EXHIBIT 62

Anti-HIV Pill Protects Against AIDS

By Jon Cohen | Nov. 23, 2010 , 8:00 AM

(See the transcript of our online Q & A about the study and drug below the story.)

For the first time, a study has demonstrated that an anti-HIV pill can protect uninfected people from contracting the AIDS virus through sex. The much-anticipated results show that an already approved drug can cut transmission rates nearly in half, which could provide a powerful new tool to curb the AIDS epidemic. "It's a game changer," says one of the dozens of clinicians who participated in the study, Kenneth Mayer of Fenway Health in Boston. But experts say the success also raises a dizzying array of complicated issues about human behavior, resources, risk, and public health.

The strategy, called pre-exposure prophylaxis, or PrEP, was tested in 2499 HIV uninfected men and transgender women who have sex with men. Half of the group received a placebo. In the treatment group, transmission dropped by 44%, despite the fact that many study participants in the trial frequently skipped doses. When the researchers analyzed a small subset of people who received the treatment and not the placebo, they found an astonishing 92% protection rate in people who had detectable levels of the drug in their blood—in other words, in those who took the drug regularly.

Nearly 30 large-scale HIV prevention studies have failed, making these results that much more heartening. The new study, called the Pre-Exposure Prophylaxis Initiative, or iPrEx, cost $43.6 million and was conducted in six countries between July 2007 and December 2009. "The iPrEx study results are extremely important and providing strong evidence that PrEP can reduce HIV

acquisition among a segment of society that is disproportionately affected by HIV/AIDS," said Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID) at a teleconference for the press held yesterday. NIAID provided two-thirds of the funding for the study, and the Bill & Melinda Gates Foundation covered the other third.

As reported online today in *The New England Journal of Medicine,* the study recruited people at extremely high risk of becoming infected with HIV: Participants reported an average of 18 sexual partners in the past 12 weeks, and about 60% said they had unprotected receptive anal intercourse in that time frame. Everyone received regular counseling about how to reduce their risks of becoming infected as well as condoms and treatment for other sexually transmitted infections. At the end of the trial, 36 out of 1251 people who received a pill that contained a combination of two anti-HIV drugs, tenofovir and emtricatbine (co-formulated as Truvada and made by Gilead Sciences of Foster City, California), became infected. Of the 1248 people who received a placebo pill, 64 became infected.

Robert Grant, a virologist at the University of California, San Francisco (UCSF), headed the study, which took place in Peru, Ecuador, Brazil, the United States, Thailand, and South Africa. "I was overjoyed that we showed clear evidence that oral Truvada added protection to [men who have sex with men] receiving comprehensive prevention services," says Grant. "It's a robust result." Although some researchers feared drug resistance might surface or that people might increase their rates of risky behavior because they believed the drug provided protection, neither problem was seen in the study, he says.

But Grant emphasizes that the findings only apply to men and transgender women who have sex with men; other studies are underway to evaluate PrEP in heterosexual men and women and injecting drug users.

Several AIDS researchers not involved in the study told *Science* that they are impressed with its thoroughness and statistically significant results. But they worry how well the strategy will work in the real world. Although participants reported taking the drugs about 90% of the time, the researchers doubt this was accurate because of studies of drug levels in blood. "The questions that remain are more behavioral than biological," says Robert Schooley, a virologist at the University of California at San Diego (UCSD). Grant of UCSF suggests that adherence to the regimen may have been low because people did not know whether the drug worked or whether they were receiving placebo. Truvada did not cause any serious side effects, but many people complained of nausea and headaches, which also may have affected adherence. Grant is planning a follow-up study to explore these and other questions.

The results come on the heels of a widely celebrated positive finding from the so-called CAPRISA 004 trial in South African women, which this summer **reported** that a vaginal gel laced with tenofovir reduced infection by 39%. "This plus CAPRISA means we've crossed the Rubicon," says Mayer, who ran one of the two iPrEx sites in the United States. "Antiviral chemoprevention works, no question."

One major difference between the iPrEx and CAPRISA trials is that the gel is an experimental product and is not on the market. Truvada, in contrast, is a popular anti-HIV treatment, and can be prescribed for "off-label use" by any physician. But it remains unclear whether insurance companies will pay for this off-label use; costs run from $11 per month for a generic version to nearly $1000 per month for product made by Gilead.

Gilead says it wants to have "frank" talks with the U.S. Food and Drug Administration and other stakeholders before it decides to seek licensure for Truvada as a preventive. "We'll have, I imagine, a very interesting discussion about the potential risks and benefits associated with this kind of a modality, and I think that will govern what we choose to do," says Howard Jaffe, president of the Gilead Foundation, a nonprofit started by the company to help poor communities combat HIV and hepatitis B and C.

This new prevention success also raises fundamental questions about how to best spend money to thwart the AIDS epidemic. "For a country that has not yet reached the level of care in terms of providing antiretovirals to save people's lives, I think it's going to be quite a while before we'd start using oral antiretrovirals for prevention," says Salim Abdool Karim, an epidemiologist a the University of KwaZulu-Natal in Durban, South Africa, who co-ran the CAPRISA study.

Another thorny ethical issue is whether vaccine and other prevention studies with men who have sex with men now should use Truvada as the placebo, which clearly offers more benefit than the standard dummy preparation. Fauci says NIAID will now examine this question in every prevention study they have planned or underway.

UCSD's Schooley, echoing many of his colleagues, cautions that no single preventive by itself can stop HIV, which infects people by different routes under a wide variety of conditions. "People looking for a single intervention to impact the epidemic are the same ones who want a single battle to end the war in Afghanistan," says Schooley. "But it's quite clear the most potent tools we have right now are drugs."

Posted in: **Biology**, **Health**

Jon Cohen

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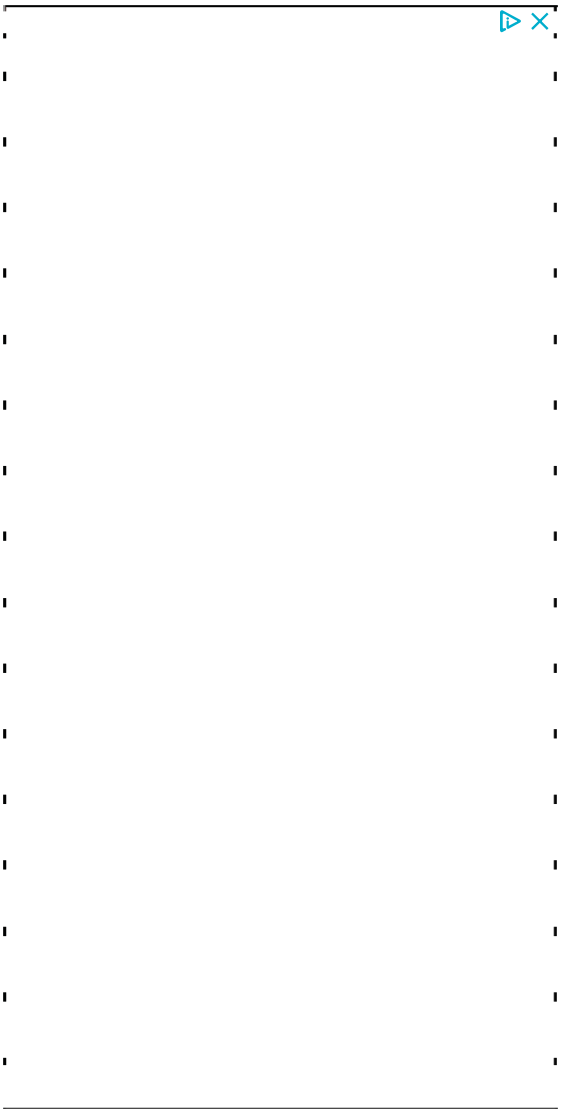

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EXHIBIT 63

THE NEW YORKER
ANNALS OF TECHNOLOGY

WHY IS NO ONE ON THE FIRST TREATMENT TO PREVENT H.I.V.?

By Christopher Glazek September 30, 2013

In November, 2010, the *New England Journal of Medicine* published the results of a three-year clinical trial, funded by the National Institutes of Health, announcing the arrival of a treatment that could reduce the risk of contracting H.I.V. by more than ninety per cent. The treatment involved a blue, oval pill containing emtricitabine and tenofovir. Marketed under the brand name Truvada, the pill was synthesized in 2004 by Gilead Sciences, the world's largest producer of branded H.I.V. drugs, and has been used in combination with other antiretrovirals as a primary treatment for people living with AIDS. The N.I.H. team discovered that a daily dose of Truvada not only suppressed the virus in people who were already infected but also prevented healthy people from contracting H.I.V. in the first place. Following the N.I.H. study, which tracked gay men in Peru, Ecuador, Brazil, South Africa, Thailand, and the United States, additional trials showed the drug to be effective for heterosexual men and women, as well as for injection-drug users. Researchers called the treatment "pre-exposure prophylaxis," or PrEP for short. Others have called it "the new condom."

On the day the N.I.H. announced the results of the PrEP study, the research team received a congratulatory phone call from President Obama. Shortly thereafter, *Time* put PrEP in the first slot on its list of the year's top medical innovations. Dr. Robert Grant, a professor at the University of California San Francisco and the N.I.H. study's lead scientist, braced for a stampede. He told me, "The evening before we announced, we had meetings with the leadership of public health in California, and they were thinking, as we were, that there

was going to be a rush, that everyone was going to descend on the clinics." The Centers for Disease Control issued interim usage guidelines, despite the fact that the treatment was more than a year away from formal F.D.A. approval. The C.D.C. knew that some doctors were already prescribing Truvada for prevention off-label, and it expected more to follow suit.

But, in fact, adoption of the drug has been slow. According to Dawn Smith, a biomedical interventions implementation officer in the C.D.C.'s epidemiology branch, at least half a million Americans are good candidates for PrEP—meaning that they are at high risk for contracting H.I.V. through sexual activity—yet only a few thousand Americans are receiving the treatment. "As in most fields, many clinicians don't want to be the first one out of the gate," Smith said. Salim Karim, the chair of United Nations' AIDS Scientific Expert Panel and the director of the Centre for the AIDS Programme of Research in South Africa, thinks that doctors' hesitance may not have anything to do with sexual health. "Clinicians fundamentally have difficulty giving healthy people drugs," he said. "This is not unique to H.I.V." Meanwhile, despite repeated demonstrations that Truvada provides protection from H.I.V., an estimated hundred and fifty thousand Americans, more than a third of whom are in their teens and twenties, have become infected with the virus since the results of the study were released.

The medical community's reluctance to prescribe Truvada—and patients' reluctance to request it—also stems from a bitter fight over the treatment. Critics have questioned PrEP's safety, efficacy, and cost, and have accused the government of colluding with the drug manufacturer at the expense of public health. Regan Hofmann, the former editor-in-chief of *Poz*, a magazine for people living with AIDS, called PrEP a "profit-driven sex toy for rich Westerners." Michael Weinstein, the head of the AIDS Healthcare Foundation (A.H.F.), the world's largest AIDS organization and the primary-care provider for more than two hundred thousand patients around the world, predicted a public-health catastrophe. "The applause for this approach shows just how disposable we consider the lives of gay men," he wrote. When I

interviewed Weinstein, he claimed the studies were "rigged" and that PrEP was essentially a plot by Gilead to force young people into buying unnecessary medication, and that it was going badly because A.H.F. wasn't letting the company get away with it.

These kinds of claims helped to shape perceptions of the drug among patients, doctors, and journalists. At an open F.D.A. hearing in May, 2012, busloads of A.H.F. employees showed up to make statements against PrEP, raising questions about the drug's side effects, its price tag, its potential to incite risky behavior, its failure to prevent other S.T.D.s, and the possibility that imperfect adherence to the pill's daily regimen would lead to the spread of a Truvada-resistant strain of H.I.V. Though data from the studies largely contradicts these criticisms, they were widely circulated. "I think the advocacy that A.H.F. did was very effective," Weinstein told me. "We were quoted in virtually every article that was written."

