals	> 90%	25–30 hours	Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine (glucuronidated metabolites; < 5% unchanged); 10% in feces	• Rash including Stevens-Johnson Syndrome* • Symptomatic hepatitis, including fatal hepatic necrosis, have been reported‡

* During clinical trials, NNRTI was discontinued because of rash among 7% of patients taking nevirapine, 4.3% of patients taking delavirdine, and 1.7% of patients taking efavirenz. Rare cases of Stevens-Johnson Syndrome have been reported with the use of all three NNRTIs, the highest incidence seen with nevirapine use.

† Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Overall frequency of any of these symptoms associated with use of efavirenz was 52%, as compared with 26% among controls subjects; 2.6% of those persons on efavirenz discontinued the drug because of these symptoms; symptoms usually subside spontaneously after 2–4 weeks.

‡ Symptomatic, sometimes serious, and even fatal hepatic events (accompanied by rash in approximately 50% of cases) occur with significantly higher frequency in female patients with pre-nevirapine $CD4^+$ T cell counts >250 cells/mm^3 or in male patients with pre-nevirapine $CD4^+$ T cell counts >400 cells/mm^3. Nevirapine should not be initiated in these patients unless the benefit clearly outweighs the risk. This toxicity has not been observed when nevirapine is given as single doses to mothers or infants for prevention of mother-to-child HIV transmission.

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Table 12. Characteristics of Protease Inhibitors (PIs)

								Adverse Events
Amprenavir (APV)/ Agenerase®	50 mg capsules, 15 mg/mL oral solution (capsules and solution NOT inter-changeable on mg per mg basis)	1400 mg two times/day (oral solution) **Note:** APV and RTV oral solution should not be co-administered due to competition of the metabolic pathway of the two vehicles. **Note:** APV 150 mg capsule is no longer available; consider using fosamprenavir in these patients.	High-fat meal decreases blood concentration 21%; can be taken with or without food, but high fat meal should be avoided.	Not determined in humans	7.1–10.6 hours	Cytochrome P450 3A4 inhibitor, inducer, and substrate Dosage adjustment in hepatic insufficiency recommended (see Table 14)	Room temperature (up to 25ºC or 77ºF)	• GI intolerance, nausea, vomiting, diarrhea • Rash • Oral paresthesias • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia **Note:** Oral solution contains propylene glycol; contraindicated in pregnant women, children <4 years old, patients with hepatic or renal failure, & patients treated with disulfiram or metronidazole
Atazanavir (ATV)/ Reyataz™	100, 150, 200 mg capsules	400 mg once daily If taken with efavirenz or tenofovir: RTV 100 mg + ATV 300 mg once daily	Administration with food increases bioavailability Take with food; avoid taking with antacids	Not determined	7 hours	Cytochrome P450 3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (see Table 14)	Room temperature (up to 25ºC or 77ºF)	• Indirect hyperbilirubinemia • Prolonged PR interval – some patients experienced asymptomatic 1st degree AV block • Use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Fosamprenavir (f-APV)/ Lexiva™	700 mg tablet	ARV-naïve patients: • f-APV 1,400 mg two times/day; or • (f-APV 1,400 + RTV 200 mg) once daily; or • (f-APV 700 mg + RTV 100mg) two times/day PI-experienced pts (once daily regimen not recommended): • (f-APV 700mg + RTV 100mg) two times/day Co-administration w/ EFV (Unboosted f-APV not recommended): • (f-APV 700 mg + RTV 100mg) two times/day; or • (f-APV 1,400 mg + RTV 300 mg) once daily	No significant change in amprenavir pharmacokinetics in fed or fasting state	Not established	7.7 hours (amprenavir)	Amprenavir is a cytochrome P450 3A4 inhibitor, inducer, and substrate Dosage adjustment in hepatic insufficiency recommended (see Table 14)	Room temperature (up to 25ºC or 77ºF)	• Skin rash (19%) • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Indinavir/ Crixivan®	200, 333, 400 mg capsules	800 mg every 8 hours; With RTV: [IDV 800 mg + RTV 100 or 200 mg] every 12 hours	For unboosted IDV Levels decrease by 77% Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal For RTV-boosted IDV: Take with or without food	65%	1.5–2 hours	Cytochrome P450 3A4 inhibitor (less than ritonavir) Dosage adjustment in hepatic insufficiency recommended (see Table 14)	Room temperature 15-30ºC (59-86ºF), protect from moisture	• Nephrolithiasis • GI intolerance, nausea • Indirect hyperbilirubinemia • Hyperlipidemia • Misc.: Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

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Table 12. Characteristics of Protease Inhibitors (PIs)

								Adverse Events
Lopinavir + Ritonavir (LPV/r)/ Kaletra®	Each capsule contains LPV 133.3 mg + RTV 33.3 mg Oral solution: Each 5 mL contains LPV 400 mg + RTV 100 mg Note: Oral solution contains 42% alcohol	[LPV 400 mg + RTV 100 mg] (3 capsules or 5 mL) two times daily With EFV or NVP [LPV 533 mg + RTV 133 mg] (4 capsules or 6.7 mL) two times daily	Moderate fat meal increases AUC of capsules and solution by 48% and 80%, respectively Take with food.	Not determined in humans	5–6 hours	Cytochrome P450 (3A4 inhibitor and substrate)	Refrigerated capsules and solution are stable until date on label; if stored at room temperature(up to 25ºC or 77ºF) stable for 2 months	• GI intolerance, nausea, vomiting, diarrhea • Asthenia • Hyperlipidemia (esp. hypertriglyceridemia) • Elevated serum transaminases • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Nelfinavir (NFV)/ Viracept®	250 mg tablets or 625 mg tablets 50 mg/g oral powder	1,250 mg two times/day or 750 mg three times/day	Levels increase 2-3 fold Take with meal or snack	20–80%	3.5–5 hours	Cytochrome P450 3A4 inhibitor and substrate	Room temperature 15-30ºC (59-86ºF)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes among patients with hemophilia • Serum transaminase elevation
Ritonavir (RTV)/ Norvir®	100 mg capsules or 600 mg/7.5 mL solution	600 mg every 12 hours* (when ritonavir is used as sole PI) As pharmacokinetic booster for other PIs – 100 mg – 400 mg per day – in 1-2 divided doses	Levels increase 15% Take with food if possible; this may improve tolerability	Not determined	3–5 hours	Cytochrome P450 (3A4 > 2D6; Potent 3A4 inhibitor)	Refrigerate capsules Capsules can be left at room temperature (up to 25ºC or 77ºF) for ≤30 days; Oral solution should NOT be refrigerated	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias – circumoral and extremities • Hyperlipidemia, esp. hypertriglyceridemia • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Saquinavir tablets and hard gel capsules (SQV)/ Invirase®	200 mg capsules, 500 mg tablets	Unboosted SQV not recommended With RTV: • (RTV 100 mg + SQV 1,000 mg) two times/day	Take within 2 hours of a meal when taken with RTV	4% erratic (when taken as sole PI)	1–2 hours	Cytochrome P450 (3A4 inhibitor and substrate)	Room temperature 15-30ºC (59-86ºF)	• GI intolerance, nausea and diarrhea • Headache • Elevated transaminase enzymes • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Saquinavir soft gel capsule (SQV-sgc)/ Fortovase®	200 mg capsules	Unboosted SQV-sgc: 1,200 mg three times/day§ With RTV: • (RTV 100 mg + SQV-sgc 1,000 mg) two times/day	Levels increase 6-fold. Take with or up to 2 hrs after a meal – as sole PI or with RTV	Not determined	1–2 hours	Cytochrome P450 (3A4 inhibitor (less than ritonavir)	Refrigerate or store at room temperature (≤ 25ºC or 77ºF) for up to 3 months)	• GI intolerance, nausea, diarrhea, abdominal pain and dyspepsia • Headache • Hyperlipidemia • Elevated transaminase enzymes • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

* Dose escalation for Ritonavir when used as sole PI: Days 1 and 2: 300 mg two times; day 3-5: 400 mg two times; day 6-13: 500 mg two times; day 14: 600 mg two times/day.

Table 13. Characteristics of Fusion Inhibitors

							Adverse Events
Enfuvirtide (T20)/ Fuzeon™	• Injectable – in lyophilized powder • Each single-use vial contains 108 mg of enfuvirtide to be reconstituted with 1.1 mL of Sterile Water for injection for delivery of approximately 90 mg/1 mL	90 mg (1 mL) subcutaneously (SC) two times/day	84.3% (SC compared to IV)	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	Store at room temperature (up to 25ºC or 77ºF) Reconstituted solution should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and used within 24 hours	• Local injection site reactions – almost 100% of patients (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) • Increased rate of bacterial pneumonia • Hypersensitivity reaction (<1%) - symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases; rechallenge is not recommended

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Table 14. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Nucleoside Reverse Transcriptase Inhibitors – Note: Use of combination NRTI formulations of: Combivir, Trizivir, Epzicom – not recommended in patients with CrCl < 50 mL/min; use of Truvada – not recommended in patients with CrCl < 30 mL/min			
Abacavir* (Ziagen®)	300 mg PO BID	No need for dosage adjustment	No dosage recommendation
Didanosine (Videx®)	≥ 60 kg 400 mg PO qd < 60 kg 250 mg qd	**Dose** **CrCl (mL/min) >60 kg <60 kg** 30-59 200 mg 125 mg 10-29 125 mg 100 mg < 10 125 mg 75 mg CAPD or hemodialysis patients: use same dose as CrCl < 10 ml/min	No dosage recommendation
Emtricitabine (Emtriva®)	200 mg PO qd	**CrCl (mL/min) Dose** 30-49 200 mg q48h 15-29 200 mg q72h <15 200 mg q96h Hemodialysis patients: 200 mg q96h (dose after dialysis if dose is due on dialysis day)	No dosage recommendation
Lamivudine* (Epivir®)	300 mg PO qd or 150 mg PO BID	**CrCl (mL/min) Dose** 30-49 150mg qd 15-29 150 mg x 1, then 100 mg qd 5-14 150 mg x 1, then 50 mg qd <5 50 mg x 1, then 25 mg qd or hemodialysis	No dosage recommendation
Stavudine (Zerit®)	≥ 60 kg 40 mg PO BID < 60 kg 30 mg PO BID	**Dose** **CrCl (mL/min) >60 kg <60 kg** 26-50 20 mg q12h 15 mg q12h 10-25 20 mg q24h 15 mg q24h Hemodialysis – same dose as CrCl 10-25 ml/min, dose after dialysis on day of dialysis	No dosage recommendation
Tenofovir (Viread®)	300 mg PO qd	**CrCl (mL/min) Dose** 30-49 300 mg q48h 10-29 300 mg twice weekly ESRD 300 mg q7d or hemodialysis	No dosage recommendation
Tenofovir + Emtricitabine (Truvada®)	1 tablet PO qd	**CrCl (mL/min) Dose** 30-49 1 tablet q48h < 30 not recommended	No dosage recommendation
Zalcitabine (Hivid®)	0.75 mg PO TID	**CrCl (mL/min) Dose** 10-40 0.75 mg BID < 10 0.75 mg qd No data on hemodialysis	No dosage recommendation
Zidovudine* (Retrovir®)	300 mg PO BID	"Severe" renal impairment or hemodialysis – 100mg TID	No dosage recommendation
Non- Nucleoside Reverse Transcriptase Inhibitors			
Delavirdine (Rescriptor®)	400 mg PO TID	No dosage adjustment necessary	No recommendation; use with caution in patients with hepatic impairment
Efavirenz (Sustiva®)	600 mg PO qd	No dosage adjustment necessary	No recommendation; use with caution in patients with hepatic impairment
Nevirapine (Viramune®)	200 mg PO BID	No dosage adjustment necessary	No data available; avoid use in patients with moderate to severe hepatic impairment

Table 14. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Protease Inhibitors			
Amprenavir (Agenerase®)	1,200 mg PO BID **Note**: oral solution not recommended in patients with renal or hepatic failure	No dosage adjustment necessary	**Child-Pugh Score** **Dose** 5-8 450 mg BID 9-12 300 mg BID
Atazanavir (Reyataz®)	400 mg PO qd	No dosage adjustment necessary	**Child-Pugh Class** **Dose** 7-9 300 mg qd > 9 not recommended
Fosamprenavir (Lexiva®)	1,400 mg PO BID	No dosage adjustment necessary	**Child-Pugh Score** **Dose** 5-8 700 mg BID 9-12 not recommended ritonavir boosting should not be used in patients with hepatic impairment
Indinavir (Crixivan®)	800 mg PO q8h	No dosage adjustment necessary	**Mild to moderate hepatic insufficiency due to cirrhosis**: 600 mg q8h
Lopinavir/ritonavir (Kaletra®)	400 mg/100 mg PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Nelfinavir (Viracept®)	1,250 mg PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Ritonavir (Norvir®)	600 mg PO BID	No dosage adjustment necessary	No dosage adjustment in mild hepatic impairment; no data for moderate to severe impairment, use with caution
Saquinavir soft gel cap (Fortovase®)	1,200 mg TID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Fusion Inhibitors			
Enfuvirtide (Fuzeon®)	90 mg SQ q12h	No dosage adjustment necessary	No dosage recommendation

* Combination products of Combivir® and Trizivir® should not be used in patients with renal insufficiency

Creatinine Clearance calculation:

Male: $\frac{(140\text{-age in yr}) \times \text{weight (kg)}}{72 \times \text{S.Cr.}}$ Female: $\frac{(140\text{-age in yr}) \times \text{weight (kg)} \times 0.85}{72 \times \text{S.Cr.}}$

Child-Pugh Score

Component	Score Given		
	1	**2**	**3**
Encephalopathy*	None	Grade 1-2	Grade 3-4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretics
Albumin	> 3.5 g/dl	2.8 to 3.5 g/dl	< 2.8 g/dl
Total Bilirubin OR Modified Total Bilirubin**	< 2 mg/dL (< 34 μ mol/L) < 4 mg/dL	2 to 3 mg/dL (34 μ mol/L to 50 μ mol/L) 4-7 mg/dL	> 3 mg/dL (> 50 μ mol/L) > 7 mg/dL
Prothrombin time (sec prolonged) OR INR	< 4 < 1.7	4-6 1.7-2.3	> 6 > 2.3

* NB: Encephalopathy Grades
Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination
Grade 2: Drowsiness, disorientation, asterixis
Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation
Grade 4: Coma, decerebrate posturing, flaccidity

** Modified Total Bilirubin used to score patients who have Gilbert's Syndrome or who are taking indinavir

Child-Pugh Classification

Child-Pugh Class A = score 5-6; Class B = score 7-9; Class C = score > 9

Table 15. Strategies to Improve Adherence to Antiretroviral Therapy

- Establish readiness to start therapy
- Provide education on medication dosing
- Review potential side effects
- Anticipate and treat side effects
- Utilize educational aids including pictures, pillboxes, and calendars
- Engage family, friends
- Simplify regimens, dosing, and food requirements
- Utilize team approach with nurses, pharmacists, and peer counselors
- Provide accessible, trusting health care team

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Table 16. Antiretroviral Therapy Associated Adverse Effects and Management Recommendations

16a. Potentially Life-Threatening and Serious Adverse Events

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY LIFE-THREATENING ADVERSE EFFECTS (Listed in alphabetical order)						
Hepatic Events (nevirapine-associated symptomatic events, including hepatic necrosis)	NVP	Onset: Greatest risk within 1st few weeks of therapy; can occur through 18 weeks Symptoms: Abrupt onset of flu-like symptoms (nausea, vomiting, myalgia, fatigue), abdominal pain, jaundice, or fever with or without skin rash; may progress to fulminant hepatic failure with encephalopathy Approximately 1/2 of the cases have accompanying skin rash Some may present as part of DRESS syndrome (drug rash with eosinophilia and systemic symptoms)	Symptomatic hepatic events: • 4% overall (2.5%-11% from different trials) • In women - 11% in those w/ pre-NVP CD4 >250 cells/mm^3 vs. 0.9% w/ CD4 <250 cells/mm^3; • In men - 6.3% w/ pre-NVP CD4 >400 cells/mm^3 vs. 2.3% w/ CD4 <400 cells/mm^3	•Higher CD4 T cell count at initiation (>250 cells/mm^3 in women & >400 cells/mm^3 in men) •Female gender (including pregnant women) •Elevated ALT or AST at baseline; •HBV and/or HCV co-infection; •Alcoholic liver disease •HIV (-) individuals when NVP is used for post-exposure prophylaxis •High NVP concentration	•Avoid initiation of NVP in women w/ CD4 >250 cells/mm^3 or men w/ CD4 >400 cells/mm^3 unless the benefit clearly outweighs the risk •Counsel pts re: signs & symptoms of hepatitis; stop NVP & seek medical attention if signs & symptoms of hepatitis, severe skin rash, or hypersensitivity reactions appear •Monitoring of ALT & AST (every 2 weeks x 1st month, then monthly x 3 months, then every 3 months •Obtain AST & ALT in patients with rash •2-week dose escalation may reduce incidence of hepatic events	•Discontinue ARV including nevirapine (caution should be taken in discontinuation of 3TC, FTC, or TDF in HBV co-infected patients) •Discontinue all other hepatotoxic agents if possible • Rule out other causes of hepatitis • Aggressive supportive care as indicated **Note:** Hepatic injury may progress despite treatment discontinuation. Careful monitoring should continue until symptom resolution. **Do not rechallenge patient with NVP** The safety of other NNRTIs (EFV or DLV) in patients who experienced significant hepatic event from NVP is unknown – use with caution.
Lactic acidosis/ hepatic steatosis +/- pancreatitis (severe mitochondrial toxicities)	NRTIs, esp. d4T, ddI, ZDV	Onset: months after initiation of NRTIs Symptoms: • Initial onset may be insidious with nonspecific gastrointestinal prodrome (nausea, anorexia, abdominal pain, vomiting), weight loss, and fatigue; • Subsequent symptoms may be rapidly progressive with tachycardia, tachypnea, hyperventilation, jaundice, muscular weakness, mental status changes, or respiratory distress • Some may present with multi-organ failure, such as fulminant hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure Laboratory findings: • Increased lactate (often > 5 mmole) • Low arterial pH (some as low as < 7.0) • Low serum bicarbonate • Increased anion gap • Elevated serum transaminases, prothrombin time, bilirubin • Low serum albumin • Increase serum amylase & lipase in patients with pancreatitis • Histologic findings of the liver – microvesicular or macrovesicular steatosis	Rare One estimate 0.85 cases per 1000 patient-years Mortality up to 50% in some case series, (esp. in patients with serum lactate > 10 mmole)	•d4T + ddI •d4T, ZDV, ddI use (d4T most frequently implicated) •Long duration of NRTI use •Female gender •Obesity •Pregnancy (esp. with d4T+ddI) •ddI + hydroxyurea or ribavirin •High baseline body mass index	•Routine monitoring of lactic acid is generally not recommended; •Consider obtaining lactate levels in patients with low serum bicarbonate or high anion gap and with complaints consistent with lactic acidosis; •Appropriate phlebotomy technique for obtaining lactate level should be employed	•Discontinue all ARVs if this syndrome is highly suspected (diagnosis is established by clinical correlations, drug history, and lactate level) •Symptomatic support with fluid hydration •Some patients may require IV bicarbonate infusion, hemodialysis or hemofiltration, parenteral nutrition or mechanical ventilation •IV thiamine and/or riboflavin – resulted in rapid resolution of hyperlactatemia in some case reports **Note:** •Interpretation of high lactate level should be done in the context of clinical findings. •The implication of asymptomatic hyperlactatemia is unknown at this point **ARV treatment options**: •May consider using NRTIs with less propensity of mitochondrial toxicities – (e.g. ABC, TDF, 3TC, FTC) – should not be introduced until lactate returns to normal. •Recommend close monitoring of serum lactate after restarting NRTIs •Some consider using NRTI-sparing regimens with PI + NNRTI +/- FI (e.g. IDV + EFV, LPV/r + EFV, etc)– efficacy and benefit of this type of regimen unknown, but currently under investigation

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Table 16. Antiretroviral Therapy Associated Adverse Effects and Management Recommendations

16a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY LIFE-THREATENING ADVERSE EFFECTS (Listed in alphabetical order)						
Lactic acidosis/ Rapidly progressive ascending neuromuscular weakness	Most frequently implicated ARV: d4T	Onset: months after initiation of ARV; then dramatic motor weakness occurring within days to weeks Symptom: very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barré Syndrome; some patients may develop respiratory paralysis requiring mechanical ventilation; resulted in deaths in some patients Laboratory findings may include: •Low arterial pH •Increased lactate •Low serum bicarbonate •Increased anion gap •Markedly increased creatine phosphokinase	Rare	Prolonged d4T use [found in 61 of 69 (88%) cases in one report]	Early recognition and discontinuation of ARVs may avoid further progression	•Discontinuation of ARVs •Supportive care, including mechanical ventilation if needed (as in cases of lactic acidosis listed previously) •Other measures attempted with variable successes: plasmapheresis, high dose corticosteroid, intravenous immunoglobulin, carnitine, acetylcarnitine •Recovery often takes months – ranging from complete recovery to substantial residual deficits •Symptoms may be irreversible in some patients **Do not rechallenge patient with offending agent**
Stevens-Johnson Syndrome (SJS)/ Toxic epidermal necrosis (TEN)	NVP > EFV, DLV; Also reported with: APV, f-APV, ABC, ZDV, ddI, IDV, LPV/r, ATV	Onset: first few days to weeks after initation of therapy Symptoms: *Cutaneous involvement:* •Skin eruption with mucosal ulcerations (may involve orogingival mucosa, conjunctiva, anogenital area); •Can rapidly evolve with blister or bullae formation; •May eventually evolve to epidermal detachment and/or necrosis *Systemic Symptoms:* fever, tachycardia, malaise, myalgia, arthralgia *Complications:* ↓ oral intake → fluid depletion; bacterial or fungal superinfection; multiorgan failure	NVP: 0.3% to 1% DLV & EFV: 0.1% 1-2 case reports for ABC, f-APV, ddI, ZDV, IDV, LPV/r, ATV	NVP – Female, Black, Asian, Hispanic	•2-week lead in period with 200mg once daily, then escalate to 200mg twice daily •Educate patients to report symptoms as soon as they appear •Avoid use of corticosteroid during NVP dose escalation – may increase incidence of rash	•Discontinue all ARVs and any other possible agent (s) (e.g. cotrimoxazole) Aggressive symptomatic support may include: •Intensive care support •Aggressive local wound care (e.g. in a burn unit) •Intravenous hydration •Parenteral nutrition, if necessary •Pain management •Antipyretics •Empiric broad-spectrum antimicrobial therapy if superinfection is suspected Controversial management strategies: •Corticosteroid •Intravenous immunoglobulin **Do not rechallenge patient with offending agent** ▪It is unknown whether patients who experienced SJS while NNRTI are more susceptible to SJS from another NNRTI – most experts would suggest avoiding use of this class unless no other option available
Hypersensitivity reaction (HSR)	ABC	Onset of 1st reaction: median onset – 9 days; approximately 90% within 1st 6 weeks Onset of rechallenge reactions: within hours of rechallenge dose Symptoms: acute onset of symptoms (in descending frequency): high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms (pharyngitis, dyspnea/tachypnea) *With continuation of ABC, symptoms may worsen to include*: hypotension, respiratory distress, vascular collapse *Rechallenge reactions:* generally greater intensity than 1st reaction, can mimic anaphylaxis	Approximately 8% in clinical trial (2-9%); 5% in retrospective analysis	•HLA-B*5701, HLA-DR7, HLA-DQ3 (from Australian data) •ARV-naïve patients •Higher incidence of grade 3 or 4 HSR with 600mg once daily dose than 300mg twice daily dose in one study (5% vs. 2%)	•Educate patients about potential signs and symptoms of HSR and need for reporting of symptoms promptly •Wallet card with warning information for patients	•Discontinue ABC and other ARVs •Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes, and other causes of skin rash, etc) •Most signs and symptoms resolve 48 hours after discontinuation of ABC *More severe cases:* •Symptomatic support – antipyretic, fluid resuscitation, pressure support (if necessary) •**Do not rechallenge patients with ABC after suspected HSR**

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Table 16. Antiretroviral Therapy Associated Adverse Effects and Management Recommendations

16a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY SERIOUS ADVERSE EFFECTS (listed in alphabetical order)						
Bleeding episodes – increase in hemophiliac patients	PIs	Onset: few weeks Symptoms: ↑ spontaneous bleeding tendency – in joints, muscles, soft tissues, and hematuria	Frequency unknown	• PI use in hemophiliac patients	• Consider using NNRTI-based regimen • Monitor for spontaneous bleeding	• May require increase use of Factor VIII products
Bone marrow suppression	ZDV	Onset: few weeks to months Laboratory abnormalities: • Anemia • Neutropenia Symptoms: fatigue due to anemia; potential for increase bacterial infections due to neutropenia	Anemia -1.1 to 4% Neutropenia – 1.8-8%	• Advanced HIV • High dose • Pre-existing anemia or neutropenia; • Concomitant use of bone marrow suppressants (such as cotrimoxazole, ribavirin, ganciclovir, etc.)	Avoid use in patients at risk Avoid other bone marrow suppressants if possible Monitor CBC with differential at least every three months (more frequently in patients at risk)	• Switch to another NRTI if there is alternative option; • Discontinue concomitant bone marrow suppressant if there is alternative option; otherwise: For neutropenia: • Identify and treat other causes • Consider treatment with filgrastim For anemia: • Identify and treat other causes of anemia (if present) • Blood transfusion if indicated • Consider erythropoietin therapy
Hepatotoxicity (clinical hepatitis or asymptomatic serum transaminase elevation)	All NNRTIs; All PIs; All NRTIs	Onset: NNRTI – for NVP - 2/3 within 1st 12 weeks NRTI – over months to years PI – generally after weeks to months Symptoms/Findings: **NNRTI** – asymptomatic to non-specific symptoms such as anorexia, weight loss, or fatigue. Approximately ½ of patients with NVP-associated symptomatic hepatic events present with skin rash. **NRTI** – • ZDV, ddI, d4T - may cause hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis due to mitochondrial toxicity • 3TC, FTC, or tenofovir – HBV co-infected patients may develop severe hepatic flare when these drugs are withdrawn or when resistance develops. **PI** – • Generally asymptomatic, some with anorexia, weight loss, jaundice, etc.		• Hepatitis B or C co-infection • Alcoholism • Concomitant hepatotoxic drugs • For NVP-associated hepatic events – female w/ pre-NVP CD_4 >250cells/mm^3 or male w/ pre-NVP CD_4 >400cells/mm^3	NVP – monitor liver associated enzymes at baseline, 2 & 4 weeks, then monthly for 1st 3 months; then every 3 months Other agents: monitor liver-associated enzymes at least every 3-4 months or more frequently in patients at risk	• Rule out other causes of hepatotoxicity – alcoholism, viral hepatitis, chronic HBV w/ 3TC, FTC or TDF withdrawal, or HBV resistance, etc. For symptomatic patients: • Discontinue all ARV (with caution in patients with chronic HBV infection treated w/ 3TC, FTC and/or TDF) and other potential hepatotoxic agents • After symptoms subside & serum transaminases returned to normal, construct a new ARV regimen without the potential offending agent(s) For asymptomatic patients: • If ALT > 5-10x ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring • After serum transaminases returned to normal, construct a new ARV regimen without the potential offending agent(s) **Note:** Please refer to information regarding NVP-associated symptomatic hepatic events & NRTI-associated lactic acidosis with hepatic steatosis in this table
Nephrolithiasis/ urolithiasis/ crystalluria	IDV – most frequent	Onset: any time after beginning of therapy – especially at times of reduced fluid intake Laboratory abnormalities: pyuria, hematuria, crystalluria; rarely – rise in serum creatinine & acute renal failure Symptoms: flank pain and/or abdominal pain (can be severe), dysuria, frequency	12.4% of nephrolithiasis reported in clinical trials (4.7% -34.4% in different trials)	• History of nephrolithiasis • Patients unable to maintain adequate fluid intake • High peak IDV concentration • ↑ duration of exposure	• Drink at least 1.5 to 2 liters of non-caffeinated fluid (preferably water) per day • Increase fluid intake at first sign of darkened urine • Monitor urinalysis and serum creatinine every 3-6 months	• Increase hydration • Pain control • May consider switching to alternative agent or therapeutic drug monitoring if treatment option is limited • Stent placement may be required