Gilead's efforts to promote Truvada for PrEP treatments have been somewhat meagre. "In any other kind of F.D.A. approval, there would have been beautiful ads, lots of TV, and lots of press touting the fact that this was the new thing to keep people protected from H.I.V.," said Ernest Hopkins, the director of legislative affairs for the San Francisco AIDS Foundation. "Gilead chose not to do that." According to Jim Rooney, Gilead's vice-president of medical affairs, the company "spends several million dollars" on educational initiatives related to PrEP, delivered through third-party groups, but it "does not view PrEP as a commercial opportunity." Truvada is already a blockbuster drug for Gilead; it earned the company more than three billion dollars in global sales in 2012. As Rooney notes, "The role of antiretrovirals in H.I.V. prevention is not yet defined and not yet broadly accepted." Although Gilead has donated drugs to researchers working on PrEP, it has not undertaken its own study. According to Jim Pickett, the director of prevention advocacy at the AIDS Foundation of Chicago, "Pharmaceutical companies had to be dragged into new prevention research. They weren't excited about it. They didn't want to do it."

PrEP's main problem is that many public-health officials believe people will see it as a substitute for condoms. *Out* magazine provoked a backlash when it printed a positive report on PrEP in early September, called "Is This the New Condom?" Commenters berated the author, Tim Murphy, and accused the magazine of irresponsibly promoting an unproven medicine at the expense of condoms.

Unfortunately, as Grant points out, when it comes to preventing H.I.V. the perceived efficacy of condoms "exceeds their public-health value." According to the C.D.C.'s Smith, condoms provide a high degree of protection when they're used consistently, but data shows that very few people use them consistently enough to derive a substantial benefit, and self-reported condom use falls precipitously when people are asked repeatedly if they're using condoms over an extended period of time. In the data analyzed by the C.D.C., the difference in protection levels for those who sometimes use condoms and those who never use them was not statistically significant.

The corresponding figures for PrEP are much better: while adherence is a concern, as it is with condoms, Truvada offers H.I.V. protection that is more effective than any other method short of abstinence. In the N.I.H. study, for example, 5.2 per cent of the placebo group "seroconverted," or became H.I.V. positive, compared with 2.9 per cent of the Truvada group. That's a forty-four-per-cent added protection over-all—better than inconsistent condom use. More impressively, patients who maintained a detectable amount of the drug in their system were protected at a rate of ninety-five per cent. (A later statistical analysis estimated that the drug would need to be taken four times a week to offer protection in that range.) Grant said that people in the study who took the drug four to seven days a week "were absolutely protected. We didn't have anyone seroconvert in our cohort in the United States."

Taking Truvada to prevent H.I.V. comes with very few risks. In the N.I.H. study, one in two hundred people had to temporarily go off the pill owing to kidney issues, but even those people were able to resume treatment after a couple of weeks. While bone-density loss occasionally occurs in Truvada takers who are already infected with the virus, no significant bone issues have

emerged in the PrEP studies. And though about one in ten PrEP takers suffer from nausea at the onset of treatment, it usually dissipates after a couple of weeks. According to the U.N. panel's Karim, Truvada's side-effects profile is "terrific," and Grant said that common daily medications like aspirin and birth control, as well as drugs to control blood pressure and cholesterol, are all arguably more toxic than Truvada.

Perhaps more important, drug resistance has not been observed in people who were H.I.V.-negative when they began treatment. "We're not seeing people getting infected who are actually taking the drug," said Grant. "There are people who take the drug home with them and choose not to take it; they get infected, but you're not going to get drug resistance from something that stays in a drawer." Some patients who entered the trials turned out to already have an H.I.V. infection that was too recent to be caught by a blood test. These subjects showed a small amount of drug resistance, which is why the F.D.A. now requires doctors to conduct an H.I.V. test before putting their patients on PrEP. The larger resistance threat, though, comes from the ten million H.I.V.-positive people around the world who take antiretrovirals for treatment, including, in some cases, Truvada. "The best way to prevent drug resistance is to prevent H.I.V. infection entirely," said Grant. "We know that when we prevent a case of H.I.V., we're preventing a lifelong risk of drug resistance."

Whether using PrEP will cause patients to abandon condoms and increase their number of sexual partners isn't known. Grant insists that the evidence does not support such a conclusion: "Everyone said that if we offer pre-exposure prophylaxis to people, even in a randomized trial, like we did, it's just going to cause them to have more sexual partners and stop using condoms. We found the opposite: that people had fewer sexual partners and used condoms more." Then again, participants in the major PrEP studies received free condoms and regular sexual-health counselling. They also may not have been telling the truth about their sexual practices. Ken Mayer, a professor of medicine at Harvard Medical School and Director of H.I.V. Prevention

Research at Beth Israel Deaconess Medical Center, believes that some migration away from condoms and toward Truvada is inevitable, but that it wouldn't necessarily be a bad trade-off, given PrEP's efficacy and the fact that many of the people likely to go on the treatment don't use condoms anyway. This squares with my own conversations with people on PrEP: most of them are seeking PrEP not because they wish to abandon condoms but because they already don't use them. The C.D.C.'s usage guidelines stress that PrEP is something to be taken in addition to using condoms, since PrEP doesn't protect against other sexually transmitted diseases.

Cost, at least in the United States, has also turned out to be a smaller concern than initially predicted. Smith said, "We were very surprised to find out the insurance companies said, 'Yes, we'll pay for it. It's much more expensive to treat people who have H.I.V. infections.' " While a lot of people at high risk for contracting H.I.V. currently lack health insurance, after January 1st many of them will be able to get coverage through Obamacare. And for those who still don't have insurance or who have unmanageable co-pays, Gilead provides assistance to purchase the drug, which has a sticker price of thirteen thousand dollars a year.

In the developing world, however, where even delivering cheap generic versions of Truvada can be a challenge, it remains unclear whether diverting resources to prevention on a wide scale makes sense. Mitchell Warren, the executive director of the AIDS Vaccine Advocacy Coalition, points out, however, that the same argument was once made against using antiretrovirals for treatment. "Ten years ago, people said you couldn't provide treatment in Africa: people wouldn't adhere, it was too expensive, it would create resistance," he said. "Many of those issues have been addressed—they haven't all been overcome—and now we have ten million people on treatment." Making PrEP available, particularly to protect young women in sub-Saharan Africa, said Karim, "is essential to achieving an AIDS-free generation."

Because H.I.V.-positive people who go on antiretrovirals have a drastically reduced risk of transmission, AIDS is spreading more slowly than it used to. Weinstein, of the A.H.F., was among the first to attempt to bring antiretrovirals to Africa. He pointed out that there are ten million people around the world on antiretrovirals today, mostly thanks to George W. Bush's global AIDS initiative. "If we can double that to twenty million," he said, "I think we will have brought H.I.V. under control." Truvada for prevention, one might conclude, is an expansion of that concept.

One of the problems is that PrEP lacks a built-in constituency to advocate for it. "ACT UP is focussed on people already living with AIDS," said Mayer. And while the opponents of PrEP have been loud and persistent, its supporters tend to be stately and circumspect. Many of the arguments made against Truvada, they note, are the same arguments that proponents of abstinence lodged against birth control in the sixties and against condoms in the eighties. "It takes a long time when it's a medical intervention that has to do with sexual practices," said Grant. Gilead predicts that it will take five to ten years for PrEP to become widely used in the U.S., by which time Truvada could be off-patent.

When I corresponded again with Pickett, of the AIDS Foundation of Chicago, after the publication of the *Out* article and the ensuing backlash, he appeared to disavow some of his enthusiasm regarding PrEP. What opponents needed to understand, he said, was that "no one was really envisioning widespread use of Truvada as PrEP. It really is a niche intervention—which should be targeted and used very strategically. No one wants to hand this out to everyone in a key population." When pressed, he clarified that he thought Truvada was for anyone in a high-risk group who struggled with monogamy or consistent use of condoms, a delineation that would seem to include millions of people in the United States alone.

While skepticism about PrEP will undoubtedly recede over time, for the moment it remains strong. I was recently speaking with a twenty-six-year-old

urban planner living in Brooklyn, who overheard me talking about PrEP. "Oh yeah," he said, with a worried look. "I've heard of that. I saw that piece in *Out*. It said it doesn't work, right?"

Photograph by Jb Reed/Bloomberg/Getty

Christopher Glazek, a freelance magazine writer, is the founder of the Yale AIDS Memorial Project. *Read more »*

EXHIBIT 64

STEPS
New Drug Reviews

Emtricitabine/Tenofovir (Truvada) for HIV Prophylaxis

BARRY COUTINHO, MBBS, and RAMAKRISHNA PRASAD, MD, MPH, *University of Pittsburgh Medical Center Shadyside Family Medicine Residency Program, Pittsburgh, Pennsylvania*

STEPS new drug reviews cover Safety, Tolerability, Effectiveness, Price, and Simplicity. Each independent review is provided by authors who have no financial association with the drug manufacturer.

The series coordinator for *AFP* is Allen F. Shaughnessy, PharmD, Tufts University Family Medicine Residency Program at Cambridge Health Alliance, Malden, Mass.

A collection of STEPS published in *AFP* is available at http://www.aafp.org/afp/steps.

Emtricitabine/tenofovir (Truvada) is a fixed-dose combination of emtricitabine (200 mg) and tenofovir (300 mg) that was initially approved to treat human immunodeficiency virus, type 1 (HIV-1) infection. It is now labeled for use as preexposure prophylaxis to prevent HIV-1 infection in high-risk patients.[1]

Drug	*Dosage*	*Dose form*	*Cost**
Emtricitabine/tenofovir (Truvada)	One tablet daily	Tablet containing emtricitabine (200 mg) and tenofovir (300 mg)	$1,258

**—Estimated retail price of one month's treatment based on information obtained at http://www.lowestmed.com (accessed June 27, 2013).*

SAFETY

Few severe adverse effects were associated with the use of emtricitabine/tenofovir in studies of preexposure prophylaxis.[2-4] The drug must not be prescribed if the patient's creatinine clearance is less than 60 mL per minute per 1.73 m^2 (1.00 mL per second per m^2) because its use has been associated with renal failure and Fanconi syndrome.[5] Although rare and not reported in premarketing studies, lactic acidosis and severe hepatomegaly with steatosis are possible in patients at risk of liver disease, according to the drug's manufacturer.[5] Because both emtricitabine and tenofovir are active against hepatitis B virus, and because of the risk of rebound hepatitis following discontinuation of therapy, this combination should be used with caution in patients coinfected with hepatitis B virus.[5] No major drug-drug interactions have been reported with commonly prescribed medications. However, the manufacturer recommends caution with coadministration of potentially nephrotoxic medications. Emtricitabine/tenofovir is a U.S. Food and Drug Administration pregnancy category B drug, and should not be given to mothers who are breastfeeding.[5] The use of emtricitabine/tenofovir as preexposure prophylaxis is not known to increase high-risk behaviors.[6]

TOLERABILITY

Emtricitabine/tenofovir is generally well tolerated. When it is used for preexposure prophylaxis in persons without HIV infection, headache, nausea, vomiting, abdominal pain, and weight loss may occur infrequently.[2-4] Nausea and vomiting affect about one in six patients at the start of treatment, but these effects often subside within the first month.[3]

EFFECTIVENESS

Based on studies conducted primarily outside the United States,[2-5] emtricitabine/tenofovir has been shown to reduce the risk of acquiring HIV infection in several subgroups of patients when used daily in combination with a comprehensive HIV prevention strategy, including safer sex practices.[2-4] Among high-risk men who have sex with men, emtricitabine/tenofovir reduced the absolute risk of acquiring HIV infection from 5.3% to 2.9% (number needed to treat [NNT] = 43 over a median 12 months of treatment; 95% confidence interval [CI], 25 to 134).[3] Among heterosexual men and women in high-prevalence regions of Botswana, it reduced ▶

the absolute risk of infection from 4.3% to 1.6% (NNT = 38; 95% CI, 21 to 135; median follow-up = 1.1 years).[2] Among heterosexual couples in Kenya in which one partner was HIV positive and the other was HIV negative, the risk decreased from 3.3% to 1.1% (NNT = 44; 95% CI, 29 to 85; median follow-up = 1.9 years).[4] Effectiveness depends on adherence to daily administration.[1,3]

Emtricitabine/tenofovir will not prevent other sexually transmitted diseases.