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Table 16. Antiretroviral Therapy Associated Adverse Effects and Management Recommendations

16a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY SERIOUS ADVERSE EFFECTS (listed in alphabetical order)						
Nephrotoxicity	IDV, potentially TDF	Onset: IDV – months after therapy TDF – weeks to months after therapy Laboratory and other findings: IDV: ↑ serum creatinine, pyruria; hydronephrosis or renal atrophy TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, non-anion gap metabolic acidosis Symptoms: IDV: asymptomatic; rarely develop to end stage renal disease TDF: asymptomatic to signs of nephrogenic diabetes insipidus, Fanconi Syndrome	Not known	•History of renal disease •Concommitant use of nephrotoxic drugs	•Avoid use of other nephrotoxic drugs •Adequate hydration if on IDV therapy •Monitor serum creatinine, urinalysis, serum potassium and phosphorus in patients at risk	•Stop offending agent, generally reversible •Supportive care •Electrolyte replacement as indicated
Pancreatitis	ddI alone; ddI + d4T; ddI + hydroxyurea (HU) or ribavirin (RBV); 3TC in children	Onset: usually weeks to months Laboratory abnormalities: increased serum amylase and lipase Symptoms: post-prandial abdominal pain, nausea, vomiting	ddI alone – 1-7% ddI with HU - ↑ by 4-5 fold ddI with RBV, d4T or TDF - ↑ frequency 3TC in children – early trials: 14-18%; later trial - <1%	•High intraceullar and/or serum ddI concentrations •History of pancreatitis •Alcoholism •Hypertriglyceridemia •Concomitant use of ddI with d4T, HU, or RBV •Use of ddI + TDF without ddI dose reduction	•ddI should not be used in patients with history of pancreatitis •Avoid concomitant use of ddI with d4T, HU or RBV •Reduce ddI dose when used with TDF •Monitoring of amylase/lipase in asymptomatic patients is generally not recommended	•Discontinue offending agent(s) •Symptomatic management of pancreatitis – bowel rest, IV hydration, pain control, then gradual resumption of oral intake •Parenteral nutrition may be necessary in patients with recurrent symptoms upon resumption of oral intake
Skin rash	NVP > EFV, DLV; APV, f-APV, ABC, ATV	Onset: within first few days to weeks after initiation of therapy Symptoms: most rashes are mild to moderate in nature; diffuse maculopapular rash with or without pruritus; severe rash, rash with fever or with mucus membrane involvement warrants immediate discontinuation of ARV **Note**: Please also see sections on Stevens-Johnson Syndrome & Systemic Hypersensitivity Reaction	All Grades (severe) NVP: 14.8% (1.5% severe) EFV: 26% (1% grades 3- 4) DLV: 35.4% (4.4% grades 3-4) APV: 20-27% (1.0% grades 3-4) f-APV: 19% (< 1% grades 3-4) ATV: 21% (<1% severe) ABC: <5% in pts w/o SHR	• NVP – female, Black, Asian, Hispanic • f-APV, APV – sulfonamide derivative – potential for cross hypersensitivity with other sulfa drugs • EFV – higher incidence in children	•NVP – always use a 2-week low dose lead-in period •Avoid use of corticosteroid during NVP dose escalation – may increase incidence of rash •Patient education – advise to report first sign of rash •Most experts suggest avoidance of EFV or DLV in patients with history of severe rash from NVP, and vice versa	•Mild to moderate rash may be managed by symptomatic treatment with antihistamine and continuation of offending agent •Discontinue therapy if skin rash progresses to severe in nature (accompanied by blisters, fever, mucous membrane involvement, conjunctivitis, edema, or arthralgias) or in presence of systemic symptoms (including fever) **Do not restart offending medication in case of severe rash** •If rash develops during first 18 weeks of NVP treatment – obtain serum transaminases to rule out symptomatic hepatic event

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Table 16. Antiretroviral Therapy Associated Adverse Effects and Management Recommendations

16b. Adverse Events with Potential Long Term Complications (listed in alphabetical order)

						Management
Cardiovascular effects	Possibly all PIs; maybe except for ATV	Onset: months to years after beginning of therapy Presentation: premature coronary artery disease	3-6 per 1000/pt years	Other risk factors for cardiovascular disease such as smoking, age, hyperlipidemia, hypertension, diabetes mellitus, family history of premature coronary artery disease and personal history of coronary artery disease	•Assess each patient's cardiac risk factors •Consider non-PI based regimen •Monitor & identify pts w/ hyperlipidemia or hyperglycemia •Counseling for life style modification - smoking cessation, diet, and exercise	•Early diagnosis, prevention, and pharmacologic management of other cardiovascular risk factors such as hyperlipidemia, hypertension, and insulin-resistance/diabetes mellitus •Assess cardiac risk factors •Lifestyle modifications: diet, exercise, and/or smoking cessation •Switch to agents with less propensity for increasing cardiovascular risk factors, ie NNRTI- or ATV-based regimen & avoid d4T use
Hyperlipidemia	All PIs (except ATV); d4T; EFV (to a lesser extent)	Onset: weeks to months after beginning of therapy Presentation: All PIs except ATV – ↑ in LDL & total cholesterol (TC) & triglyceride (TG), ↓ in HDL LPV/r & RTV – disproportionate ↑ in TG d4T – mostly ↑ in TG; may also have ↑ in LDL & total cholesterol (TC) EFV or NVP: ↑ in HDL, slight ↑ TG	Varies with different agents; 47% -75% of pts receiving PI in some clinics; Swiss Cohort: ↑TC & TG – 1.7-2.3x higher in pts receiving (non-ATV) PI	•Underlying hyperlipidemia •Risk based on ARV therapy PI: LPV/r & RTV > NFV & APV > IDV & SQV > ATV; NNRTI: less than PIs; NRTI: d4T > ZDV & TDF	•Use non-PI, non-d4T based regimen •Use ATV-based regimen •Fasting lipid profile at baseline, 3-6 months after starting new regimen, then annually or more frequently if indicated (in high risk patients, or patients with abnormal baseline levels)	•Follow ACTG guidelines's recommendations for management *[1]* •Assess cardiac risk factor •Lifestyle modification: diet, exercise, and/or smoking cessation •Switching to agents with less propensity for causing hyperlipidemia Pharmacologic Management: •↑ total cholesterol, LDL, TG 200-500 mg/dL: "statins" – pravastatin or atorvastatin (see **Tables 19 & 20** for Drug Interaction information) •TG > 500 mg/dL – gemfibrozil or micronized fenofibrate
Insulin resistance/ Diabetes mellitus	All PIs	Onset: weeks to months after beginning of therapy Presentation: Polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycemia in patients with underlying diabetes	Up to 3-5% of patients developed diabetes in some series	Underlying hyperglycemia, family history of diabetes mellitus	•Use PI-sparing regimens •Fasting blood glucose 1-3 months after starting new regimen, then at least every 3-6 months	•Diet and exercise •Consider switching to an NNRTI-based regimen •Metformin •"glitazones" •Sulfonylurea •Insulin
Osteonecrosis	All PIs	Clinical Presentation (generally similar to non-HIV population): •Insidious in onset, with subtle symptoms of mild to moderate periarticular pain •85% of the cases involving one or both femoral heads, but other bones may also be affected •Pain may be triggered by weight bearing or movement	Reported incidence on the rise. Symptomatic osteonecrosis: 0.08% to 1.33%; Asymptomatic osteonecrosis: 4% from MRI reports	•Diabetes •Prior steroid use •Old age •Alcohol use •Hyperlipidemia •Role of ARVs and osteonecrosis – still controversial	•Risk reduction (e.g. limit steroid and alcohol use) •Asymptomatic cases w/ < 15% bony head involvement – follow with MRI every 3-6 months x 1 yr, then every 6 mon x 1 yr, then annually – to assess for disease progression	Conservative management: • ↓ weight bearing on affected joint; • Remove or reduce risk factors • Analgesics as needed Surgical Intervention: •Core decompression +/- bone grafting – for early stages of disease •For more severe and debilitating disease – total joint arthroplasty

1. Dubé MP, Stein JH, Aberg JA, et al for the Adults AIDS Clinical Trials Group Cardiovascular Subcommittee. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003; 613-27.

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Table 16. Antiretroviral Therapy Associated Adverse Effects and Management Recommendations

16c. Adverse Effects Compromising Quality of Life and/or With Potential Impact on Medication Adherence (listed in alphabetical order)

						Management
Central nervous system effects	EFV	Onset: begin with first few doses Symptoms: may include one or more of the following: drowsiness, somnolence, insomnia, abnormal dreams, dizziness, impaired concentration & attention span, depression, hallucination; exacerbation of psychiatric disorders; psychosis; suicidal ideation Most symptoms subside or diminish after 2-4 weeks	> 50% of patients may have some symptoms	• Pre-existing or unstable psychiatric illnesses; • Use of concomitant drugs with CNS effects	• Take at bedtime or 2-3 hours before bedtime; • Take on an empty stomach to reduce drug concentration & CNS effects • Warn patients regarding restriction of risky activities – such as operating heavy machinery during the 1st 2-4 weeks of therapy	• Symptoms usually diminish or disappear after 2-4 weeks • May consider discontinuing therapy if symptoms persist and cause significant impairment in daily function or exacerbation of psychiatric illness
Fat maldistribution	PIs, d4T	Onset: gradual - months after initiation of therapy Symptoms: • Lipoatrophy – peripheral fat loss manifested as facial thinning, thinning of extremities and buttocks (d4T) • Increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump)	High – exact frequency uncertain; increases with duration on offending agents	Lipoatrophy – low baseline body mass index	None to date	• Switching to other agents – may slow or halt progression, however, may not reverse effects • Injectable poly-L-lactic acid for treatment of facial lipoatrophy
Gastrointestinal (GI) intolerance	All PIs, ZDV, ddI	Onset: Begin within first doses Symptoms: • Nausea, vomiting, abdominal pain – all listed agents • Diarrhea – commonly seen with NFV, LPV/r, & ddI buffered formulations	Varies with different agents	All patients	• Taking with food may reduce symptoms (not recommended for ddI or unboosted IDV) • Some patients may require antiemetics or antidiarrheals pre-emptively to reduce symptoms	May spontaneously resolve or become tolerable with time; if not: For nausea & vomiting, consider: • Antiemetic prior to dosing • Switch to less emetogenic ARV For diarrhea, consider: • Antimotility agents – such as loperamide, diphenoxylate/atropine • Calcium tablets • Bulk-forming agents, such as psyllium products • Pancreatic enzymes In case of severe GI loss: • Rehydration & electrolyte replacement as indicated
Injection site reactions	Enfuvirtide	Onset: Within first few doses Symptoms: pain, pruritus, erythema, ecchymosis, warmth, nodules, rarely injection site infection	98%	All patients	Educate patients regarding use of sterile technique, ensure solution at room temperature before injection, rotate injection sites, avoid injection into sites with little subcutaneous fat or sites of existing or previous reactions	• Massaging area after injection may reduce pain • Wear loose clothing – especially around the injection site areas or areas of previous reactions • Rarely, warm compact or analgesics may be necessary
Peripheral neuropathy	ddI, d4T, ddC	Onset: weeks to months after initiation of therapy (may be sooner in patients with pre-existing neuropathy) Symptoms: • Begins with numbness & paresthesia of toes and feet; • May progress to painful neuropathy of feet and calf; • Upper extremities less frequently involved • Can be debilitating for some patients. • May be irreversible despite discontinuation of offending agent(s)	ddI: 12-34% in clinical trials d4T: 52% in monotherapy trial ddC: 22-35% in clinical trials Incidence increases with prolonged exposure	• Pre-existing peripheral neuropathy; • Combined use of these NRTIs or concomitant use of other drugs which may cause neuropathy • Advanced HIV disease • High dose or concomitant use of drugs which may increase ddI intracellular activities (e.g. HU or RBV)	• Avoid using these agents in patients at risk – if possible • Avoid combined use of these agents • Patient query at each encounter	• May consider discontinuing offending agent before pain becomes disabling – may halt further progression, but symptoms maybe irreversible Pharmacological management (with variable successes): • Gabapentin (most experience), tricyclic antidepressants, lamotrigine, oxycarbamazepine (potential for CYP interactions), topiramate, tramadol • Narcotic analgesics • Capsaicin cream • Topical lidocaine

Table 17. HIV-Related Drugs with Overlapping Toxicities

Bone Marrow Suppression	Peripheral Neuropathy	Pancreatitis	Nephrotoxicity	Hepato-toxicity	Rash	Diarrhea	Ocular Effects
Amphotericin B Cidofovir Cotrimoxazole Cytotoxic Chemotherapy Dapsone Flucytosine Ganciclovir Hydroxyurea Interferon-α Linezolid Peginterferon-α Primaquine Pyrimethamine Ribavirin Rifabutin Sulfadiazine Trimetrexate Valganciclovir Zidovudine	Didanosine Isoniazid Linezolid Stavudine Zalcitabine	Cotrimoxazole Didanosine Lamivudine (children) Pentamidine Ritonavir Stavudine Zalcitabine	Acyclovir (IV, high dose) Adefovir Aminoglycosides Amphotericin B Cidofovir Foscarnet Indinavir Pentamidine Tenofovir	Azithromycin Clarithromycin Delavirdine Efavirenz Fluconazole Isoniazid Itraconazole Ketoconazole Nevirapine NRTIs PI Rifabutin Rifampin Voriconazole	Abacavir Amprenavir Atazanavir Atovaquone Cotrimoxazole Dapsone Delavirdine Efavirenz Fosamprenavir Nevirapine Sulfadiazine Voriconazole	Atovequone Clindamycin Didanosine (buffered formulations) Lopinavir/ ritonavir Nelfinavir Ritonavir	Cidofovir Didanosine Ethambutol Linezolid Rifabutin Voriconazole

Table 18. Adverse Drug Reactions and Related "Black Box Warnings" in Product Labeling for Antiretroviral Agents

The Food and Drug Administration can require that warnings regarding special problems associated with a prescription drug, including those that might lead to death or serious injury, be placed in a prominently displayed box, commonly known as a "black box." Please note that other serious toxicities associated with antiretroviral agents are not listed in this table.

Antiretroviral Drug	Pertinent Black Box Warning Information
Abacavir (Ziagen®, or as combination products in Epzicom® and Trizivir®)	• Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir: – This is a multi-organ clinical syndrome, characterized by two or more groups of the following signs or symptoms including (1) fever, (2) rash, (3) gastrointestinal (e.g., nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory symptoms (including dyspnea, cough, or pharyngitis). – Abacavir should be discontinued as soon as hypersensitivity reaction is suspected. – Any product containing abacavir should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible – because more severe symptoms can occur within hours after restarting abacavir and may include life-threatening hypotension and death. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
Amprenavir (Agenerase®) Oral Solution	• Because of the potential risk of toxicity from substantial amounts of the excipient propylene glycol in Agenerase Oral Solution, it is contraindicated for the following patient populations: – children age <4 years – pregnant women – patients with renal or hepatic failure – patients treated with disulfiram or metronidazole • Oral solution should be used only when amprenavir capsules or other protease inhibitors cannot be used.
Atazanavir (Reyataz™)	No box warning.
Delavirdine (Rescriptor®)	No box warning.
Didanosine (Videx® or Videx-EC®)	• Fatal and nonfatal pancreatitis have occurred with didanosine alone or in combination with other antiretroviral agents. – Didanosine should be withheld if pancreatitis is suspected. – Didanosine should be discontinued if pancreatitis is confirmed. • Fatal lactic acidosis has been reported among pregnant women who received a combination of didanosine and stavudine with other antiretroviral combinations. – Didanosine and stavudine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
Efavirenz (Sustiva®)	No box warning.
Emtricitabine (Emtriva™); or in combination product with tenofovir DF (Truvada™)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals. • Emtricitabine is not indicated for the treatment of hepatitis B infection (HBV), the safety and efficacy have not be established in patients with HIV/HBV co-infection. • Severe acute exacerbations of hepatitis B have been reported in patients who discontinued emtricitabine – hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of tenofovir in HIV/HBV co-infected patients. • If appropriate, initiation of anti-HBV therapy may be warranted after discontinuation of tenofovir.
Enfuvirtide (Fuzeon)	No box warning.
Fosamprenavir (Lexiva™)	No box warning.
Indinavir (Crixivan®)	No box warning.

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Table 18. Adverse Drug Reactions and Related "Black Box Warnings" in Product Labeling for Antiretroviral Agents

Antiretroviral Drug	Pertinent Black Box Warning Information
Lamivudine (Epivir®), or in combination products Combivir®, Epizicom®, and Trizivir®)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination. • Epivir tablets and oral solution (used to treat HIV infection) contain a higher dose of lamivudine than Epivir-HBV tablets and oral solution (used to treat chronic hepatitis B). **Patients with HIV infection should receive only dosage and formulations appropriate for treatment of HIV.** • Severe acute exacerbations of hepatitis B infection have been reported in HBV/HIV co-infected patients upon discontinuation of lamivudine-containing products. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of lamivudine in patients with HIV/HBV co-infection. • If appropriate, initiation of anti-hepatitis B therapy may be warranted.
Lopinavir/ritonavir (Kaletra®)	No box warning.
Nelfinavir (Viracept®)	No box warning.
Nevirapine (Viramune®)	• Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, has been reported. Patients may present with non-specific prodromes of hepatitis and progress to hepatic failure. • Women with CD4 counts > 250 cells/mm^3, including pregnant women receiving chronic treatment for HIV infection are at considerably higher risk of hepatotoxicities. • Severe, life-threatening, and even fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction have occurred with nevirapine treatment. • Patients should be monitored intensively during the first 18 weeks of nevirapine therapy to detect potentially life-threatening hepatotoxicity or skin reactions. • A 14-day lead-in period with nevirapine 200 mg daily must be followed strictly. • Nevirapine should not be restarted after severe hepatic, skin, or hypersensitivity reactions.
Ritonavir (Norvir®)	• Co-administration of ritonavir with certain non-sedating antihistamines, sedative hypnotics, antiarrhythmics, or ergot alkaloids may result in potentially serious or life-threatening adverse events due to possible effects of ritonavir on hepatic metabolism of certain drugs.
Saquinavir (Fortovase®, Invirase®)	• INVIRASE (saquinavir mesylate) hard gelatin capsules and tablets and FORTOVASE (saquinavir) soft gelatin capsules are not bioequivalent and cannot be used interchangeably. • INVIRASE may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with FORTOVASE. • When using saquinavir as the sole protease inhibitor in an antiviral regimen, FORTOVASE is the recommended formulation.
Stavudine (Zerit®)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination. • Fatal lactic acidosis has been reported among pregnant women who received combination of stavudine and didanosine with other antiretroviral combinations. • Stavudine and didanosine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks. • Fatal and non-fatal pancreatitis have occurred when stavudine was part of a combination regimen with didanosine with or without hydroxyurea.
Tenofovir (Viread®) or in combination product with emtricitabine (Truvada™)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. • Tenofovir is not indicated for the treatment of chronic hepatitis B (HBV) infection, safety and efficacy in patients with HIV/HBV co-infection have not been established. • Severe acute exacerbations of hepatitis B have been reported in patients who discontinued tenofovir – hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of tenofovir in HIV/HBV co-infected patients. • If appropriate, initiation of anti-HBV therapy may be warranted after discontinuation of tenofovir.
Zalcitabine (Hivid®)	• Zalcitabine can cause severe peripheral neuropathy, use with caution among patients with pre-existing neuropathy. • In rare cases, zalcitabine can cause pancreatitis, therapy should be withheld until pancreatitis is excluded. • Rare cases of hepatic failure and death have been reported among patients with underlying hepatitis B infection. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
Zidovudine (Retrovir®), or in combination products Combivir® and Trizivir®	• Zidovudine can be associated with hematologic toxicities, including granulocytopenia and severe anemia, including among advanced HIV patients. • Prolonged zidovudine use has been associated with symptomatic myopathy. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.

Table 19. Drugs That Should Not Be Used With PI or NNRTI Antiretrovirals

				-		-					Other
Protease Inhibitors											
Indinavir	(none)	amiodarone	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam$^{\Sigma}$ triazolam	dihydroergotamine (D.H.E. 45) ergotamine† (various forms) ergonovine methylergonovine	St. John's wort	atazanavir
Ritonavir	bepridil	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam$^{\Sigma}$ triazolam	dihydroergotamine (D.H.E. 45) ergotamine† (various forms) ergonovine methylergonovine	St. John's wort	voriconazole (with RTV ≥ 400mg bid) fluticasone$^{\otimes}$ alfuzosin
Saquinavir	(none)	(none)	simvastatin lovastatin	rifampin rifabutin$^{\Delta}$ rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam $^{\Sigma}$ triazolam	dihydroergotamine (D.H.E. 45) ergotamine† (various forms) ergonovine methylergonovine	St. John's wort garlic supplements	
Nelfinavir	(none)	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam$^{\Sigma}$ triazolam	dihydroergotamine (D.H.E. 45) ergotamine† (various forms) ergonovine methylergonovine	St. John's wort	
Amprenavir* and Fosamprenavir	bepridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam$^{\Sigma}$ triazolam	dihydroergotamine (D.H.E. 45) ergotamine† (various forms) ergonovine methylergonovine	St. John's wort	delavirdine oral contraceptives
Lopinavir + Ritonavir	(none)	flecainide propafenone	simvastatin lovastatin	rifampin$^{\int}$ rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam$^{\Sigma}$ triazolam	dihydroergotamine (D.H.E. 45) ergotamine† (various forms) ergonovine methylergonovine	St. John's wort	fluticasone$^{\otimes}$
Atazanavir	bepridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride proton pump inhibitors	pimozide	midazolam$^{\Sigma}$ triazolam	dihydroergotamine (D.H.E. 45) ergotamine† (various forms) ergonovine methylergonovine	St. John's wort	indinavir irinotecan
Non-nucleoside Reverse Transcriptase Inhibitors											
Nevirapine	(none)	(none)	(none)	rifampin rifapentine‡	(none)	(none)	(none)	(none)	(none)	St. John's wort	
Delavirdine	(none)	(none)	simvastatin lovastatin	rifampin rifapentine‡ rifabutin	astemizole terfenadine	cisapride H2 blockers proton pump inhibitors	(none)	alprazolam midazolam$^{\Sigma}$ triazolam	dihydroergotamine (D.H.E. 45) ergotamine† (various forms) ergonovine methylergonovine	St. John's wort	amprenavir fosamprenavir carbamazepine phenobarbital phenytoin
Efavirenz	(none)	(none)	(none)	rifapentine‡	astemizole terfenadine	cisapride	(none)	midazolam$^{\Sigma}$ triazolam	dihydroergotamine (D.H.E. 45) ergotamine† (various forms) ergonovine methylergonovine	St. John's wort	voriconazole

\# Certain listed drugs are contraindicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with P450–3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur among patients.

‡ HIV patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended.

Δ Rifabutin may be used with saquinavir only if it is combined with ritonavir.

∫ In one small study, higher doses of RTV or LPV/RTV offset rifampin-inducing activity of LPV. Of note, 28% of subjects discontinued due to increases in LFTs. The safety of this combination is still under evaluation. Further studies are needed.

Σ Midazolam can be used with caution as a single dose and given in a monitored situation for procedural sedation.

† This is likely a class effect.

∂ Astemizole and terfenadine are not marketed in the U.S. The manufacturer of cisapride has a limited-access protocol for patients meeting specific clinical eligibility criteria.

* Each 150 mg amprenavir Agenerase® capsule has 109 IU (International Units) of Vitamin E and 1 milliliter of amprenavir oral solution has 46 IU of vitamin E. At FDA approved doses, the daily amount of vitamin E in Agenerase is 58-fold increase over the federal government reference daily intake for adults. Patients should be cautioned to avoid supplemental doses of vitamin E. Multivitamin products containing minimal amounts of vitamin E are likely acceptable.

⊗ Concomitant use of fluticasone and ritonavir results in significantly reduced serum cortisol concentrations. Coadministration of fluticasone and ritonavir or lopinavir/ritonavir is not recommended unless the potential benefit outweighs the risk of systemic corticosteroid side effects.

Suggested Alternatives

Cerivastatin (no longer marketed in the United States), simvastatin, lovastatin: pravastatin and fluvastatin have the least potential for drug-drug interactions; atorvastatin should be used with caution, using the lowest possible starting dose and monitor closely; no pharmacokinetic data or safety data are available for coadministration of rosuvastatin with the antiretroviral agents.

Rifabutin: clarithromycin, azithromycin (MAI prophylaxis); clarithromycin, azithromycin, ethambutol (MAI treatment)
Astemizole, terfenadine (no longer marketed in the United States): desloratadine, loratadine, fexofenadine, cetirizine
Midazolam, triazolam: temazepam, lorazepam

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Table 20. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use			
	Indinavir (IDV)	**Ritonavir* (RTV)**	**Saquinavir† (SQV)**
ANTIFUNGALS			
Itraconazole	Level: when IDV 600 mg q8h given with itraconazole 200 mg bid, IDV AUC similar to IDV 800 mg q8h Dose: IDV 600 mg q8h; Itraconazole: do not exceed 200 mg bid.	No data, but potential for bi-directional inhibition between itraconazole and RTV, monitor for toxicities. Dose: dose adjustment for patients receiving > 400 mg itraconazole may be needed, or consider monitoring itraconazole level	Bi-directional intenaction between itraconazole & SQV has been observed. Dose: Not established, but decreased itraconazole dosage may be warranted. Consider therapeutic drug monitoring for both SQV (if unboosted) and itraconazole.
Ketoconazole	Levels: IDV ↑ 68%. Dose: IDV 600 mg tid.	Levels: ketoconazole ↑ 3X. Dose: Use with caution; do not exceed 200 mg ketoconazole daily.	Levels: SQV ↑ 3X. Dose: No dosage adjustment necessary.
Voriconazole	Levels: No significant changes in AUC of azole or IDV (healthy subjects). Dose: Standard	Levels: voriconazole AUC ↓ 82% when coadministered with 400 mg BID of RTV, and concomitant therapy is contraindicated. There are no data on the interaction when boosting doses of RTV (100-400 mg per day) are given with voriconazole.	No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities
ANTI-MYCOBACTERIALS			
Rifampin	Levels: IDV (unboosted) ↓ 89%; IDV (boosted) ↓ 87%; Contraindicated.	Levels: RTV ↓ 35%. Dose: No change. Increased liver toxicity possible. Co-administration may lead to loss of virologic response if RTV sole PI. Alternate antimycobacterial agents, such as rifabutin, should be considered.	Levels: SQV ↓ 84%. Contraindicated. Marked elevation of transaminases was seen in a pharmacokinetic study where healthy volunteers received a combination of rifampin 600 mg QD + RTV 100 mg/SQV 1000 mg BID. This combination should not be used.
Rifabutin	Levels: IDV ↓ 32%. Rifabutin ↑ 2X. Dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week. IDV 1000 mg tid. If RTV boosted, use rifabutin dosing recommendations for co-administration with RTV; continue current dose of boosted IDV.	Levels: Rifabutin ↑ 4X. Dose: ↓ rifabutin to 150 mg qod or dose 3x/week.¢ RTV: Maintain current dose if sole PI or part of a boosted regimen.	Levels: SQV ↓ 40%. Contraindicated unless SQV/RTV. Dose: Rifabutin 150 mg qod or 3x/week.¢
Clarithromycin	Levels: Clarithromycin ↑ 53%. No dose adjustment.	Levels: Clarithromycin ↑ 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.	Levels: Clarithromycin ↑ 45%. SQV ↑ 177%. No dose adjustment.
ORAL CONTRACEPTIVES			
	Levels: Norethindrone ↑ 26%. Ethinylestradiol ↑ 24%. No dose adjustment.	Levels: Ethinyl estradiol ↓ 40%. Use alternative or additional method.	No data.
LIPID–LOWERING AGENTS			
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
Atorvastatin	Levels: potential for increase in AUC Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No Data	Levels: 50% ↓ when administered with SQV/RTV combination. Dose: Pravastatin dosage adjustment based on lipid response.	Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed. Dose: Pravastatin dosage adjustment based on lipid response.