PRICE

A one-month supply of emtricitabine/tenofovir for preexposure prophylaxis costs approximately $1,258.[7] Only some insurance plans currently provide coverage for use of emtricitabine/tenofovir as preexposure prophylaxis.

SIMPLICITY

Although emtricitabine/tenofovir requires only a single daily dose, strict adherence is essential. It may be taken without regard to mealtimes. Because of the risk of developing drug resistance, all patients must be confirmed HIV negative before initiation of treatment. In persons with signs or symptoms of acute HIV-1 infection or those reporting potential exposure to HIV within the previous month, HIV infection should be ruled out by repeat testing before starting prophylaxis. Once a patient begins taking the medication, repeat screening for HIV infection, risk-behavior assessment, and counseling must occur every two to three months, and adherence must be assessed at every visit with a physician. Screening for sexually transmitted infections should be performed at least every six months. Renal function must be checked three months after initiation of therapy, and at least annually thereafter.[1]

Bottom Line

When used with a comprehensive HIV prevention strategy, emtricitabine/tenofovir effectively prevents HIV-1 infection in high-risk patients. Adherence to daily dosing is important to maintain protection. The cost of therapy may limit access, and not all insurance companies currently cover its use for HIV prophylaxis.

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EXHIBIT 65

POLICY BRIEF

PRE-EXPOSURE PROPHYLAXIS (PrEP)

WHO EXPANDS RECOMMENDATION ON ORAL PRE-EXPOSURE PROPHYLAXIS OF HIV INFECTION (PrEP)

NOVEMBER 2015

World Health Organization

What is PrEP?

Oral pre-exposure prophylaxis of HIV infection – PrEP – is the use of antiretroviral (ARV) drugs by people who do not have HIV infection in order to prevent the acquisition of HIV.

What does WHO recommend?

The World Health Organization (WHO) now recommends that people at substantial risk of HIV should be offered PrEP.

In 2014 WHO recommended offering PrEP to men who have sex with men (MSM). On the basis of further evidence of the effectiveness and acceptability of PrEP, WHO has now broadened the recommendation to include all population groups at substantial risk of HIV infection. Offering PrEP should be a priority for populations with an HIV incidence of about 3 per 100 person-years or higher. PrEP should be an additional prevention choice in a comprehensive package of services that also includes HIV testing, counselling, male and female condoms, lubricants, ARV treatment for partners with HIV infection, voluntary medical male circumcision and harm reduction interventions for people who use drugs.

New recommendation

Oral PrEP containing tenofovir disoproxil fumarate (TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches.

STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE

Key evidence

High-quality evidence strongly supports use of PrEP by any person at substantial risk of acquiring HIV infection.

- Twelve trials of the effectiveness of oral PrEP have been conducted among serodiscordant couples, heterosexual men, women, MSM, people who inject drugs and transgender women. These trials took place in Africa, Asia, Europe, South America and the United States.
- PrEP works, when taken. A systematic review and meta-analysis of trials using TDF finds that PrEP is effective. The level of protection did not differ by age, gender, ARV regimen (TDF versus emtricitabine (FTC) + TDF) or mode of acquiring HIV (rectal or penile/vaginal). The level of protection was strongly correlated with adherence.
- PrEP has an excellent safety profile. Across 10 randomized controlled trials, rates of any adverse event did not differ between PrEP and a placebo.
- Risk of drug resistance is low, occurring in approximately 1 in 1000 PrEP users in clinical trials. Drug resistance occurred almost exclusively among people who already had acute undetected HIV infection when they started PrEP. Therefore, testing for HIV before people start PrEP is essential to avoid drug resistance. Moreover, offering PrEP reduces the number of new HIV infections, each of which would require lifelong therapy, with substantial ongoing risk of drug resistance. Thus, PrEP is expected to decrease the public health burden of HIV drug resistance.
- No evidence for risk compensation in sexual practices, such as decreased condom use or more sexual partners, has emerged in any PrEP studies or programmes.
- PrEP can be used with hormonal contraception. Recommended PrEP regimens do not appear to alter the effectiveness of hormonal contraception.
- PrEP can be used during pregnancy. No increase occurred in adverse pregnancy-related events among women taking PrEP in early pregnancy. This is important because both mother and infant are more vulnerable to HIV acquisition during pregnancy and breastfeeding.
- PrEP is acceptable. Various populations report that they find PrEP acceptable, and individuals have shown substantial interest in PrEP as an additional choice for HIV prevention.

WHO/HIV/2015.48

#OfferPrEP

- Adherence can be maintained. Demonstration projects and experience in every-day settings are proving that people can adhere to daily oral PrEP.

Will PrEP be cost-effective?

Offering PrEP is expected to be cost-effective where the incidence of HIV is greater than 3 per 100 person-years and perhaps also at lower incidence. Incidence as high as 3 per 100 person-years remains common among young women in some settings in southern Africa, among some sex workers in Africa and among MSM in many countries. Drug costs of PrEP are lower than treatment drug costs, both per-dose and for the duration of use, which is as-needed for PrEP but lifelong for treatment.

Considerations for PrEP implementation

PrEP should not displace or compete with effective and well-established HIV prevention interventions, such as comprehensive condom programming for sex workers and MSM and harm reduction for people who inject drugs. Many people who could benefit most from PrEP belong to key population groups that may face legal and social barriers to accessing health services. This needs to be considered when developing PrEP services. The decision to use PrEP should always be made by the individual.

Where will PrEP offer the most benefit?

Countries with high HIV incidence in certain geographical areas or specific populations may consider introducing PrEP as an additional prevention option. In these high incidence populations, programmes can use simple screening questions to identify, and then offer PrEP to, people who would benefit most from PrEP. Implementation in low- and middle-income settings has been limited to date, but increasing experience in demonstration projects can guide wider implementation. WHO is developing PrEP implementation guidance that will be published in 2016.

Key elements of PrEP services

- Offer PrEP as part of combination HIV prevention approaches. Continued advocacy for and investment in effective combination HIV prevention services is essential.
- Involve communities and support an enabling environment. The full participation of communities is critical to developing and implementing services. In many places community-based organizations have taken the lead in limiting the spread of HIV infection. Countries should support these organizations to lead PrEP implementation and to provide accurate information about PrEP.
- Provide training. Health-care providers should be trained and supported to provide culturally appropriate PrEP services to persons at substantial risk for HIV, especially young women and people from key populations.
- Ensure HIV testing. HIV testing is required before starting PrEP and regularly while taking PrEP. Using quality-assured HIV testing is important, and referral of people who test positive to HIV treatment and prevention services is essential.
- Monitor renal function. Given the use of TDF-based PrEP regimens creatinine testing is desirable before starting PrEP and quarterly during PrEP use for the first 12 months, then annually thereafter.
- Test for hepatitis B infection. Hepatitis B (HBV) is endemic in much of the world where HIV prevalence is highest. Testing PrEP users for HBV surface antigen is desirable, with HBV vaccination for those who are uninfected. WHO recommends TDF or entecavir for treatment of liver disease due to HBV. If PrEP is stopped in such people, continuing an alternative therapy for HBV should be considered.
- Encourage adherence for effectiveness. Demonstration projects have shown that most people can use daily oral PrEP effectively. Effective PrEP use is different from adherence to HIV treatment in that PrEP can be started and stopped as a person moves through "seasons of risk", whereas treatment is lifelong. Ways to increase PrEP adherence include informing people that PrEP is highly effective when taken and that PrEP is safe; the great majority of PrEP users have no side-effects. Support groups, including those using social media, may help with adherence by enabling PrEP users to share experience and challenges.

For more information, contact:

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1211 Geneva 27
Switzerland

E-mail: hiv-aids@who.int
www.who.int/hiv

POLICY BRIEF

WHO EXPANDS ITS RECOMMENDATION ON THE USE OF ORAL PrEP

EXHIBIT 66

Mapping PrEP: First Ever Data on PrEP Users Across the U.S.

New Maps Show More Than 77,000 People Prescribed HIV Prevention Medicine in 2016

AIDSVu has released the first-ever interactive state-level maps visualizing a 73 percent increase year over year in persons using PrEP across the U.S. from 2012 to 2016, with 77,120 PrEP users in 2016. PrEP, or pre-exposure prophylaxis, is when people at high risk for HIV take HIV medicine daily to lower their chances of getting infected with HIV. AIDSVu's maps visualize the growth in PrEP use at the state-level by year and break down the data by age and sex. These data and maps offer important information and tools to public health officials, policymakers, and researchers to inform efforts to improve PrEP awareness and increase uptake where it is needed most.

Mapping PrEP

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The Centers for Disease Control and Prevention (CDC) has estimated that approximately 1.2 million people are at high-risk for HIV exposure and could benefit from comprehensive HIV prevention strategies, including PrEP. Data presented on AIDSVu reveal that the growth and distribution of PrEP use has been inconsistent across different sexes, age groups, and geographic regions. For example, the Southern U.S. accounted for more than half (52 percent) of all new HIV diagnoses in 2016 but represented only

30 percent of all PrEP users in 2016. That same year, women comprised 19 percent of all new HIV diagnoses but made up only seven percent of all PrEP users.

"PrEP is a revolution in HIV prevention and has the potential to dramatically reduce new HIV infections; however, significant disparities in the use of PrEP exist across the country," said Patrick Sullivan, Ph.D., Professor of Epidemiology at Emory University's Rollins School of Public Health and Principal Scientist for AIDSVu. "Expanding access to PrEP is a core component of Getting to Zero campaigns in cities and states across the country and is one of four key focus areas in the National HIV/AIDS Strategy. We hope that the newly available data on AIDSVu will allow health departments, elected officials, medical professionals, and community leaders to better understand and visualize the realities of who has access to this important prevention tool so they can develop programs and policies to decrease barriers."

The AIDSVu maps illustrate the following key trends:

The number of PrEP users has increased by 880 percent since 2012, an average 73 percent increase year over year from 2012 to 2016.

In 2016, there were 77,120 PrEP users in the U.S., up from 8,768 PrEP users in 2012.

Men and 25- to 44-year olds were more likely to be PrEP users.

93 percent of all PrEP users in 2016 were male, which is about 14 times higher than the number of female PrEP users. Men accounted for 81 percent of all new HIV diagnoses in 2016.

In 2016, 64 percent of all PrEP users were 25- to 44-years old. This age group represented more than half (54 percent) of all new HIV diagnoses during the same period.

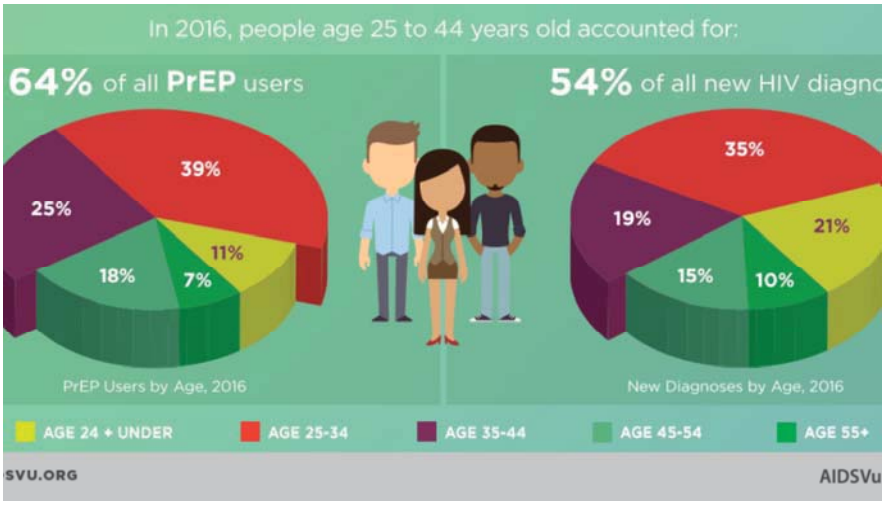
Nearly 50% of PrEP users in 2016 were located in just five states: New York, California, Florida, Texas, and Illinois.