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Table 20. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use			
	Indinavir (IDV)	**Ritonavir* (RTV)**	**Saquinavir† (SQV)**
ANTICONVULSANTS			
Carbamazepine **Phenobarbital** **Phenytoin**	Carbamazepine markedly ↓ IDV AUC. Consider alternative agent or monitoring IDV level.	Carbamazepine: ↑ serum levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels.	Unknown, but may markedly ↓ SQV levels. Monitor anticonvulsant levels and consider obtaining SQV level.
METHADONE	No change in methadone levels.	Methadone ↓ 37%. Monitor and titrate dose if needed. May require ↑ methadone dose.	Methadone AUC ↓ 20%. When co-administered with SQV/RTV 400/400 mg BID. Dose: No adjustment for this PI regimen, but monitor and titrate to methadone response as necessary.
ERECTILE DYSFUNCTION AGENTS			
Sildenafil	Sildenafil AUC ↑ 3 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 11 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 2 fold. Use a 25 mg starting dose of sildenafil.
Vardenafil	Vardenafil AUC ↑ 16 fold. IDV (unboosted) AUC ↓ 30% Dose: Consider sildenafil instead of vardenafil if IDV unboosted. Do not exceed vardenafil 2.5 mg in 72 hours if administered with RTV.	Vardenafil AUC ↑ 49 fold. RTV AUC ↓ 20% Dose: Vardenafil: Start with a 2.5 mg dose, and do not exceed a single 2.5 mg dose in 72 hours. RTV: Maintain current dose.	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed a single 2.5 mg dose in 72 hours if administered with RTV.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Tadalafil AUC ↑ 124%. Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.
MISCELLANEOUS	Grapefruit juice ↓ IDV levels by 26%. Vitamin C ≥ 1 gram/day ↓ IDV AUC by 14% and Cmin by 32% Amlodipine: Amlodipine AUC ↑ 90% when coadministered with IDV/RTV. No change in IDV/RTV levels. Monitor closely.	Many possible interactions Desipramine ↑ 145%, reduce dose. Trazodone AUC ↑ 2.4 fold when given with 200 mg BID or RTV. Use lowest dose of trazodone and monitor for CNS and CV adverse effects. Theophylline ↓ 47%, monitor theophylline levels. RTV 100mg bid significantly increase systemic exposure of inhaled (oral or nasal) fluticasone, may predispose patients to systemic corticosteroid effects. Co-administration not recommended unless benefit of fluticasone outweighs the risk.	Grapefruit juice ↑ SQV levels. Dexamethasone ↓ SQV levels.

* Drugs for which plasma concentrations may be decreased by coadministration with ritonavir: anticoagulants (warfarin), anticonvulsants (phenytoin, divaproex, lamotrigine), antiparasitics (atovaquone).

† Some drug interaction studies were conducted with Invirase®. May not necessarily apply to use with Fortovase.

¢ Rifabutin 3x/week is recommended if CD4 cell count is < 100/mm^3

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Table 20. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use			
			Fosamprenavir (f-APV)
ANTIFUNGALS			
Itraconazole	No data, but potential for bi-directional inhibition between itraconazole and PIs, monitor for toxicities	No data, but potential for bi-directional inhibition between itraconazole and PIs, monitor for toxicities. Dose: Dose adjustment for patients receiving > 400 mg/day may be needed.	No data, but potential for bi-directional inhibition between itraconazole and PIs, monitor for toxicities. Dose: Dose adjustment for patients receiving > 400 mg/day may be needed.
Ketoconazole	No dose adjustment necessary.	Levels: APV ↑ 31% Ketoconazole ↑ 44%. Dose: Consider ketoconazole dose reduction if dose is > 400 mg/day.	Presumably similar interactions (an increase in both APV and ketoconazole levels) and recommendation as APV. Dose: Consider ketoconazole dose reduction if dose is > 400 mg/day If f-APV/r: Use with caution; do not exceed 200 mg ketoconazole daily.
Voriconazole	No data, but potential for bi-directional inhibition between voriconazole and PIs exists, monitor for toxicities.	No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities. See RTV recommendations if boosted with RTV.	Presumably similar interaction and recommendation as APV. See RTV recommendations if boosted with RTV.
ANTI-MYCOBACTERIALS			
Rifampin$^{\Sigma}$	Levels: NFV ↓ 82%. Should not be coadministered.	Levels: APV AUC ↓ 82% No change in rifampin AUC. Should not be coadministered.	Presumably similar interaction and recommendation as APV.
Rifabutin	Levels: NFV ↓ 32% if 750 mg q8h dose was given; no change if 1,250 mg q12h used. Rifabutin ↑ 2X. Dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week. NFV 1,250 BID.	Levels: APV AUC ↓ 15%. Rifabutin ↑ 193%. Dose: No change in APV dose; decrease rifabutin to 150 mg qd or 300 mg 3x/week[¢]. If RTV boosted, use dose reduce rifabutin to 150 mg QOD or 3x/week[¢].	Similar interaction and recommendation as APV if f-APV unboosted. Dose: No change in f-APV dose; decrease rifabutin to 150 mg qd or 300 mg 3x/week[¢]. If RTV boosted f-APV, dose reduce rifabutin to 150 mg QOD or 3x/week[¢].
Clarithromycin	No data.	Levels: APV AUC ↑ 18%. No change in clarithromycin AUC. No dose adjustment.	Presumably similar interaction and recommendation as APV.
ORAL CONTRACEPTIVES			
	Levels: Norethindrone ↓ 18%. Ethinyl estradiol ↓ 47%. Use alternative or additional method.	Levels: ↑ Ethinyl estradiol and norethindrone levels; APV levels ↓ 20%. Do not co-administer; alternative methods of contraception are recommended.	Presumably similar interaction as APV. Do not co-administer; alternative methods of contraception are recommended.
LIPID–LOWERING AGENTS			
Simvastatin **Lovastatin**	Simvastatin AUC ↑ 505%. Potential for large increase in lovastatin AUC. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Presumably similar interaction and recommendation as APV.
Atorvastatin	Atorvastatin AUC ↑ 74%–use lowest possible starting dose of atorvastatin with careful monitoring.	Atorvastatin levels have potential for large increase. Use lowest possible starting dose of atorvastatin with careful monitoring	Atorvastatin AUC ↑ 150% - use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No data.	No data.	No data.

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Table 20. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use			
			Fosamprenavir (f-APV)
ANTICONVULSANTS			
Carbamazepine **Phenobarbital** **Phenytoin**	Unknown, but may decrease NFV levels substantially. Monitor anticonvulsant levels and virologic response. Consider obtaining NFV levels.	Unknown, but may decrease APV levels substantially. Monitor anticonvulsant levels and virologic response. Consider obtaining APV levels.	Presumably similar interaction and recommendation as APV.
METHADONE	NFV may decrease methadone levels, but opiate withdrawal rarely occurs. Monitor and titrate dose if needed. May require ↑ methadone dose.	Methadone levels ↓ 13%. APV Cmin ↓ 25%. Monitor and titrate methadone if needed.	Presumably similar interaction and recommendation as APV.
ERECTILE DYSFUNCTION AGENTS			
Sildenafil	Sildenafil AUC ↑ 2-11 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 2-11 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Similar interaction and recommendations as APV.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg in 72 hours if administered with RTV.	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg in 72 hours if administered with RTV.	Similar interaction and recommendations as APV.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal=17.5 h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Tadalafil half-life = 17.5 hours. Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal=17.5 h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Similar interaction and recommendations as APV.
MISCELLANEOUS			H2 Blockers: Co-administration with ranitidine decreases (↓) APV AUC 30%; Cmin unchanged. Separate administration if co-administration is necessary. Monitor closely for desired virologic response. Proton-Pump Inhibitors: Co-administration with these agents is expected to decrease APV concentrations. Do not co-administer if possible.

Σ There are limited data on RTV-SQV and LPV-RTV demonstrating that RTV compensates, to a degree, for rifampin induction. In one small study, higher doses of ritonavir (up to 400 mg per dose) or an increased dose of LPV/RTV 800/200 mg were needed to offset rifampin-inducing activity of LPV; the standard dose of rifampin was used in these studies. Of note, 28% of subjects discontinued due to increases in LFTs. The safety of this combination is not established. If co-administered, close monitoring is recommended, as is measuring LPV concentrations.

¢ Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm^3

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Table 20. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use		
		Lopinavir (LPV)
ANTIFUNGALS		
Itraconazole	No data, but potential for bi-directional inhibition between itraconazole and PIs, monitor for toxicities	Levels: itraconazole ↑ when administered with LPV/r. Dose: itraconazole – consider not to exceed 200mg/day or monitor level and toxicity
Ketoconazole	Unboosted: No dosage adjustment necessary. RTV boosted: See RTV recommendations.	Levels: LPV AUC ↓ 13%. Azole ↑ 3-fold. Dose: Use with caution; do not exceed 200 mg ketoconazole daily.
Voriconazole	RTV boosted: No data, but potential for bi-directional inhibition between voriconazole and PIs exists; monitor for toxicities. See RTV recommendations if boosted with RTV.	No data, but potential for bi-directional inhibition between voriconazole and PIs exists. RTV 400mg bid reduces voriconazole AUC by 82%. Effect of low dose RTV (100-400mg/day) has not been studied. Some suggest not to co-administer until data become available..
ANTI-MYCOBACTERIALS		
Rifampin [Σ]	Should not be coadministered.	Levels: LPV AUC ↓ 75%. Should not be coadministered as a safe and effective dose of LPV/r that can be given with rifampin has not been established.[Σ]
Rifabutin	Levels: Rifabutin AUC ↑ 2.5-fold Dose: ↓ rifabutin dose to 150 mg qod or 3x/week[¢]	Levels: Rifabutin AUC ↑ 3-fold. 25-O-desacetyl metabolite ↑ 47.5-fold. Dose: Decrease rifabutin dose to 150 mg QOD or 3x/week; LPV/r: Standard.
Clarithromycin	Levels: clarithromycin AUC ↑ 94% and may cause QTc prolongation. Clarithromycin active metabolite concentrations are significantly reduced Dose: ↓ clarithromycin dose by 50%. Consider alternative therapy.	Levels: ↑ Clarithromycin AUC 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.
ORAL CONTRACEPTIVES		
	Levels: Ethinyl estradiol AUC ↑ 48%, norethindrone AUC ↑ 110% Dose: use lowest effective dose or alternative methods.	Levels: ethinyl estradiol ↓ 42%. Use alternative or additional method.
LIPID–LOWERING AGENTS		
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
Atorvastatin	Atorvastatin levels have potential for large increase. Use lowest possible starting dose of atorvastatin with careful monitoring.	Atorvastatin AUC ↑ 5.88-fold. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No data.	Pravastatin AUC ↑ 33%; no dosage adjustment necessary.
ANTICONVULSANTS		
Carbamazepine **Phenobarbital** **Phenytoin**	Unknown, but may decrease ATV levels substantially. Monitor anticonvulsant level, may consider monitoring ATV level.	Many possible interactions: carbamazepine: ↑ levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels. Phenytoin: ↓ levels of LPV, RTV, and ↓ levels of phenytoin when administered together. Avoid concomitant use or monitor LPV level.
METHADONE	No change in methadone or ATV levels.	Methadone AUC ↓ 53%. Opiate withdrawal may occur. Monitor and titrate dose if needed. May require ↑ methadone dose.
ERECTILE DYSFUNCTION AGENTS		
Sildenafil	Sildenafil levels have potential for increase. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 11-fold in combination with RTV. Do not exceed 25 mg every 48 hours.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg in 72 hours if administered with RTV.	No data, but vardenafil AUC may be substantially increased. Do not exceed a single 2.5 mg dose in 72 hours.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal=17.5h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Tadalafil AUC ↑ 124% when co-administered with RTV. Do not exceed a single dose of 10 mg every 72 hours.
MISCELLANEOUS	Diltiazem AUC ↑ 125%, ↓ diltiazem dose by 50%; ECG monitoring is recommended. Other calcium channel blockers: caution is warranted; dose titration should be considered; ECG monitoring is recommended. ATV inhibits UGT and may interfere with irinotecan metabolism; avoid concomitant use. H2-receptor antagonists: reduced ATV concentrations are expected with simultaneous administration; separate dosing by 12 hours. Proton-Pump Inhibitors: Co-administration with these agents is expected to significantly decrease ATV solubility. Do not co-administer. Antacids and buffered medications: reduced ATV concentrations are expected with simultaneous administration; give ATV 2 hr before or 1 hr after these medications.	

[Σ] There are limited data on RTV-SQV and LPV-RTV demonstrating that RTV compensates, to a degree, for rifampin induction. In one small study, higher doses of ritonavir (up to 400 mg per dose) or an increased dose of LPV/RTV 800/200 mg were needed to offset rifampin-inducing activity of LPV; the standard dose of rifampin was used in these studies. Of note, 28% of subjects discontinued due to increases in LFTs. The safety of this combination is not established. If co-administered, close monitoring is recommended, as is measuring LPV concentrations.

[¢] Rifabutin 3x/week is recommended if CD4 cell count is <100/mm^3

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Table 20. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use			
			Efavirenz (EFV)
ANTIFUNGALS			
Ketoconazole	Levels: Keto. ↓ 63%. NVP ↑ 15-30%. Dose: Not recommended.	DLV Cmin ↑ 50%. Ketoconazole: No data Dose: Standard.	No data.
Voriconazole	Metabolism of voriconazole may be induced by NVP. Voriconazole may inhibit NNRTI metabolism. Frequently monitor for NNRTI toxicity and antifungal outcome.	Metabolism of voriconazole may be inhibited by DLV. Voriconazole may inhibit NNRTI metabolism. Frequently monitor for NNRTI toxicity and antifungal outcome.	Levels: EFV ↑ 44%. Vori ↓ 77%. This combination is not recommended.
Fluconazole	NVP Levels: Cmax, AUC, and Cmin ↑ 100%. Fluconazole levels: No change. Risk of hepatotoxicity may increase with this combination. If concomitant use is necessary, recommend monitoring NVP toxicity	No clinically significant changes in DLV or fluconazole concentrations.	No clinically significant changes in EFV or fluconazole concentrations.
ANTI-MYCOBACTERIALS			
Rifampin	Levels: NVP ↓ 20%-58%. Virologic consequences are uncertain; the potential for additive hepatotoxicity exists. Use of this combination is not recommended; however, if used, coadministration should be done with careful monitoring.	Levels: DLV ↓ 96%. Contraindicated.	Levels: EFV ↓ 25%. Dose: Consider ↑ EFV to 800 mg qd.
Rifabutin	Levels: NVP ↓ 16%. No dose adjustment.*	Levels: DLV ↓ 80%. Rifabutin ↑ 100%. Not recommended.	Levels: EFV unchanged; Rifabutin ↓ 35% Dose: ↑ rifabutin dose to 450-600 mg qd or 600 mg 3x/week.* EFV: Standard
Clarithromycin	Levels: NVP ↑ 26%.Clarithromycin ↓ 30%. Monitor for efficacy or use alternative agent	Levels: Clarithromycin ↑ 100%, DLV ↑ 44%. Dose adjust for renal failure.	Levels: Clarithromycin ↓ 39%. Monitor for efficacy or use alternative agent.
ORAL CONTRACEPTIVES			
	Levels: ethinyl estradiol ↓ approx 20%. Use alternative or additional methods.	Levels of ethinyl estradiol may increase. Clinical significance is unknown.	Levels: Ethinyl estradiol ↑ 37%. No data on other component. Use alternative or additional methods.
LIPID–LOWERING AGENTS			
Simvastatin **Lovastatin**	No data.	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Simvastatin AUC ↓ by 58%; EFV unchanged Dose: Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose
Atorvastatin	No data	Potential for inhibition of atorvastatin metabolism. Use lowest possible dose and monitor for toxicity.	Levels: Atorvastatin AUC ↓43%; EFV unchanged Dose: Adjust atorvastatin dose according to lipid responses, not to exceed the maximum recommended dose
Pravastatin	No data.	No data.	No data.
ANTICONVULSANTS			
Carbamazepine **Phenobarbital** **Phenytoin**	Unknown. Use with caution. Monitor anticonvulsant levels.	Levels: DLV Cmin ↓ 90% when coadministered with phenytoin, phenobarbital, or carbamazepine. Contraindicated.	Use with caution. Monitor anticonvulsant levels.
METHADONE	Levels: NVP unchanged. methadone ↓ significantly. Opiate withdrawal common when this combination is used. Increased methadone dose often necessary. Titrate methadone dose to effect.	Levels: DLV unchanged; no data on methadone levels, but potential for increased levels. Monitor for methadone toxicity, may require a dose reduction.	Levels: methadone ↓ 60%. Opiate withdrawal common, increase methadone dose often necessary. Titrate methadone dose to effect.
MISCELLANEOUS	No data.	May increase levels of dapsone, warfarin, and quinidine. Sildenafil: potential for increased concentrations and adverse effects. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects. Vardenafil: No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Tadalafil: No data, but concomitant administration will likely result in substantial increase in tadalafil AUC and half-life (normal=17.5 h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours. Coadministration of fluoxetine increases DLV Cmin 50%.	Monitor warfarin when used concomitantly.

***** These recommendations apply to regimens that do not include PIs, which can substantially increase rifabutin levels.

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Table 20. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use				
			Didanosine (ddI)	**Tenofovir (TDF)**
Methadone	ZDV AUC increase 43%. Monitor for ZDV related adverse effects.	Levels: d4T ↓ 27%, methadone unchanged. No dose adjustment.	Levels: EC ddI unchanged. Buffered ddI AUC ↓ 63%, methadone unchanged. Dose: No change EC ddI. May consider buffered ddI dose increase or maintain standard.	No change in methadone or TDF levels
Ribavirin	Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible or closely monitor virologic response.	No data.	Coadministration not recommended. Ribavirin increases the intracellular levels of the active metabolite of ddI and may cause serious toxicities.	Level: Ribavirin unchanged, no data on TDF level
Didanosine	No significant interactions	Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination; use with caution and only if potential benefit outweighs potential risks.	No data.	Levels: ddI EC AUC ↑ by 48-60%, Cmax ↑ by 48-64% Monitor for ddI-associated toxicities; For patients > 60 kg, 250 mg/day of ddI EC is recommended.
Atazanavir (ATV)	ZDV: No change in AUC but 30% ↓ in Cmin . Significance unknown	No data.	Buffered ddI + ATV simultaneously: Levels: ↓ AUC of ATV 87%; take ATV (with food) 2 hrs before or 1 hr after buffered ddI. No interaction is expected with ddI-EC; however, dosing should be at different times as ATV should be taken with food and ddI-EC on an empty stomach.	ATV 400 + TDF 300 Levels: ATV AUC ↓ 25% and Cmin ↓ by 40%. TDF AUC was ↑ by 24%. Avoid concomitant use. ATV + RTV 300/100 mg qd + TDF 300 mg qd Levels: ATV AUC was ↓ by 25% and Cmin by 23%; ATV Cmin was higher with RTV than ATV without RTV; Consider ATV + RTV (300/100 mg qd) for coadministration with TDF (300 mg qd); however, pharmacokinetic, safety and virologic data are limited.
Indinavir (IDV)	No significant PK interaction.	No significant PK interaction.	Buffered ddI and IDV simultaneously: Levels: ↓ AUC of IDV; take IDV 1 hr before or after buffered ddI. Enteric coated ddI can be taken together with IDV	Levels: IDV Cmax ↑ 14%. Dose: Standard
Lopinavir/ritonavir (LPV/r)	No data.	No data.	No data.	LPV/r 400/100 AUC ↓ 15%; TDF AUC ↑ 34%; clinical significance of interaction is unknown; monitor for tenofovir toxicities
Cidofovir, Valganciclovir	Ganciclovir + ZDV: no significant changes in levels for either drug Potential increase in hematologic toxicities	No data.	ddI + oral ganciclovir (GCV): ddI AUC ↑ 111%; GCV AUC ↓ 21%; Appropriate doses for the combination of ddI and oral GCV have not been established	Serum concentration of these drugs and/or tenofovir may be increased; Monitor for dose-related toxicities.

Table 21a. Drug Effects on Concentration of PIs

Drug Affected	Ritonavir	Saquinavir*	Nelfinavir	Amprenavir	Lopinavir/Ritonavir	Atazanavir
Protease Inhibitors						
Indinavir (IDV)	Levels: IDV increase 2-5 times. Dose: 400/400 mg or 800/100 mg or 800/200 mg IDV/RTV bid Caution: renal events may be increased with higher IDV concentrations	Levels: IDV no effect SQV increase 4-7 times†. Dose: Insufficient data.	Levels: IDV increase 50%; NFV increase 80%. Dose: Limited data for IDV 1200 mg bid + NFV 1250 mg bid.	Levels: APV AUC increase 33%. Dose: not established.	Levels: IDV AUC and Cmin increased. Dose: IDV 600 mg bid.	Coadministration of these agents is not recommended because of potential for additive hyperbilirubinema
Ritonavir (RTV)	•	Levels: RTV no effect SQV increase 20 times†‡. Dose: 1000/100 mg SQV sgc or hgc/RTV bid or 400/400 mg bid	Levels: RTV no effect; NFV increase 1.5 times.	Levels: APV AUC increase 2.5–3.5-fold. Dose: 600/100 mg APV/RTV bid; Or 1200/200 mg APV/RTV qd	Lopinavir is co-formulated with ritonavir as Kaletra.	Levels: ATV AUC increase by 238%. Dose: ATV 300 mg qd + RTV 100 mg qd
Saquinavir (SQV)	•	•	Levels: SQV increase 3-5 times; NFV increase 20%†. Dose: Standard NFV; Fortovase 800 mg tid or 1200 mg bid.	Levels: APV AUC decrease 32%. Dose: insufficient data.	Levels: SQV† AUC and Cmin increased. Dose: SQV 1000 mg bid, LPV/r standard.	SQV 1200 mg qd + ATV 400 qd produces similar SQV AUC as SQV 1200 mg TID alone
Nelfinavir (NFV)	•	•	•	Levels: APV AUC increase 1.5-fold. Dose: insufficient data.	Levels: LPV decrease 27%; NFV increase 25% Dose: LPV/r 533/133 mg bid; NFV 1000 mg bid	•
Amprenavir (APV)	•	•	•	•	APV: AUC and Cmin increased relative to APV without RTV; APV AUC and Cmin are reduced relative to APV + RTV; LPV Cmin may be decreased relative to LPV/r Dose: APV 750 mg bid; LPV/r standard or consider dose increase to 533/133 mg bid. Consider monitoring PI concentrations.	•
Fosamprenavir (f-APV)	Levels: f-APVAUC and Cmin increase 100% and 400%, respectively, with 200 mg RTV. Dose: (f-APV 1,400 mg + RTV 200 mg) qd; or (f-APV 700 mg + RTV 100 mg) bid	Levels: APV AUC decrease 32%. Dose: insufficient data.	•	•	f-APV: Cmin decreased 64% (at dose of 700 mg bid with 100 mg bid of RTV.) LPV: Cmin decreased 53% (at LPV/r dose of 400/100). Increase rate of adverse events seen with co-administered. Should not be co-administered as doses are not established	•
Lopinavir/ Ritonavir (LPV/r)	•	•	•	•	•	No information with LPV/ATV; RTV 100 mg increases ATV AUC 238%

* Several drug interaction studies have been completed with saquinavir given as Invirase or Fortovase. Results from studies conducted with Invirase may not be applicable to Fortovase.
† Study conducted with Fortovase.
‡ Study conducted with Invirase.

Table 21b. Drug Effects on Concentration of NNRTIs

			Efavirenz
PIs and NNRTIs			
Indinavir (IDV)	Levels: IDV decrease 28%; NVP no effect. Dose: IDV 1000 mg q8h or consider IDV/RTV, NVP standard.	Levels: IDV increase >40%; DLV no effect. Dose: IDV 600 mg q8h. DLV: standard.	Levels: IDV decrease 31%. Dose: IDV 1000 mg q8h or consider IDV/RTV, EFV standard.
Ritonavir (RTV)	Levels: RTV decrease 11%. NVP no effect. Dose: Standard.	Levels: RTV increase 70%. DLV: no effect. Dose: DLV standard. RTV: no data.	Levels: RTV increase 18%. EFV increase 21%. Dose: Standard.
Saquinavir (SQV)	Levels: SQV decrease 25%. NVP no effect. Dose: Consider SQV-sgc/RTV 400/400 or 1000/100 BID or SQV- hgc/RTV 1000/100 BID.	Levels: SQV‡ increase 5 times; DLV no effect. Dose: Fortovase 800 mg tid, DLV standard (monitor transaminase levels).	Levels: SQV‡ decrease 62%. EFV decrease 12%. SQV is not recommended to be used as sole PI when EFV is used. Dose: Consider SQV/RTV 400/400.
Nelfinavir (NFV)	Levels: NFV increase 10%. NVP no effect. Dose: Standard.	Levels: NFV increase 2 times; DLV decrease 50%. Dose: No data (monitor for neutropenic complications).	Levels: NFV increase 20%. Dose: Standard.
Amprenavir (APV)	**No data.**	Levels: APV AUC increase 130%. DLV AUC decrease 61%. Dose: Co-administration not recommended.	Levels: APV AUC decrease 36%. Dose: Add RTV 200 mg to APV 1,200 mg BID; EFV dose standard.
Fosamprenavir (f-APV)	**No data.**	Presumably similar PK affects as APV. Dose: Co-administration not recommended.	Levels: f-APV Cmin decreases 36% (when dosed at 1400 mg qd with 200 mg of RTV). Dose: (f-APV 1,400 mg + RTV 300 mg) qd; or (f-APV 700 mg + RTV 100 mg) bid.
Lopinavir/ Ritonavir (LPV/RTV)	Levels: LPV Cmin decrease 55%. Dose: LPV/r 533/133 mg bid; NVP standard.	Levels: LPV levels expected to increase. Dose: Insufficient data.	Levels: LPV AUC decrease 40%. EFV no change. Dose: LPV/r 533/133 mg bid. EFV standard.
Atazanavir (ATV)	No data. A decrease in ATV levels is expected. Co-administration is not recommended. Effect of NVP on RTV/ATV combination unknown; if used, consider monitoring ATV level.	No data.	Levels: ATV AUC decrease 74%, EFV no change. Dose: ATV 300 + RTV 100 mg each given once daily with food; EFV dose standard.
Nevirapine (NVP)	No data.	No data.	Levels: NVP: no effect. EFV: AUC decrease 22%.
Delavirdine (DLV)	No data.	No data.	No data.

‡ Study conducted with Invirase.

Table 22. Recommendations for Using Drug-Resistance Assays

	Rationale
Drug-resistance assay recommended	
Virologic failure during combination antiretroviral therapy **(BII)**	Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen, if indicated.
Suboptimal suppression of viral load after antiretroviral therapy initiation **(BIII)**	Determine the role of resistance and maximize the number of active drugs in the new regimen, if indicated.
Acute human immunodeficiency virus (HIV) infection, if decision is made to initiate therapy **(BIII)**	Determine if drug-resistant virus was transmitted to help design an initial regimen or to change regimen accordingly (if therapy was initiated prior to test results).
Drug-resistance assay should be considered	
Chronic HIV infection before therapy initiation **(CIII)**	Available assays might not detect minor drug-resistant species. However, should consider if significant probability that patient was infected with drug-resistant virus (i.e., if the patient is thought to have been infected by a person receiving antiretroviral drugs).
Drug resistance assay not usually recommended	
After discontinuation of drugs **(DIII)**	Drug-resistance mutations might become minor species in the absence of selective drug pressure, and available assays might not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value, but its absence does not rule out the presence of minor drug-resistant species.
Plasma viral load < 1,000 HIV RNA copies/mL **(DIII)**	Resistance assays cannot be consistently performed because of low copy number of HIV RNA; patients/providers may incur charges and not receive results.

Table 23. Summary of Guidelines For Changing An Antiretroviral Regimen For Suspected Treatment Regimen Failure

Patient Assessment (AIII)

- Review antiretroviral treatment history.
- Assess for evidence of clinical progression.(e.g. physical exam, laboratory and/or radiologic tests)
- Assess adherence, tolerability, and pharmacokinetic issues.
- Distinguish between limited, intermediate, and extensive prior therapy and drug resistance.
- Perform resistance testing while patient is taking therapy (or within 4 weeks after regimen discontinuation).
- Identify active drugs and drug classes to use in designing new regimen.