When looking at the rate of PrEP use—the number of people in a state using PrEP per 100,000 population—the five states with the highest rates in 2016 were New York, Massachusetts, Rhode Island, Washington, and Illinois.

In 2016, the Northeast region of the U.S. had approximately twice the rate of PrEP use (47.4 PrEP users per 100,000 population) compared to the West (28.1 PrEP users per 100,000 population), the South (22.6 PrEP users per 100,000 population), and the Midwest (23.5 PrEP users per 100,000 population) regions.

The South is the region with the highest number of new HIV diagnoses in the U.S. but has disproportionately fewer people using PrEP.

The Southern U.S. accounted for only 30 percent (23,091 persons) of all PrEP users in 2016. The region represented more than half (52 percent) of all new HIV diagnoses in 2016.



Who uses PrEP?

Get the facts about using PrEP. Learn more on our Deeper Look: PrEP.

SHARE

Data on PrEP users displayed on AIDSVu represent the number of unique persons who had at least one day in a calendar year of prescribed tenofovir [TDF]/emtricitabine [FTC] (TDF/FTC) for PrEP. TDF/FTC is the only medicine currently approved by the U.S. Food and Drug Administration (FDA) for PrEP use. De-identified, aggregate data were obtained from Source Healthcare Analytics, LLC (SHA) with the support of Gilead Sciences, Inc., and compiled by researchers at the Rollins School of Public Health at Emory University. SHA collects data from over 54,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices across the U.S. SHA's dataset contains prescription, medical, and hospital claims data for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. From this overall sample, AIDSVu presents a subset of data comprising prescriptions for TDF/FTC for PrEP.

There is currently no single data source that includes data on all unique users of PrEP across the U.S. SHA's dataset is an open sample of commercially available data, which excludes entities that do not make their data available, such as closed healthcare systems. As a result, the data displayed on AIDSVu underestimates the total number of PrEP users in the U.S. Other publicly shared data on PrEP utilization have used estimates from multiple data sources to project for the total number of unique persons using TDF/FTC for PrEP in the U.S. at a given point in time. This method, however, does not provide state-level estimates.

Now in its eighth year, AIDSVu continues to advance its mission to make HIV data widely available, easily accessible and locally relevant to inform public health decision making. State-level PrEP data on AIDSVu can be viewed alongside social determinants of health and other HIV data, such as new diagnoses, prevalence, and mortality. Additionally, AIDSVu provides downloadable PrEP datasets at the state- and ZIP3-level for researchers and health departments to utilize in their own analyses. ZIP3 refers to the three digit ZIP code prefix assigned by the U.S. Postal Service. AIDSVu is also an inaugural user of the PrEP Locator, a national directory of providers of PrEP in the U.S. developed by Emory University's Rollins School of Public Health with support from M•A•C AIDS Fund.

About AIDSVu
AIDSVu was developed by Emory University's Rollins School of Public Health in partnership with Gilead Sciences, Inc. The project is guided by an Advisory Committee, a Prevention and Treatment Advisory Committee, and a Technical Advisory Group with representatives from federal agencies, state health departments, and non-governmental organizations working in HIV prevention, care, and research.

About the Rollins School of Public Health
The Rollins School of Public Health is part of Emory University in Atlanta, Georgia. The school houses six academic departments, 20 multidisciplinary centers – including an NIH-supported Center for AIDS Research – and more than 160 full-time doctoral-level faculty members.

Learn From Experts

Read our series of AIDSVu Q&A's with leading PrEP experts to learn more.

Vu Q&A: Dr. Charlene Flash on Gender Disparities in PrEP Use

EXHIBIT 67

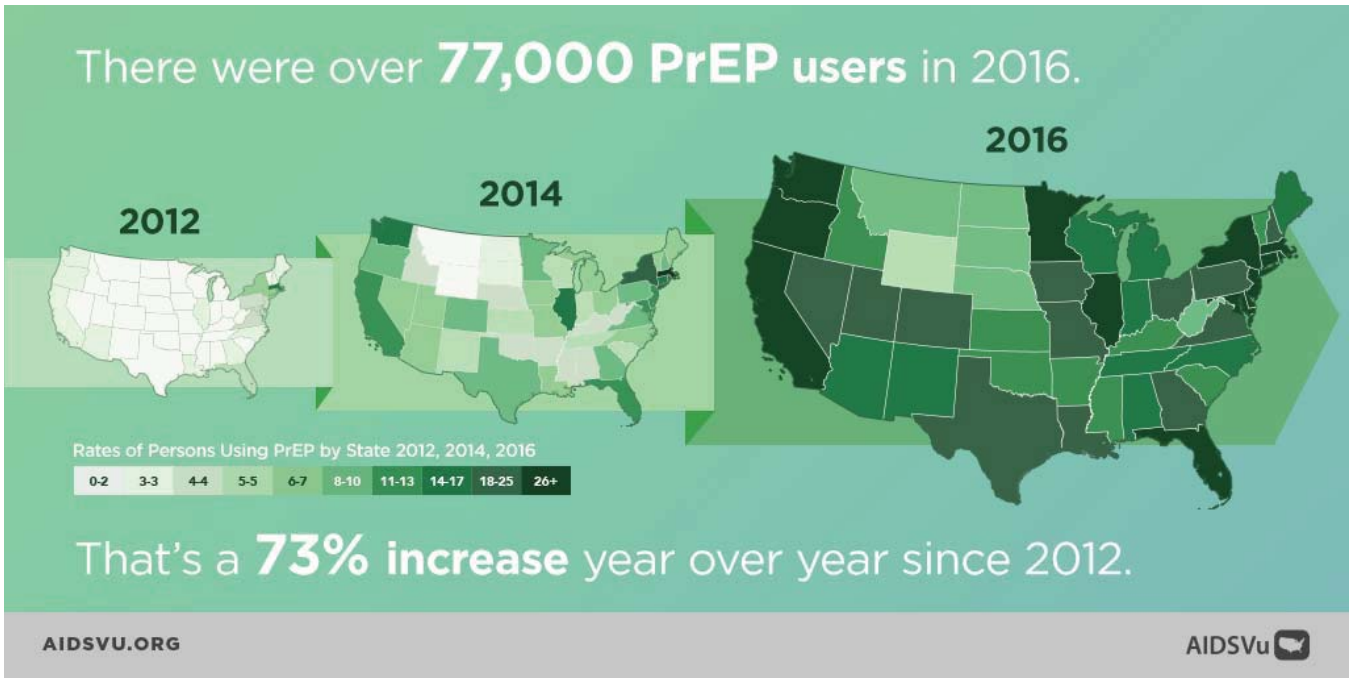

There were over 77,000 PrEP users in 2016.
2012
2014
2016
Rates of Persons Using PrEP by State 2012, 2014, 2016
0-2
3-3
4-4
5-5
6-7
8-10
11-13
14-17
18-25
26+
That's a 73% increase year over year since 2012.
AIDSVU.ORG
AIDSVu

EXHIBIT 68

Shots

HEALTH INC.

Rising Cost Of PrEP To Prevent HIV Infection Pushes It Out Of Reach For Many

June 30, 2018 · 6:00 AM ET

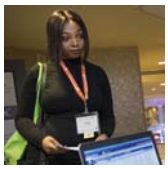
SHEFALI LUTHRA ANNA GORMAN

FROM KHN

Gilead Sciences makes Truvada, a medicine known generically as "pre-exposure prophylaxis," or PrEP. Consistent, daily doses of the drug are thought to reduce the risk of getting HIV from sex by more than 90 percent.
Paul Sakuma/AP

Public health officials are expanding efforts to get the HIV prevention pill into the hands of those at risk, in a nationwide effort to curb infections. But the officials are hitting roadblocks — the drug's price tag, which has surged in recent years, and changes in insurance coverage that put a heftier financial burden on patients.

Since brand-name Truvada was approved for HIV prevention six years ago, its average wholesale price has increased by about 45 percent. Now, the drug — which rakes in billions of dollars in annual global revenue for its manufacturer, Gilead Sciences — carries a list price of close to $2,000 for a 30-day supply.



SHOTS - HEALTH NEWS

PrEP Campaign Aims To Block HIV Infection And Save Lives In D.C.

Most insurers cover treatment with the pill, also known as pre-exposure prophylaxis, or PrEP. It has been shown to be more than 90 percent effective in HIV prevention when the medicine is taken daily, according to the Centers for Disease Control and Prevention.

But patients can get stuck with out-of-pocket costs that make the medicine unaffordable.

"If there is any example of the dysfunction in the American pharmaceutical system, it is this case," says James Krellenstein, a member of the AIDS advocacy group ACT UP New York. "We have the most effective tool for ending the HIV epidemic, and one reason we're unable to scale up is because it costs so [much] unnecessarily."

As policymakers and the health system debate how to control ever-climbing drug prices, experts say this case underscores how patients are left holding the bag.

Private health plans are making patients responsible for a larger share of drug costs. And more are restricting use of the copay coupons pharmaceutical companies have used to shield patients from out-of-pocket expenses. Insurers say the drug companies use coupons to steer consumers toward pricier meds. One way health plans are limiting their use is by no longer allowing them to count toward patients' deductibles.

SHOTS - HEALTH NEWS

If Drug Copays Have You Down, Check For A Coupon

"This is one more thing that is going to push people off their medications," says Jim Pickett, a senior director at the AIDS Foundation of Chicago.

Jared Wile, who lives in Chicago, started PrEP about three years ago, when he was dating someone with HIV. Wile, who has a $2,750 deductible, used a coupon to obtain the drug. He never paid anything out-of-pocket, he says.

Gilead waives up to $4,800 in out-of-pocket expenses for commercially insured patients.

That changed for Wile this past May, when he learned the coupon no longer counted toward his deductible and that he would have to pay the full cost of the prescription — $1,600 per month — until he hit his deductible. Wile says he felt "blindsided" and stopped taking the medication.

Gilead spokesman Ryan McKeel says the company has made extra efforts to help patients overcome financial barriers. He cites assistance programs for uninsured and underinsured people.

"We have designed our assistance programs with the intent that people can benefit from their full value, and we cannot control the actions or decisions of health insurers," McKeel said via email.

The federal Centers for Disease Control and Prevention estimates that more than 1 million people are at high risk of contracting HIV, but Gilead says only about 167,000 people currently are receiving PrEP.

Beyond the money crunch

Price is one of many barriers — alongside patients' lack of awareness and doctors' hesitation to prescribe — that threaten to exacerbate the already stark disparities in PrEP use and HIV infection rates.

One major disparity is along geographic lines. The South, for example, accounts for over half of new HIV diagnoses but only about 30 percent of new PrEP users, according to data from AIDSVu, which maps HIV disease and PrEP use. HIV rates and PrEP use also vary by race and ethnicity.

"We are not necessarily seeing that those most at risk are the ones starting PrEP," says Kristin Keglovitz Baker, chief operating officer of Howard Brown Health, a Chicago health center.

Gilead has recently gone all-in with advertising to reach people at risk, including print campaigns and TV ads that will air through the summer. Since 2012, it has spent $28 million to fund U.S. organizations that seek to raise awareness of HIV, says McKeel, the company spokesman.