Patient Management: Specific Clinical Scenarios

- ***Limited or intermediate prior treatment with low (but not suppressed) HIV RNA level (e.g., up to 5000 copies/mL):*** The goal of treatment is to re-suppress HIV RNA to below level of assay detection. Consider intensifying with one drug (e.g., tenofovir) **(BII)** or pharmacokinetic enhancement (use of ritonavir boosting of a protease inhibitor) **(BII)**, perform resistance testing if possible, or most aggressively, change two or more drugs in the regimen **(CIII)**. If continuing the same treatment regimen, HIV RNA levels should be followed closely because ongoing viral replication will lead to accumulation of additional resistance mutations.
- ***Limited or intermediate prior treatment with resistance to one drug:*** Consider changing the one drug **(CIII)**, pharmacokinetic enhancement (few data available) **(BII)**, or, most aggressively, change two or more drugs in the regimen **(BII)**.
- ***Limited or intermediate prior treatment with resistance to more than one drug:*** The goal of treatment is to suppress viremia to prevent further selection of resistance mutations. Consider optimizing the regimen by changing classes (e.g., PI-based to NNRTI-based and vice versa) and/or adding new active drugs **(AII)**. (See **Table 25**: ***Treatment options following virologic failure on initial recommended therapy regimens***).
- ***Prior treatment with no resistance identified:*** Consider the timing of the drug resistance test (e.g., was the patient off antiretroviral medications?) and/or nonadherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., 2–4 weeks) to determine if a resistant virus becomes evident **(CIII).**
- ***Extensive prior treatment and drug resistance:*** It is reasonable to continue the same antiretroviral regimen if there are few or no treatment options **(CIII)**. In general, avoid adding a single active drug because of the risk for the rapid development of resistance to that drug. In advanced HIV disease with a high likelihood of clinical progression (e.g., CD4 cell count <100 cells/mm^3), adding a single drug may reduce the risk of immediate clinical progression **(CIII)**. In this complicated scenario, expert advice should be sought. (See **Table 24**: ***Novel strategies to consider for treatment-experienced patients with few available active treatment options***).

Table 24. Novel Strategies To Consider For Treatment-Experienced Patients With Few Available Active Treatment Options

- **Pharmacokinetic enhancement** with ritonavir may increase drug concentrations of most PIs (except nelfinavir) and may overcome some degree of drug resistance **(CII)**.
- **Therapeutic Drug Monitoring** may be considered (see **Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents** section).
- **Re-treating with prior medications** may be useful, particularly if they were discontinued previously for toxicities that can now be better addressed **(BII)**. Continued drug therapy and maintenance of drug-resistant virus may compromise viral fitness, but it is not known if this has clinical applicability.
- **The use of empiric multi-drug regimens** (including up to 3 PIs and/or 2 NNRTIs) has been advocated by some *[1-2]*, but may be limited ultimately by complexity, poor tolerability, and unfavorable drug-drug interactions **(CII)**.
- **New antiretroviral drugs** (drugs in existing classes with activity against resistant viral strains, or new drug classes with novel mechanisms of action) including those available on expanded access or through clinical trials may be used. The first approved HIV-1 entry inhibitor, enfuvirtide (T-20) was approved for use in the treatment-experienced patient with ongoing viremia on the basis of antiretroviral activity in this population *[3-4]*. Given the necessity for parenteral (subcutaneous) administration twice daily, this drug should be reserved for treatment-experienced patients with fewer other options **(BII)**. Optimally, a new active agent (e.g., enfuvirtide) should be used with one or more other active agents in the regimen **(BII)**.

Novel Strategy Not Recommended at This Time:

- **Structured treatment interruptions** in the setting of virologic failure have been investigated prospectively, and most trials have shown no virologic benefit *[5-7]*. The risks of this approach (CD4 cell decline, HIV-related clinical events including death, acute retroviral syndrome) appear to outweigh any possible benefit (decreased HIV RNA levels on the next treatment regimen). Given the seriousness of the risks and the unproven benefits, this strategy cannot be recommended **(DII)**.

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Table 25. Treatment Options Following Virologic Failure on Initial Recommended Therapy Regimens

Regimen Class	Initial Regimen	Recommended Change
NNRTI	2 NRTIs + NNRTI	• 2 NRTIs (based on resistance testing) + PI (with or without low-dose ritonavir) (**AII**)
PI	2 NRTIs + PI (with or without low-dose ritonavir)	• 2 NRTIs (based on resistance testing) + NNRTI (**AII**)
3-NRTI	3 nucleosides	• 2 NRTIs (based on resistance testing) + NNRTI or PI (with or without low-dose ritonavir) (**AIII**) • NNRTI + PI (with or without low-dose ritonavir) (**CIII**) • Nucleoside(s) (based on resistance testing) + NNRTI + PI (with or without low-dose ritonavir) (**CII**)

Table 26. Suggested Minimum Target Trough Concentrations for Persons with Wild-Type HIV-1

Drug	Concentration (ng/mL)
Amprenavir (Agenerase)	400
Indinavir (Crixivan)	100
Lopinavir/ritonavir (Kaletra)	1000
Nelfinavir (Viracept) [a]	800
Ritonavir (Norvir) [b]	2100
Saquinavir (Fortovase, Invirase)	100-250
Efavirenz (Sustiva)	1000
Nevirapine (Viramune)	3400

a. Measurable active (M8) metabolite.
b. Ritonavir given as a single PI.

Sources:

- Acosta EP, and Gerber JG. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Research Human Retroviruses* 2002; 18(12) :825-34.
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Table 27. Associated Signs and Symptoms of Acute Retroviral Syndrome and Percentage of Expected Frequency

- 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
  - ✓ Cognitive impairment or psychosis

Source: Niu MT, Stein DS, Schnittman SM. Primary human immunodeficiency virus type 1 infection: review of pathogenesis and early treatment intervention in humans and animal retrovirus infections. *J Infect Dis* 1993; 168(6):1490-501.

Table 28. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals During Pregnancy

(see *Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy* for more detail on drugs)

Antiretroviral drug	FDA pregnancy category †	Placental passage (newborn: mother drug ratio)	Long-term animal carcinogenicity studies	Animal teratogen studies
Nucleoside and nucleotide analogue reverse transcriptase inhibitors				
Abacavir (Ziagen, ABC)	C	Yes (rats)	Positive (malignant and non-malignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats)	Positive (rodent anasarca and skeletal malformations at 1000 mg/kg (35x human exposure) during organogenesis; not seen in rabbits)
Didanosine (Videx, ddI)	B	Yes (human) [0.5]	Negative (no tumors, lifetime rodent study)	Negative
Emtricitabine (Emtriva, FTC)	B	Unknown	Not completed	Negative
Lamivudine (Epivir, 3TC)	C	Yes (human) [~1.0]	Negative (no tumors, lifetime rodent study)	Negative
Stavudine (Zerit, d4T)	C	Yes (rhesus monkey) [0.76]	Positive (mice and rats, at very high dose exposure, liver and bladder tumors)	Negative (but sternal bone calcium decreases in rodents)
Tenofovir DF (Viread)	B	Yes (rat and monkey)	Positive (hepatic adenomas in female mice at high doses)	Negative (osteomalacia when given to juvenile animals at high doses)
Zalcitabine (HIVID, ddC)	C	Yes (rhesus monkey) [0.30–0.50]	Positive (rodent, thymic lymphomas)	Positive (rodent-hydrocephalus at high dose)
Zidovudine† (Retrovir, AZT, ZDV)	C	Yes (human) [0.85]	Positive (rodent, noninvasive vaginal epithelial tumors)	Positive (rodent-near lethal dose)
Non-nucleoside reverse transcriptase inhibitors				
Delavirdine (Rescriptor)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male and female mice but not rats, bladder tumors in male mice)	Positive (rodent-ventricular septal defect)
Efavirenz (Sustiva)	D	Yes (cynomologus monkey, rat, rabbit) [~1.0]	Positive (hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas in female but not male mice)	Positive (cynomologus monkey- anencephaly, anophthalmia, microophthalmia)
Nevirapine (Viramune)	C	Yes (human) [~1.0]	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative
Protease inhibitors				
Amprenavir (Agenerase)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male mice and rats)	Negative (but deficient ossification and thymic elongation in rats and rabbits)
Atazanavir	B	Unknown	Positive (hepatocellular adenomas in female mice)	Negative
Fosamprenavir (Lexiva)	C	Unknown	Positive (benign and malignant liver tumors in male rodents)	Negative (deficient ossification with amprenavir but not fosamprenavir)
Indinavir (Crixivan)	C	Minimal (humans)	Positive (thyroid adenomas in male rats at highest dose)	Negative (but extra ribs in rodents)
Lopinavir/Ritonavir (Kaletra)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)
Nelfinavir (Viracept)	B	Minimal (humans)	Positive (thyroid follicular adenomas and carcinomas in rats)	Negative
Ritonavir (Norvir)	B	Minimal (humans)	Positive (liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rodents)
Saquinavir (Fortovase)	B	Minimal (humans)	Negative	Negative
Fusion inhibitors				
Enfuvirtide (Fuzeon)	B	Unknown	Not done	Negative

† Food and Drug Administration Pregnancy Categories:
A - Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters).
B - Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.
C - Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
D - Positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks.
X - Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

Table 29. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

(*see also "**Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy**" Supplement for additional toxicity data and "**Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States**" for detailed guidelines regarding treatment options*)

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
NRTIs/ NtRTIs		See text for discussion of potential maternal and infant mitochondrial toxicity.	NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection (AZT alone may be considered for prophylaxis of perinatal transmission in pregnant women with HIV RNA <1,000 copies/mL).
Recommended agents			
Zidovudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination antiretroviral regimens in pregnancy based on efficacy studies and extensive experience; should be included in regimen unless significant toxicity or stavudine use.
Lamivudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Because of extensive experience with lamivudine in pregnancy in combination with zidovudine, lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.
Alternate agents			
Didanosine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together.	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.
Emtricitabine	No studies in human pregnancy.	No studies in human pregnancy.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together.	Alternate NRTI for dual nucleoside backbone of combination regimens. Stavudine should be used with didanosine only if no other alternatives are available. Do not use with zidovudine due to potential for antagonism.
Abacavir*	Phase I/II study in progress.	Hypersensitivity reactions occur in ~5-8% of non-pregnant persons; a much smaller percentage are fatal and are usually associated with rechallenge. Rate in pregnancy unknown. Patient should be educated regarding symptoms of hypersensitivity reaction.	Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen.#
Insufficient data to recommend use			
Tenofovir	No studies in human pregnancy. Phase I study in late pregnancy in progress.	Studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within two months of starting maternal therapy. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown.	Because of lack of data on use in human pregnancy and concern regarding potential fetal bone effects, tenofovir should be used as a component of a maternal combination regimen only after careful consideration of alternatives.
Not recommended			
Zalcitabine	No studies in human pregnancy.	Rodent studies indicate potential for teratogenicity and developmental toxicity (see **Table 28**).	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.

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Table 29. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
NNRTIs			
Recommended agents			
Nevirapine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with $CD4^+$ counts >250 cells/mm^3 when first initiating therapy; unclear if pregnancy increases risk.	Nevirapine should be initiated in pregnant women with $CD4^+$ counts >250 cells/mm^3 only if benefit clearly outweighs risk, due to the increased risk of potentially life-threatening hepatotoxicity in women with high $CD4^+$ counts. Women who enter pregnancy on nevirapine regimens and are tolerating them well may continue therapy, regardless of $CD4^+$ count.
Not recommended			
Efavirenz	No studies in human pregnancy.	FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving efavirenz during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure; there are three case reports of neural tube defects in humans after first trimester exposure; relative risk unclear.	Use of efavirenz should be avoided in the first trimester, and women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Because of the known failure rates of contraception, alternate regimens should be strongly considered in women of child bearing potential. Use after the second trimester of pregnancy can be considered if other alternatives are not available and if adequate contraception can be assured postpartum.
Delavirdine	No studies in human pregnancy.	Rodent studies indicate potential for carcinogenicity and teratogenicity (see **Table 28**).	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.
Protease inhibitors		Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see text).	
Recommended agents			
Nelfinavir	Adequate drug levels are achieved in pregnant women with nelfinavir 1250 mg, given twice daily.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant. Nelfinavir dosing at 750 mg three times daily produced variable and generally low levels in pregnant women.	Given pharmacokinetic data and extensive experience with use in pregnancy compared to other PIs, preferred PI for combination regimens in pregnant women, particularly if HAART is being given solely for perinatal prophylaxis. In clinical trials of initial therapy in non-pregnant adults, nelfinavir-based regimens had a lower rate of viral response compared to lopinavir/ritonavir or efavirenz-based regimens, but similar viral response compared with atazanavir or nevirapine-based regimens.
Saquinavir-soft gel capsule [SGC] (Fortovase®)/ ritonavir	Adequate drug levels are achieved in pregnant women with saquinavir-SGC 800 mg boosted with ritonavir 100 mg, given twice daily. Recommended adult dosing of saquinavir-SGC 1000 mg plus ritonavir 100 mg may be used. No pharmacokinetic data on saquinavir-hard gel capsule [HGC]/ ritonavir in pregnancy, but better GI tolerance in non-pregnant adults.	Well-tolerated, short-term safety demonstrated for mother and infant. Inadequate drug levels observed in pregnant women with saquinavir-SGC given alone at 1200 mg three times daily.	Given pharmacokinetic data and moderate experience with use in pregnancy, ritonavir-boosted saquinavir-SGC can be considered a preferred PI for combination regimens in pregnancy.

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Table 29. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Alternate agents			
Indinavir	Two studies including 18 women receiving indinavir 800 mg three times daily showed markedly lower levels during pregnancy compared to postpartum, although suppression of HIV RNA was seen *[288, 289]*.	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Use of unboosted indinavir during pregnancy is not recommended.	Alternate PI to consider if unable to use nelfinavir or saquinavir-SGC/ritonavir, but would need to give indinavir as ritonavir-boosted regimen. Optimal dosing for the combination of indinavir/ritonavir in pregnancy is unknown.
Lopinavir/ ritonavir	Phase I/II safety and pharmacokinetic study in progress using twice daily lopinavir 400 mg and ritonavir 100 mg.	Limited experience in human pregnancy.	Preliminary studies suggest increased dose may be required during pregnancy, though specific dosing recommendations not established. If used during pregnancy, monitor response to therapy closely. If expected virologic result is not observed, consult with a specialist with expertise in HIV in pregnancy.
Ritonavir	Phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum.	Minimal experience in human pregnancy.	Given low levels in pregnant women when used alone, recommended for use in combination with second PI as low-dose ritonavir "boost" to increase levels of second PI.
Insufficient data to recommend use			
Amprenavir	No studies in human pregnancy.	Oral solution contraindicated in pregnant women because of high levels of propylene glycol, which may not be adequately metabolized during pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use of capsules during pregnancy.
Fosamprenavir	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Atazanavir	No studies in human pregnancy.	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental passage of other PIs has been low.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Fusion inhibitors			
Insufficient data to recommend use			
Enfuvirtide	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SGC = soft gel capsule; HGC = hard gel capsule.