"We recognize that many people who are at high risk for HIV infection still face challenges in accessing Truvada for PrEP, and we are in regular dialogue with public health officials, advocates and physicians to better understand and, where possible, help to address these challenges," he added.

But price is also an impediment for publicly funded programs, which have limited budgets and are now shelling out more cash for the prevention effort.

"If it was only pennies ... we would be throwing it around," says Joey Mattingly, an assistant professor at the University of Maryland School of Pharmacy. "Because of how costly it is, we have to control it."

Some states — California and Florida among them — have launched PrEP assistance programs that can help patients cover the cost of the medication, along with required lab work and medical visits.

Beyond these state-based programs, some public health departments and HIV service organizations are hiring PrEP navigators to help patients traverse the maze of copays and deductibles, and to improve recruitment and retention of new PrEP users.

Washington, D.C.'s health department has doubled down on prevention, and Truvada is key in that effort, says Michael Kharfen, the department's senior deputy director for HIV/AIDS, Hepatitis, STD and TB Administration.

Insurance usually covers PrEP, and patient assistance programs should fill any financial gaps, he says. But when that isn't feasible, the department steps in, distributing free Truvada starter packs to at-risk patients.

Kharfen says the city has in the past three years spent almost a million dollars just on Truvada pills, which it purchases at a discounted rate through the federal 340B program, which benefits certain health care providers that treat low-income people. And because of new publicity efforts, he expects the department will need to buy and distribute more pills — posing a conundrum.

Treating more people is net positive, he says. But "how do we sustain this?"

Medicaid programs generally cover PrEP, so they confront a similar situation. Outreach efforts lead to more beneficiaries who take the drug, but that, in turn, could subject the states' Medicaid budgets to financial hardship.

States are spending millions of dollars on the drug. California's Medicaid program, for example, spent about $50 million in 2017 and expects the costs to continue climbing. But officials said the expense is offset by long-term savings in preventing new HIV cases.

Massachusetts' Medicaid program spent about $22 million on Truvada that same year — about $18,000 per beneficiary, according to a spokeswoman for the agency's Executive Office of Health and Human Services. Those figures don't account for rebates the state receives from Gilead, which are undisclosed and considered proprietary information.

A complex solution and no competition

PrEP is only one part of HIV prevention, so help paying for the pill is only one piece of the puzzle.

Patients also need regular HIV testing and medical care, which add to the cost borne both by patients and the health system. Some experts warn that Truvada's high price point could financially undermine such broad prevention efforts.

Competition could help.

SHOTS - HEALTH NEWS

'Here It Goes': Coming Out To Your Doctor In Rural America

A generic version of the drug, manufactured by Teva Pharmaceuticals, is available abroad and gained approval for use last year from the federal Food and Drug Administration. When it becomes available in the United States, it could bring down prices, though it's unclear when that will happen. Gilead's own forecasts reflect that expectation, showing declines in future revenue from Truvada.

"When generics enter, brands lose market share," says David Howard, a health economist and professor at Emory University, who previously worked in the pharmaceutical industry.

For now, though, Truvada is the only PrEP option available in the U.S., he says. "From a company standpoint ... their best strategy is to make as much money as they can."

Kaiser Health News, a nonprofit news service covering health issues, is an editorially independent program of the Kaiser Family Foundation that is not affiliated with Kaiser Permanente. KHN's coverage of prescription drug development, costs and pricing is supported in part by the Laura and John Arnold Foundation.

hiv aids hiv prevention truvada prescription drugs

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EXHIBIT 69

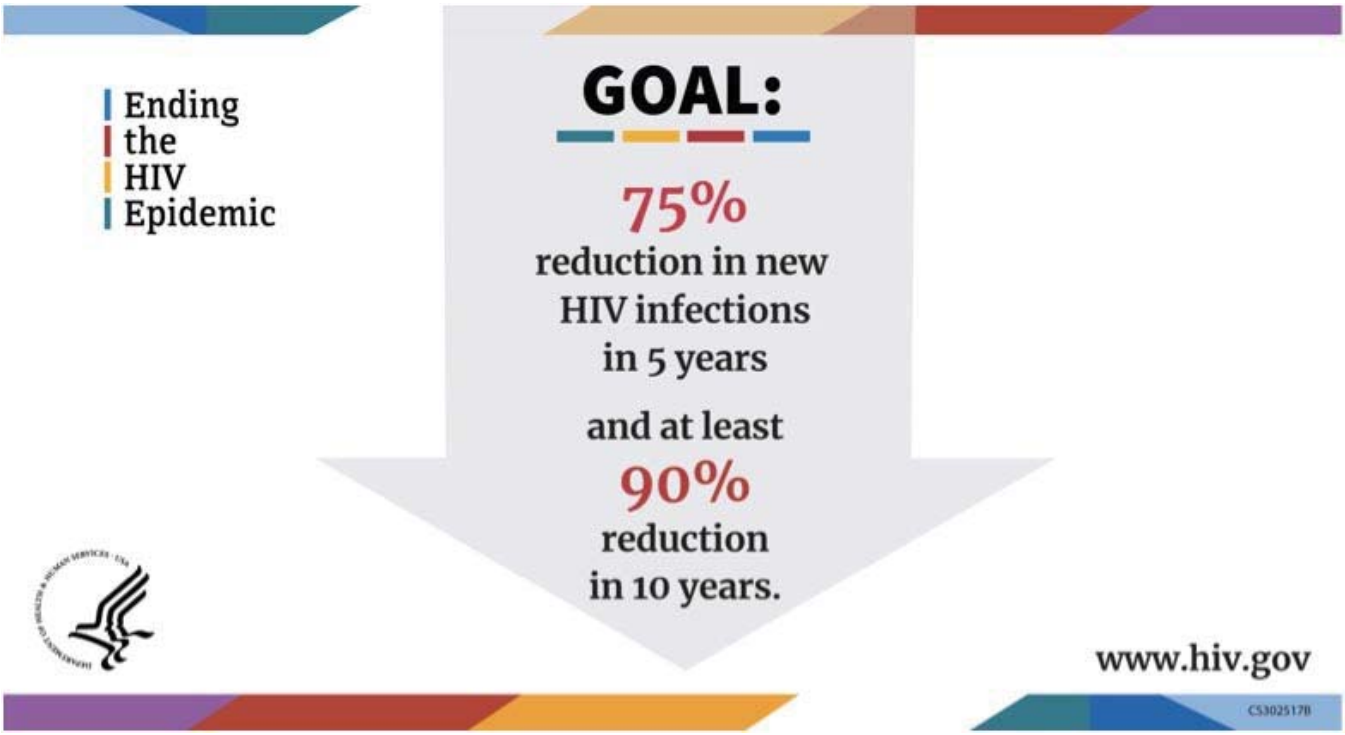
What is ‘Ending the HIV Epidemic: A Plan for America’?

Topics

Ending HIV

> **We have a once-in-a-generation opportunity to end the HIV epidemic in the United States. Now is the time.**

In the State of the Union Address on February 5, 2019, President Donald J. Trump announced his Administration’s goal to end the HIV epidemic in the United States within 10 years. To achieve this goal and address the ongoing public health crisis of HIV, the proposed *Ending the HIV Epidemic: A Plan for America* will leverage the powerful data and tools now available to reduce new HIV infections in the United States by 75 percent in five years and by 90 percent by 2030.



Background

HIV has cost America too much for too long and remains a significant public health issue:

- More than 700,000 American lives have been lost to HIV since 1981.
- More than 1.1 million Americans are currently living with HIV and many more are at risk of HIV infection.
- While new HIV diagnoses have declined significantly from their peak, progress on further reducing them has stalled with an estimated 40,000 Americans being newly diagnosed each year. Without intervention another 400,000 Americans will be newly diagnosed over 10 years despite the available tools to prevent infections.
- The U.S. government spends $20 billion in annual direct health expenditures for HIV prevention and care.
- There is a real risk of an HIV resurgence due to several factors, including injection drug use and diagnostic complacency among healthcare providers.

Goal

The new initiative seeks to reduce the number of new HIV infections in the United States by 75 percent within five years, and then by at least 90 percent within 10 years, for an estimated 250,000 total HIV infections averted.

"Today we have the
Right Data, Right Tools, and Right Leadership
to end the HIV epidemic."

Right Data & Right Tools

Today we have the tools available to end the HIV epidemic. Landmark biomedical and scientific research advances have led to the development of many successful HIV treatment regimens, prevention strategies, and improved care for persons living with HIV.

- **Data** tell us that most new infections occur in a limited number of counties and among specific populations.
- Thanks to advances in **antiretroviral therapy**, the medicine used to treat HIV, individuals with HIV who take their medicine as prescribed and, as a result, maintain an undetectable viral load can live long, healthy lives and have effectively no risk of sexually transmitting HIV to a partner.
- We have **proven models of effective HIV care and prevention** based on over two decades of experience engaging and retaining patients in effective care.
- **Pre-exposure prophylaxis (PrEP)**, a daily regimen of two oral antiretroviral drugs in a single pill, has proven to be highly effective in preventing HIV infection for individuals at high risk, reducing the risk of acquiring HIV by up to 97 percent.
- **New laboratory and epidemiological techniques** allow us to pinpoint where HIV infections are spreading most rapidly so health officials can respond swiftly with resources to stop the further spread of new infections.

With these powerful data and tools, the Administration sees a once-in-a-generation opportunity to end the epidemic.

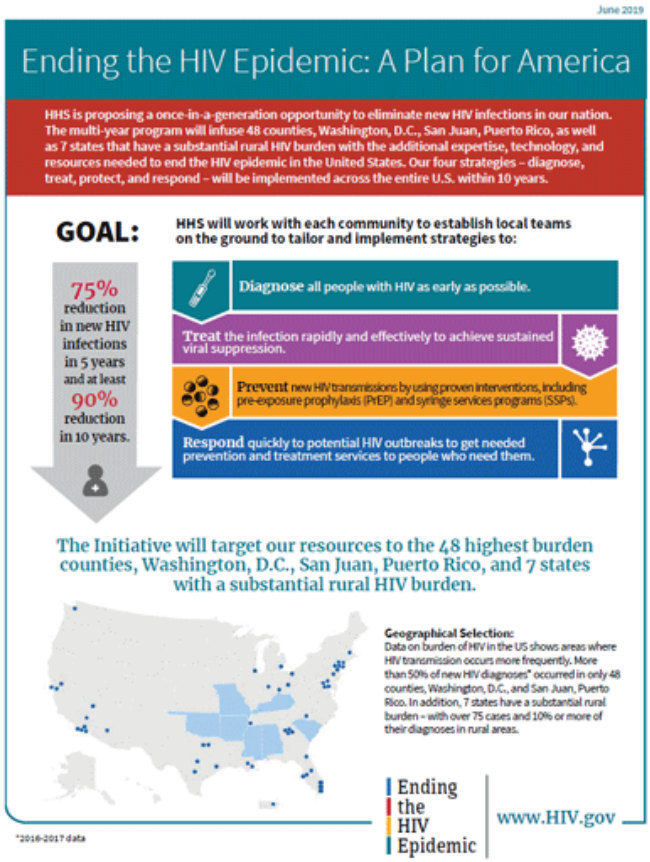
Right Leadership

This initiative will leverage critical scientific advances in HIV prevention, diagnosis, treatment, and care by coordinating the highly successful programs, resources, and infrastructure of many HHS agencies and offices, including the:

- Centers for Disease Control and Prevention (CDC)
- Health Resources and Services Administration (HRSA)
- Indian Health Service (IHS)
- National Institutes of Health (NIH)
- Office of the HHS Assistant Secretary for Health
- Substance Abuse and Mental Health Services Administration (SAMHSA)

The HHS Office of the Assistant Secretary for Health is coordinating this cross-agency Plan.

Fact Sheet



English (PDF 211 KB)

Whole-of-Society Initiative

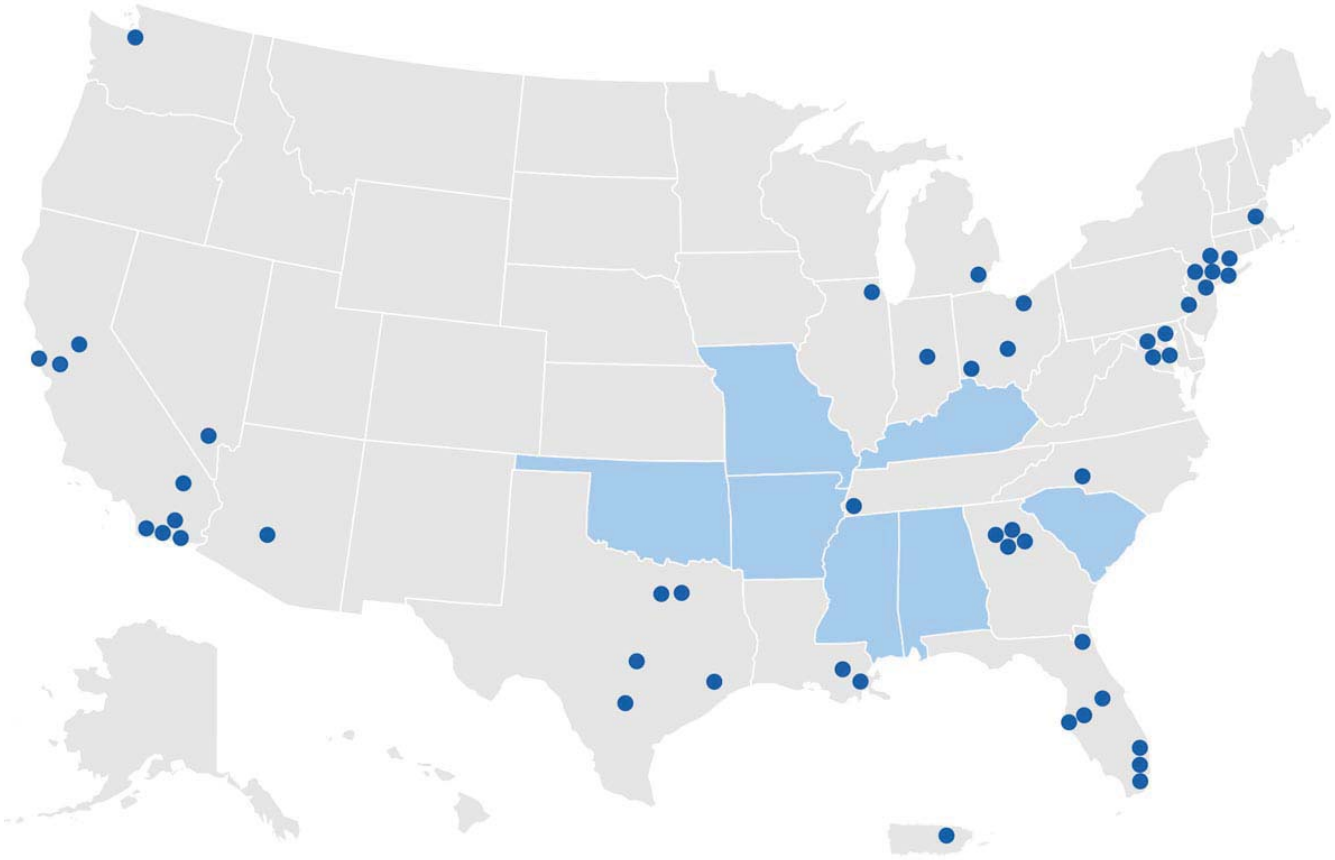
In addition to the coordination of federal agencies, key components for the success of this initiative will be active partnerships with city, county, tribal, and state public health departments, local and regional clinics and healthcare facilities, clinicians, providers of medication-assisted treatment for opioid use disorder, professional associations, advocates, community- and faith-based organizations, and academic and research institutions.

Budget Request

President Trump proposed $291 million in the FY2020 HHS budget to begin his Administration's multiyear initiative focused on ending the HIV epidemic in America by 2030.

Phase I: Geographic Focus

Most new HIV infections in the United States are highly concentrated in certain geographic hotspots. More than 50 percent of new HIV diagnoses in 2016 and 2017 occurred in 48 counties, Washington, DC, and San Juan, Puerto Rico. We also know that seven states have a disproportionate occurrence of HIV in rural areas. For the first five years (Phase I), the initiative will focus on a rapid infusion of new resources, expertise, and technology into those parts of the country now most impacted by HIV.



Geographic Hotspots: The 48 counties, plus Washington, DC, and San Juan, PR, where >50% of HIV diagnoses occurred in 2016 and 2017, and an additional seven states with a substantial number of HIV diagnoses in rural areas

Read a list of the 48 counties with the highest number of new HIV diagnoses, as well as Washington, DC, and San Juan, Puerto Rico and the seven states with a high proportion of HIV diagnoses in rural areas (PDF, 44 KB).

Phases II and III

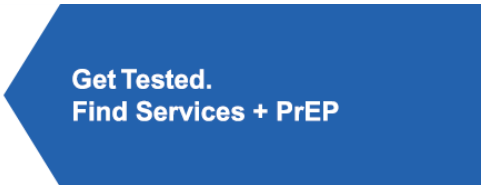
In **Phase II**, efforts will be even more widely disseminated across the nation to reduce new infections by 90 percent by 2030. In **Phase III**, intensive case management will be implemented to maintain the number of new infections at fewer than 3,000 per year.

Challenges

Despite the game-changing developments in HIV prevention and treatment tools, not everyone is benefiting equally from these advances. **New infections are highly concentrated** among men who have sex with men; minorities, especially African Americans, Hispanics/Latinos, and American Indians and Alaska Natives; and those who live in the southern United States.

Further, new analysis from CDC shows the vast majority (about 80 percent) of new HIV infections in the U.S. in 2016 were transmitted from the nearly 40 percent of people with HIV who either did not know they had HIV, or who had been diagnosed but were not receiving HIV care. These data underscore the impact of undiagnosed and untreated HIV in the nation and also the critical need to expand HIV testing and treatment in the United States.

And **stigma**—which can be a debilitating barrier preventing people living with, or at risk for, HIV from receiving the health care, services, and respect they need and deserve—still tragically surrounds HIV. Responding to HIV is not just a biomedical issue, but a social challenge, too.



Take action to end the epidemic. Encourage testing and help others access this HIV services tool.

Effective interventions have driven the number of new HIV infections down to approximately 40,000 per year—the lowest level ever. However, recent data show that our **progress reducing the number of new HIV infections has plateaued.** Now there are new threats to the progress

we've made, the most significant being the **opioid crisis**: One in 10 new HIV infections occurs among people who inject drugs.

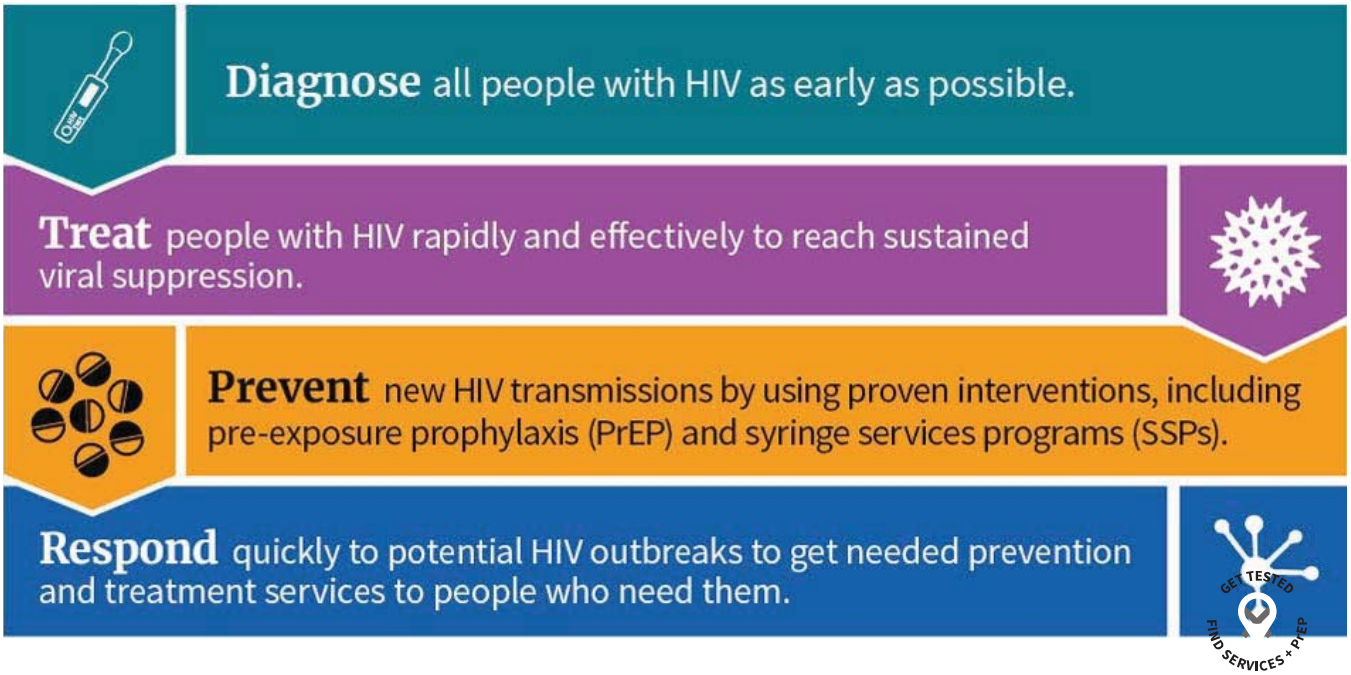
Key Strategies in the Plan

Ending the HIV Epidemic: A Plan for America will provide the hardest hit communities with the additional expertise, technology, and resources required to address the HIV epidemic locally.

The Plan's major areas of action include:

- **Increasing investments in geographic hotspots** through our existing, effective programs, such as the Ryan White HIV/AIDS Program, as well as a new program through community health centers that will provide PrEP to protect people at highest risk for getting HIV.
- **Using data** to identify where HIV is spreading most rapidly and guide decision-making to address prevention, care, and treatment needs at the local level.
- • Supporting the jurisdictions to **establish local teams committed to the success of the Initiative** and expand HIV prevention and treatment services.

The efforts will focus on four key strategies that together can end the HIV epidemic in the U.S.: **Diagnose, Treat, Prevent, and Respond**.



- *Diagnose all individuals with HIV as early as possible.* Approximately 165,000 Americans are living with HIV but don't know they have it. Early detection is critical and can lead to quicker results in treatment and prevent transmission to others. Using the latest diagnostics and advanced automation systems, we will make HIV testing simple, accessible, and routine. And we will diagnose infection early and connect people with HIV immediately to care.

- *Treat people with HIV rapidly and effectively to reach sustained viral suppression.* People with HIV who take medication as prescribed and stay virally suppressed can live long, healthy lives and have effectively no risk of sexually transmitting HIV to a partner. Eighty percent of annual new infections are transmitted by those living with HIV who are not receiving HIV care and treatment. We will establish and expand programs to follow up with people with HIV no longer receiving care—and provide the resources needed to re-engage them in effective HIV care and treatment. The Ryan White HIV/AIDS Program has achieved a viral suppression rate of nearly 86 percent. We aim to leverage the program's comprehensive system of care and treatment to increase viral suppression around the country to 90 percent.