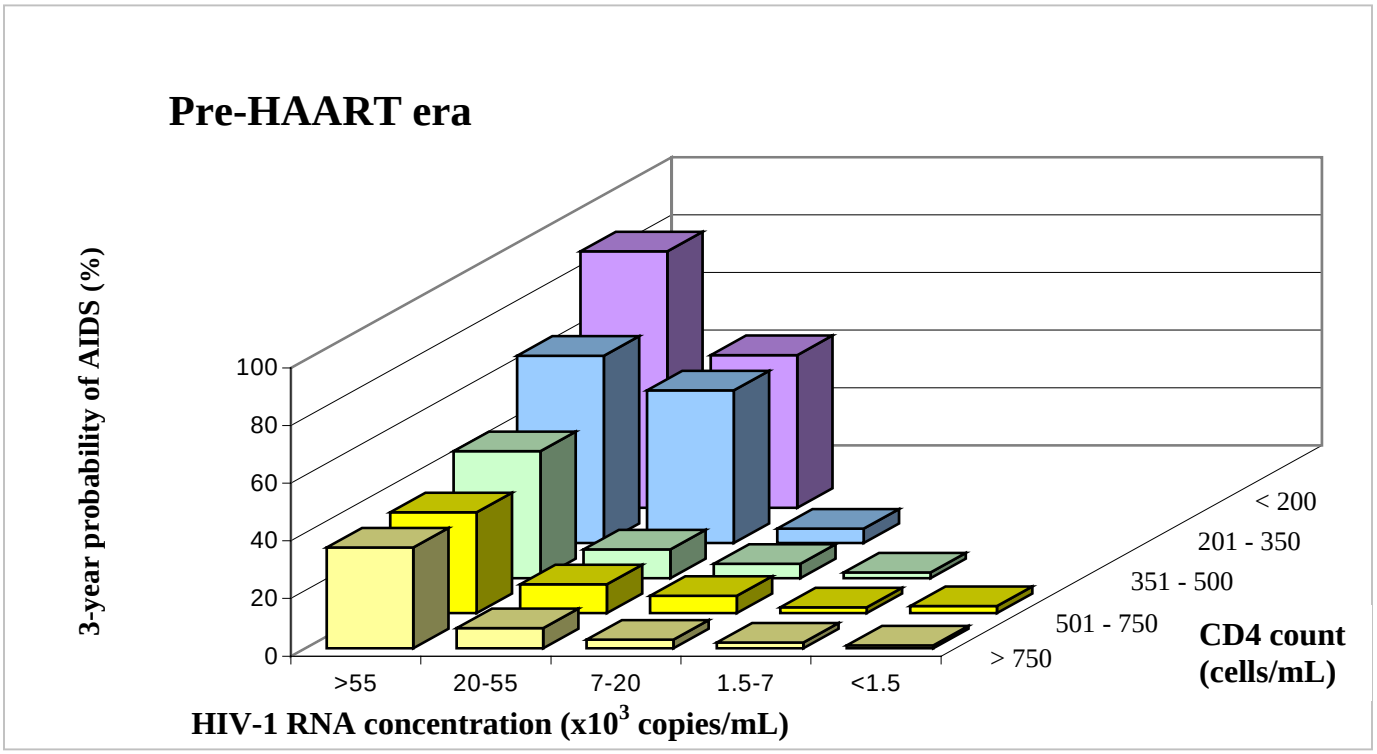
* Zidovudine and lamivudine are included as a fixed-dose combination in Combivir®; zidovudine, lamivudine, and abacavir are included as a fixed-dose combination in Trizivir®.

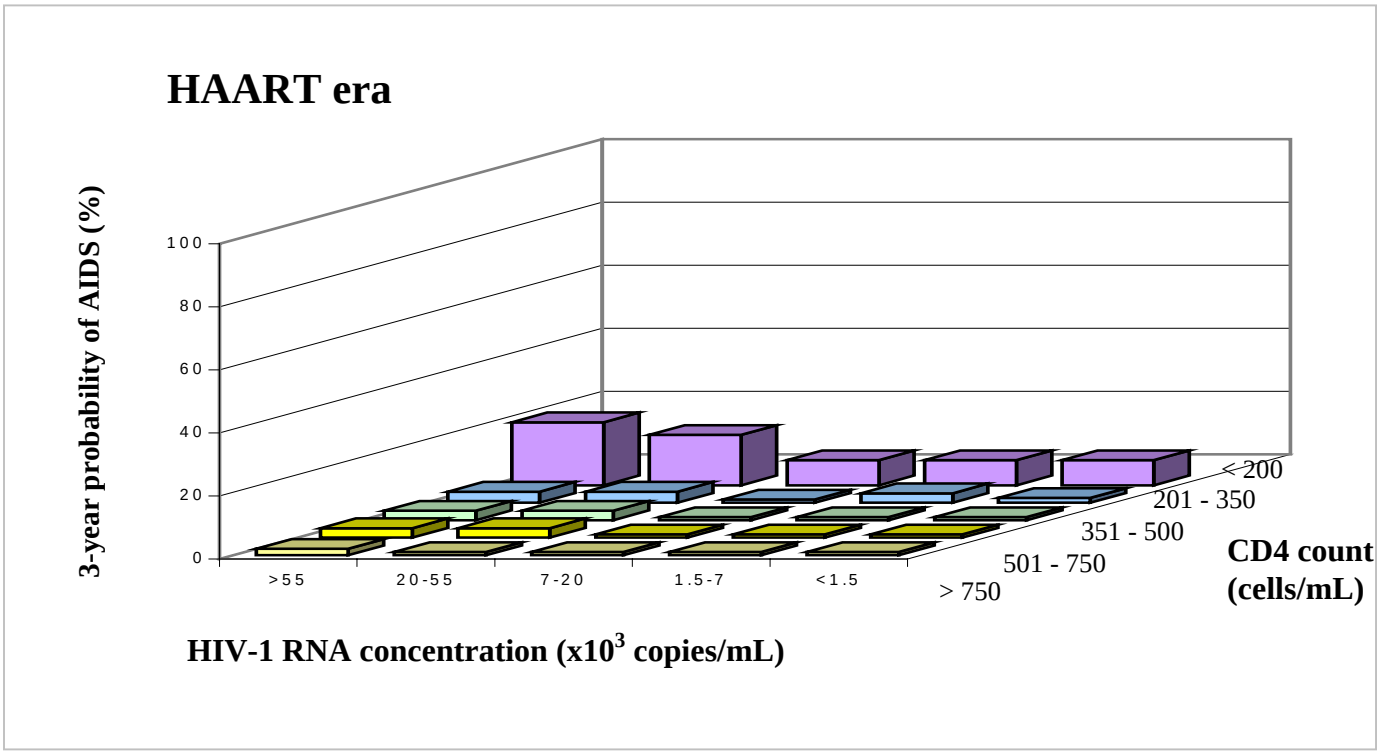
\# Triple NRTI regimens including abacavir have been less potent virologically compared to PI-based HAART regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based HAART regimen cannot be used (e.g., due to significant drug interactions). A study evaluating use of zidovudine/lamivudine/abacavir among pregnant women with HIV RNA <55,000 copies/mL as a class-sparing regimen is in development.

Table 30. Antiretroviral Agent Available Through Expanded Access Program

Drug	Tipranavir
Source	Boehringer Ingelheim Expanded Access Program 1-888-524-8675 or **http://www.tpv-eap.com**
Class	Protease Inhibitor
Usual Dose	Tipranavir 500mg twice daily + ritonavir 200mg twice daily
Adverse Effects	Nausea, vomiting, diarrhea, abdominal pain, headache, fatigue, hyperlipidemia
Enrollment Criteria	▪ ≥ 18 years old ▪ Triple antiretroviral class experience, with at least two prior PI-based regimens ▪ Documented PI resistance within past 12 months

Figure A: Prognosis According to CD4 Cell Count and Viral Load in the Pre-HAART and HAART Eras





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Appendix A: DHHS Panel on Clinical Practices for Treatment of HIV Infection Conflict of Interest Disclosure – October 2004

Name	Panel Status*	Company	Relationship
Jean Anderson	M	Abbott Agouron/Pfizer Boehringer-Ingelheim Glaxo-Smith Kline	• Speakers bureau, recipient of support for educational program • Speakers' bureau, recipient of support for research and educational programs, advisory board member • Recipient of support for educational program • Speakers bureau, recipient of support for educational program
A. Cornelius Baker	M	None	N/A
John G. Bartlett	C	Abbott Bristol-Myers Squibb	• HIV Advisory Board • HIV Advisory Board
Debra Birnkrant	M	None	N/A
Sam Bozzette	M	Abbott Bristol-Myers Squibb EMEA Consortium* Roche	• Speakers bureau • Consultant • Grantee • Grantee
Victoria Cargill	M	None	N/A
Charles Carpenter	M	None	N/A
Laura Cheever	M	None	N/A
Martin Delaney	M	None	N/A
Lawrence Deyton	M	None	N/A
Wafaa El-Sadr	M	None	N/A
Mark Dybul	M	None	N/A
Courtney V. Fletcher	M	Bristol-Myers Squibb Glaxo-Smith Kline	• Speakers bureau • Speakers bureau
Gregg Gonsalves	M	None	N/A
Eric Goosby	M	Gilead Johnson & Johnson Kaiser Family Foundation Pfizer/Agouron Pfizer	• Ad-hoc consultant • Grant support • Ad-hoc consultant • Grant support • Grant support
Fred Gordin	M	None	N/A
Roy M. Gulick	M	Abbott Boehringer-Ingelheim Bristol-Myers Squibb Gilead GlaxoSmithKline Merck Panacos Progenics Pfizer Roche/Trimeris Schering Tibotec Virologic	• Research grant, ad-hoc consultant • Research grant, ad hoc consultant • Ad hoc consultant, speaker honoraria • Speaker honoraria • Ad-hoc consultant • Research grant, speaker honoraria • Ad-hoc consultant • Research grant • Research grant, ad-hoc consultant • Ad hoc consultant, speaker honoraria • Ad-hoc consultant • Research grant, ad-hoc consultant

Appendix A: DHHS Panel on Clinical Practices for Treatment of HIV Infection Conflict of Interest Disclosure – October 2004

Name	Panel Status*	Company	Relationship
Mark Harrington	M	None	N/A
Martin Hirsch	M	Bristol-Myers Squibb Glaxo-Smith Kline Millennium Schering Plough Takeda	• Ad-hoc Consultant • Ad-hoc Consultant • Research support • Ad-hoc Consultant • Research support
Jonathan Kaplan	M	None	N/A
H. Clifford Lane	C	Chiron	• Research support (CRADA)
Richard Marlink	O	African Comprehensive HIV/AIDS Partnerships (Gates/Merck NGO) Secure the Future (a BMS Foundation)	• Board of Directors • Grant/Research support
Henry Masur	M	Cubist Gilead Virco	• Advisory Board member • Data Safety Monitoring Board (DSMB) • DSMB
Celia Maxwell	O	Pfizer/Agouron	• Support for conference
John Mellors	M	Achillion Pharmaceuticals Boehringer Ingelheim Bristol Myers-Squibb Gilead Sciences GlaxoSmithKline Idenix Pharmaceuticals Merck and Co., Inc. Pharmasset Tibotec-Virco	• Stock holder • Advisory Board member • Research Grant • Advisory Board member • Advisory Board member/Research Grant • Stock holder • Advisory Board member • Stock options • Advisory Board member
Lynne Mofenson	M	None	N/A
Jeffrey Murray	M	None	N/A
James Neaton	M	Bristol-Myers Squibb Chiron Glaxo-Smith Kline Merck	• DSMB (non-HIV trial) • Research grant • Speaker honoraria • DSMB (non-HIV trial)
James Oleske	O	None	N/A
Alice Pau	M	None	N/A
Robert Schooley	M	Achillion Bristol-Myers Squibb Gilead Glaxo-Smith Kline Merck Pfizer Roche Vertex Virologic	• Scientific Advisory Board, stock option • Consultant • Consultant, Scientific Advisory Board • Consultant, research support • Consultant, research support, Scientific Advisory Board • Consultant • Consultant • Scientific Advisory Board, stock • Scientific Advisory Board, stock options

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Name	Panel Status*	Company	Relationship
Renslow Sherer	M	Abbott Agouron Boehringer-Ingelheim Bristol Myers-Squibb Chiron Dupont Gilead Glaxo-Smith Kline Merck Ortho-Biotech Roxanne Sarawak-Medichem Tibotec-Virco US Bioscience	• Consultant, grant/research support, speakers bureau • Consultant, grant/research support, speakers bureau • Consultant • Consultant, grant/research support, speakers bureau • Grant/research support, speakers bureau • Consultant, grant/research support, speakers bureau • Consultant, speakers bureau • Consultant, grant/research support, speakers bureau • Consultant • Consultant, grant/research support, speakers bureau • Speakers bureau • Grant/research support, speakers bureau • Consultant • Speakers bureau
Daniel Simpson	O	No	N/A
Stephen Spector	M	Bristol Myers-Squibb	Grant support
Sharilyn Stanley	M	No	N/A
Paul Volberding	M	Boehringer-Ingelheim Bristol Myers-Squibb Gilead Glaxo-Smith Kline Immune Response Ortho-Biotech Pfizer	• Advisory Board • Advisory Board, speaker • Advisory Board, speaker • Speaker • Advisory Board, stock option • Advisory Board • Advisory Board
Suzanne Willard	M	Glaxo-Smith Kline Roche	• Speaker • Speakers bureau

* C=co-chair; M=member; O=Observer
N/A = not applicable