- *Prevent new HIV transmissions by using proven interventions, including PrEP and syringe services programs (SSPs).* Of the estimated 1 million Americans at substantial risk for HIV and who could benefit from PrEP, less than 1 in 4 are actually using this medication. In May 2019, HHS and Gilead Sciences announced that the pharmaceutical company has agreed to donate PrEP medication for up to 200,000 individuals each year for up to 11 years. HHS will make the medication available to individuals who are at risk for HIV and who are uninsured and might otherwise not be able to access or afford this powerful HIV prevention tool. In addition, SSPs are an effective component of a comprehensive, integrated approach to HIV prevention among people who inject drugs. Nearly 30 years of research has shown that comprehensive SSPs are safe, effective, and cost-saving, do not increase illegal drug use or crime, and play an important role in reducing the transmission of viral hepatitis, HIV and other infections.

- *Respond quickly to potential HIV outbreaks to get needed prevention and treatment services to people who need them.* New laboratory methods and epidemiological techniques allow us to see where HIV may be spreading most rapidly, thereby allowing

CDC and other partners to quickly develop and implement strategies to stop ongoing transmission. We will work with impacted communities to ensure they have the technology, personnel, and prevention resources to follow up on all HIV cases and to intervene to stop chains of transmission, and to get those impacted into appropriate care and treatment.

Topics

Ending HIV

Content Source: HIV.gov
Date last updated: September 03, 2019

WAS THIS PAGE HELPFUL?

Yes

No

Next

Form Approved OMB# 0990-0379 Exp. Date 9/30/2020

MORE FROM HIV.GOV

Welcoming Harold J. Phillips to Senior Role in Ending the HIV Epidemic Efforts

Funding Opportunity to Address HIV and Other Health

Issues in Delta States

HRSA Pathway on Ending the HIV Epidemic at USCA 2019

EXHIBIT 70

Ending the HIV Epidemic

A PLAN FOR AMERICA

HHS is proposing a once-in-a-generation opportunity to eliminate new HIV infections in our nation. This initiative will work to accelerate progress and end the HIV epidemic by directing new funds to those communities affected by HIV in a phased approach, starting with the areas with the highest burden. The multi-year program will infuse 48 counties, Washington, D.C., San Juan, Puerto Rico, as well as 7 states that have a substantial rural HIV burden, with the additional expertise, technology, and resources needed to end the HIV epidemic in the United States. Data on the burden of the current epidemic were analyzed to identify the counties with the highest number of new HIV diagnoses, the states with the heaviest rural HIV burden, and the territorial area now hardest hit. These areas accounted for more than 50 percent of new HIV diagnoses in recent years.

COUNTIES, TERRITORIES, AND STATES

COUNTIES

Arizona
- Maricopa County

California
- Alameda County
- Los Angeles County
- Orange County
- Riverside County
- Sacramento County
- San Bernardino County
- San Diego County
- San Francisco County

Florida
- Broward County
- Duval County
- Hillsborough County
- Miami-Dade County
- Orange County
- Palm Beach County
- Pinellas County

Georgia
- Cobb County
- DeKalb County
- Fulton County
- Gwinnett County

Illinois
- Cook County

Indiana
- Marion County

Louisiana
- East Baton Rouge Parish
- Orleans Parish

Maryland
- Baltimore City
- Montgomery County
- Prince George's County

Massachusetts
- Suffolk County

Michigan
- Wayne County

Nevada
- Clark County

New Jersey
- Essex County
- Hudson County

New York
- Bronx County
- Kings County
- New York County
- Queens County

North Carolina
- Mecklenburg County

Ohio
- Cuyahoga County
- Franklin County
- Hamilton County

Pennsylvania
- Philadelphia County

Tennessee
- Shelby County

Texas
- Bexar County
- Dallas County
- Harris County
- Tarrant County
- Travis County

Washington
- King County

Washington, DC

TERRITORIES

Puerto Rico
- San Juan Municipio

STATES

Alabama

Arkansas

Kentucky

Mississippi

Missouri

Oklahoma

South Carolina

EXHIBIT 71

#BREAKTHEPATENT

The drug Truvada has the ability to reduce the risk of HIV transmission by more than 99%, but it's being withheld from the American public because of the greed of its manufacturer.

Gilead Sciences has inflated the cost from $6 to more than $1,600 per month, despite the US taxpayer paying for almost the full cost of its development. If we could lower the price of the drug, we could end the HIV epidemic without a vaccine. **Drug companies have held the American people hostage for too long. Join the campaign to #BreakThePatent.**

SIGN THE PETITION TO CALL ON THE NATIONAL INSTITUTES OF HEALTH TO BREAK THE PATENT AROUND TRUVADA AS PREP:

FIRST NAME* LAST NAME*

EMAIL ADDRESS*

ZIP

ADD YOUR NAME

OUR MISSION

Right now, a miracle drug is being withheld from the American public that can reduce the risk of HIV transmission by more than 99%. The drug is called Truvada and when taken daily as Pre-Exposure Prophylaxis (PrEP) can help provide almost absolute protection against the virus.

So why aren't more people taking it?

The manufacturer of the Truvada, Gilead Sciences, has inflated the price by more than 25,000%.

You read that right. The drug costs less than $6 a month to make but Gilead charges patients more than $1,600 for a 30 day supply. This cost barrier has translated to less than 10% of the at risk population currently taking the medication.

The truly infuriating part of that equation is that the drug manufacturer did not pay for the research that went into the development of the drug. YOU did. The US taxpayer, through the National Institutes of Health (NIH), paid for almost all of the research that went into developing Truvada as PrEP.

All the while, as Gilead lines its pockets by profiting off of taxpayer investment, the HIV epidemic continues to persist. More than 100 Americans contract HIV everyday, with people of color and the LGBT community disproportionately affected.

But it doesn't have to be this way. The NIH could "march-in" and break the patents around the drug at any time, immediately lowering the price and allowing the millions to gain access to this life saving treatment.

The time is now. Sign the petition and tell the National Institutes of Health to #BreakThePatent!

Together we can send a clear message to the Pharmaceutical industry that the American people will not tolerate their greed.

5 TAKEAWAYS

PrEP WORKS!

When taken daily, Truvada (or a generic equivalent) reduces the risk of HIV transmission by more than 99%. That's more effective than the vaccines for Polio, Measles, Mumps, and Tuberculosis. If we can get enough people to take the medication, we can end the epidemic once and for all. When we have the technology to prevent HIV transmission, it's a moral outrage that the drug is still being withheld from the public.

PrEP DOESN'T HAVE TO BE SO EXPENSIVE

Though Gilead charges an average of $1,600 for a monthly supply Truvada, it costs less than $6 to produce! What Gilead charges for just two pills could pay for an entire year's supply of a generic equivalent.

THE US ALREADY PAYS FOR GENERIC TRUVADA

– just not for Americans. As part of international HIV programs, the US pays for generic Truvada within Africa, Southeast Asia, and elsewhere for ~$6 a month. Meanwhile, Americans pay 250+ times that price due to Gilead's patents.

GILEAD DID NOT INVENT PrEP

The US government and taxpayers paid for almost 100% of the research that went into the development of Truvada as PrEP, and still retains the relevant intellectual property rights.

GILEAD'S PATENT CAN BE BROKEN

The Bayh-Dole Act of 1980 gives federal funding agencies the right to "March In" and ignore patent exclusivity should the holder fail to acknowledge "health or safety needs" of consumers by, for instance, engaging in price gouging.

TAKE ACTION

HELP SPREAD THE WORD

SHARE TWEET

ADD YOUR NAME

FIRST NAME* LAST NAME*

EMAIL ADDRESS*

ZIP

ADD YOUR NAME

EXHIBIT 72

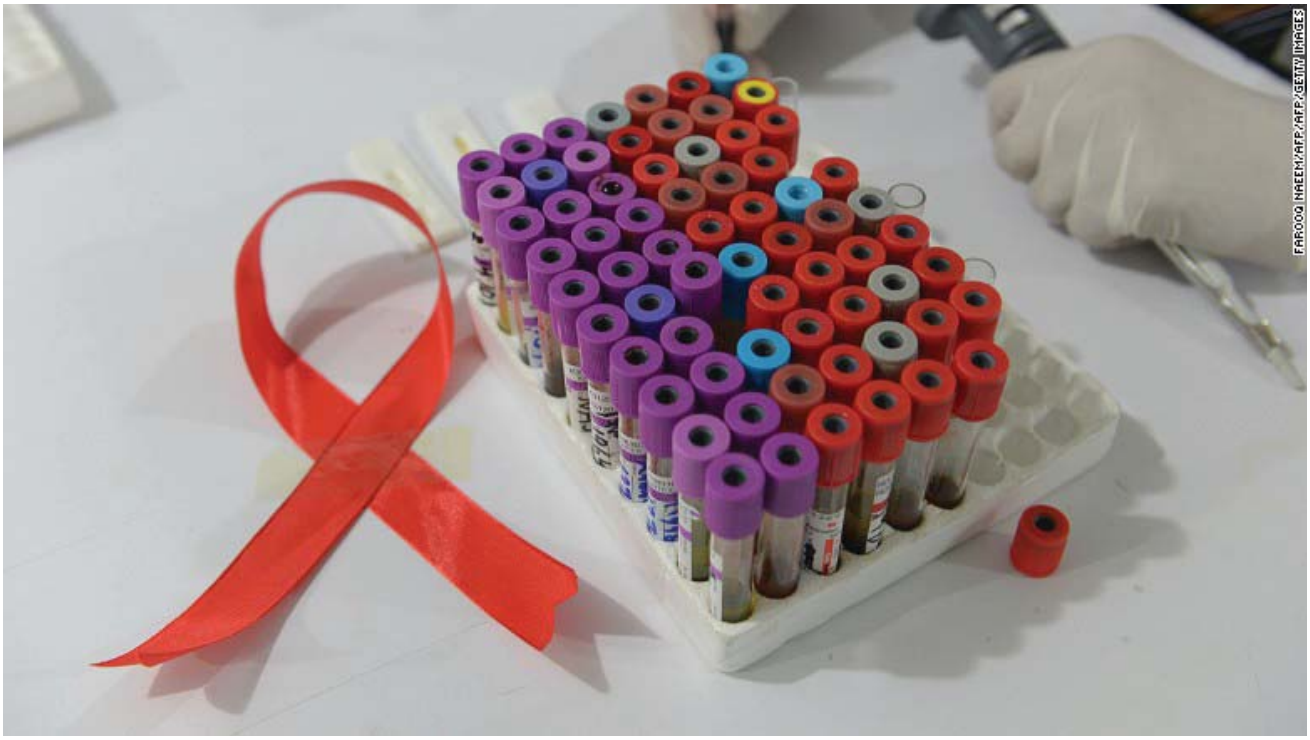
CNN health

LIVE TV

PrEP can 'significantly' reduce HIV rates across populations, study says

By Nina Avramova, CNN

Updated 3:00 PM ET, Wed October 17, 2018



The turbulent history of HIV/AIDS 01:52

Story highlights

There was a 25% decline in HIV diagnoses in a group of high-risk Australian men taking PrEP for one year

Herd immunity has led to fewer people becoming infected overall, researcher says

(CNN) — HIV pre-exposure prophylaxis or PrEP, the use of drugs to prevent HIV infection, among men who have sex with men can significantly reduce new infections across an entire population of men, a new study finds.

Based on introduction of the intervention, HIV infections diagnosed in men who have sex with men in the Australian state of New South Wales fell by a quarter -- 25.1% -- in one year in the research, published Wednesday in the journal the Lancet.

Diagnoses fell from from 295 in October 2016, before the study, to 221 just 12 months after the PrEP rollout -- the lowest number since HIV surveillance started in New South Wales in 1985.

"The speed and magnitude of response was remarkable," said Andrew Grulich, lead author of the paper and professor of the HIV epidemiology and prevention program at the Kirby Institute in the University of New South Wales.

G believes that the large decline is because PrEP "is acting in a similar way to a vaccine," meaning h ...unity has led to fewer people becoming infected overall in the state of 7 million.

University College London professor of cellular and molecular virology Ariberto Fassati, who was not involved in the new research, explained that there is a "benefit for the larger community if there is a core of individuals that are taking PrEP."

In the study, 3,700 HIV-negative homosexual and bisexual men across 21 clinics in New South Wales were prescribed a daily dose of PrEP, followed up with HIV tests over one year.

HIV PrEP is made up of the drugs tenofovir and emtricitabine, taken before sex, and prevents people from becoming infected with HIV. For this study, the participants were prescribed 300 milligrams of tenofovir disoproxil dumarate and 200 milligrams of emtricitabine.

Only two of the 3,700 men were diagnosed as HIV-positive after the study; both were not adherent to the preventive treatment, according to the study.

The expected occurrence rate of HIV for this high-risk population in the absence of PrEP is at least 2 per 100 people.

The researchers identified men to be at high risk if they engaged in anal intercourse without condoms with casual partners of HIV-positive or unknown status, if they had a sexually transmitted infection such as rectal chlamydia or gonorrhea, if they used crystal methamphetamine or if they engaged in unprotected anal intercourse with a HIV-positive partner who isn't on treatment.

Statewide, the authors found 25% fewer HIV diagnoses after PrEP rollout. Recent cases, infections likely to have been acquired within the previous 12 months, were reported as 149 before the study and declined to 102, a 31.5% drop.

Declines were reported across all ages. The groups that saw the most rapid downturn were Australian-born men, those over 45 and men living in gay neighborhoods in Sydney.

Related Article: In medical first, HIV-positive mother donates liver to her uninfected baby, in South Africa

Will Nutland, honorary professor at the London School of Hygiene & Tropical Medicine and PrEP activist, said the findings "confirmed what we already suspected."

"It is exciting but not surprising," said Nutland, who was not involved in the study.

Previous studies have proved the efficacy of PrEP.

French and Canadian research showed effectiveness levels of 86% during daily or intermittent PrEP courses, with only men who were non-adherent becoming infected with HIV. San Francisco witnessed a 50% decline of HIV diagnoses between 2012 and 2016, after PrEP was introduced.

The new study had a wider and faster reach. Grulich's team used mathematical models to calculate the effects of the preventive drug on entire populations. "If you introduce PrEP rapidly and target it to high-risk people, you get a rapid reduction in HIV," he said.

But Nutland said it is hard to "unpick the direct impact with PrEP compared to other HIV prevention methods." Early interventions for HIV-positive patients, like treatment as prevention -- which reduce the virus' presence to an undetectable and therefore untransmittable level -- make it impossible for a HIV-positive person to pass on the virus.

Fassati said it would be helpful to see a long-term analysis of PrEP's effect on populations. He also would like to see the results replicated in communities that are not so adherent or motivated, as PrEP's effectiveness is much reduced if it is not taken regularly.

Related Article: An emotional call to eradicate ancient cousin of HIV

PrEP has been introduced in several countries. England offers the preventive treatment for men who have sex with men in its National Health Service. But there has been some pushback due to claims that it would encourage sex without a condom.

Another problem some men face is the cost of the drug. "If PrEP can be provided in a target way, high coverage rate, for free and easily accessible in clinics, then this removes some of the barriers of accessing PrEP, as we have seen in the USA," Nutland noted.

The preventive regimen can have short-term side effects such as stomach and headaches, and in the longer term, it could lead to kidney toxicity. Another effect of the drug, as PrEP user Nutland has described it, is a reduction in fear and anxiety over having sex. "It makes our collective sex lives way better than they has ever been," he said.

The new study is "another reminder is that PrEP works," Nutland said, "and this should galvanize our policy-makers and politicians to make PrEP available for those who need it most, as soon as possible."

EXHIBIT 73

of individuals for whom confinement is not essential for public safety would be beneficial. Care disruption by incarceration was a major impediment for HIV control in the ALIVE cohort.[12] Promoting alternatives to incarceration, such as diversion to mental health and drug courts, might be the best approach to prevent death among people with HIV.

Anne C Spaulding, Marcia McDonnell Holstad
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ACS reports fees for clinical services from Naphcare and CorrectCare Solutions; honoraria for speaking from Merck, through Clinical Director's Network and the National Commission on Correctional Healthcare; grants and consulting fees from Gilead Sciences; and grants from Abbvie and ViiV, outside the submitted work. MMH declares no competing interests.

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What happens when PrEP is scaled up? Results from EPIC-NSW

Published **Online**
October 17, 2018
http://dx.doi.org/10.1016/S2352-3018(18)30253-4

See **Articles** page e629

In *The Lancet HIV*, Andrew E Grulich and colleagues[1] describe the rapid roll-out of pre-exposure prophylaxis (PrEP) in New South Wales, Australia (the Expanded PrEP Implementation in Communities–New South Wales [EPIC-NSW] study), a setting where the 90-90-90 targets for the proportion of individuals with HIV diagnosed, treated, and virally suppressed were already surpassed in 2016, and which is therefore ideal for identifying the added value of PrEP. This prospective empirical evaluation of population impact showed a relatve risk reduction of 25·1% (95% CI 10·5–37·4) in HIV diagnoses among men who have sex with men in the 12 months after 3700 participants were enrolled and started on PrEP, compared with the 12 months before recruitment began. The investigators correctly predicted that the decline would be greatest in recently acquired infections (31·5%, 95% CI 11·3–47·3), but this observation was not universal across New South Wales when divided into regions (gay suburbs of Sydney, the rest of Sydney, and the remainder of New South Wales). The reduction in recent HIV infections exceeded 50% in Sydney's gay suburbs and the rest of New South Wales, but was only 7·3% in the non-gay suburbs of the city, highlighting the challenge of reaching all communities. Nonetheless, the overall benefit from the introduction of PrEP was impressive, given the evidence from behaviour surveys[2] and notifications of sexually transmitted infections[3] suggesting that risk was increasing during this period.

The disparity in benefit has also been observed in new diagnosis trends in England. In the year to Sept 30, 2016, a 32% reduction was observed among MSM attending five large clinics in central London compared with the previous period, but only 7% in MSM at other London clinics, and 5% nationally.[4] More than 40% of the tests in MSM were done at one clinic, Dean Street, where early treatment to prevent onward transmission became routine after findings from the PARTNER study showed zero transmissions in serodifferent MSM couples in early 2014.[5] The main change in service thereafter was the introduction of PrEP, which was actively promoted through self-purchase from Sept 26, 2015. PrEP filled a crucial gap in

the package offered to MSM struggling to use condoms consistently with one or more partners. The decline in new diagnoses continued through 2017,[6] but was difficult to attribute to PrEP as uptake was not captured in surveillance data. Now, the EPIC-NSW study has provided robust evidence for the added value of PrEP at the population level, as well as endorsing the biological efficacy in individuals who use PrEP consistently during periods of possible exposure to HIV.

By contrast with Australia, most countries are unlikely to reach the 90-90-90 targets by 2020. The WHO European Region (consisting of 53 countries divided into East, West, and Central regions) is the only region with an increase in new HIV diagnoses. Data for progress towards the 90-90-90 targets reported to the European Centre for Disease Prevention and Control in 2016 revealed that the region was failing to deliver adequate services,[7] and preliminary data in 2018 suggested that this scenario is still the case—particularly in the East Europe region, where an average of 76% of all people living with HIV are aware of their diagnosis, only 34% are on treatment, and 26% are suppressed.[8] Testing is the first step in the pathway to treatment or prevention, and the technology is in place to enable individuals to take control of testing, but policies are slow to change; only nine countries in Europe have implemented self-testing for HIV, and no more than 14 have community testing initiatives delivered by non-medical staff.[8] Getting to zero new infections that could have been prevented in clinic by people who are already attending clinic is highly achievable, but reaching all undiagnosed individuals remains difficult. Raising awareness could help, as the EPIC investigators suggest, but in many populations there are more complex barriers to testing including poverty, discrimination, poor mental health, and addiction. In this context individuals have other priorities and fears, and HIV services need to be incorporated into services they are more motivated to access. There is an opportunity to address these barriers at the same time as PrEP implementation, but governments have to be willing to invest and clinicians to embrace differentiated care and prevention.

New South Wales has shown how effective the combined efforts of government leadership, civil society, and a state-wide sexual health service can be at achieving high coverage with a new technology. Others need to follow suit.

Sheena McCormack
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s.mccormack@ucl.ac.uk

SMC received financial support from the UK Medical Research Council.

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Optimising the accuracy of HIV drug resistance assays

Published Online
September 30, 2018
http://dx.doi.org/10.1016/S2352-3018(18)30211-X

See Articles page e638

About 22 million people globally received antiretroviral therapy (ART) in 2017.[1] In patients on ART, viral suppression is crucial for both the individual patient's clinical benefit and the community's HIV prevention benefit. A key reason for failure to achieve viral suppression is resistance to one or more drugs in the patient's antiretroviral regimen. Maintenance of a strict daily pill regimen can be challenging for patients; suboptimal adherence fosters drug resistance and the transmission of drug-resistant strains of HIV to others. Furthermore, resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) is widespread,

EXHIBIT 74

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-Q

☒ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the quarterly period ended March 31, 2019

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from _____ to _____

Commission File No. 0-19731

GILEAD SCIENCES, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**94-3047598**
(State or Other Jurisdiction of Incorporation or Organization)	**(IRS Employer Identification No.)**
333 Lakeside Drive, Foster City, California	**94404**
(Address of principal executive offices)	**(Zip Code)**

650-574-3000
Registrant's Telephone Number, Including Area Code

Title of each class	**Securities registered pursuant to Section 12(b) of the Act: Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, par value, $0.001 per share	**GILD**	**The Nasdaq Global Select Market**

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer" "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐
Smaller reporting company ☐ Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

Number of shares outstanding of the issuer's common stock, par value $0.001 per share, as of April 30, 2019: 1,271,554,672

GILEAD SCIENCES, INC.

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PART I. FINANCIAL INFORMATION

Item 1. CONDENSED CONSOLIDATED FINANCIAL STATEMENTS

GILEAD SCIENCES, INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(unaudited)
(in millions, except per share amounts)

	March 31, 2019	December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 16,927	$ 17,940
Short-term marketable securities	10,977	12,149
Accounts receivable, net of allowances of $669 and $583, respectively	3,283	3,327
Inventories	898	814
Prepaid and other current assets	1,939	1,606
Total current assets	34,024	35,836
Property, plant and equipment, net	4,116	4,006
Long-term marketable securities	2,221	1,423
Intangible assets, net	15,438	15,738
Goodwill	4,117	4,117
Other long-term assets	2,921	2,555
Total assets	$ 62,837	$ 63,675
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 577	$ 790
Accrued government and other rebates	3,974	3,928
Other accrued liabilities	2,348	3,139
Current portion of long-term debt and other obligations, net	2,498	2,748
Total current liabilities	9,397	10,605
Long-term debt, net	24,080	24,574
Long-term income taxes payable	5,809	5,922
Other long-term obligations	1,460	1,040
Commitments and contingencies (Note 11)		
Stockholders' equity:		
Preferred stock, par value $0.001 per share; 5 shares authorized; none outstanding	—	—
Common stock, par value $0.001 per share; 5,600 shares authorized; 1,274 and 1,282 shares issued and outstanding, respectively	1	1
Additional paid-in capital	2,494	2,282
Accumulated other comprehensive income	130	80
Retained earnings	19,326	19,024
Total Gilead stockholders' equity	21,951	21,387
Noncontrolling interest	140	147
Total stockholders' equity	22,091	21,534
Total liabilities and stockholders' equity	$ 62,837	$ 63,675

See accompanying notes.

GILEAD SCIENCES, INC.
CONDENSED CONSOLIDATED STATEMENTS OF INCOME
(unaudited)
(in millions, except per share amounts)

	Three Months Ended March 31,	
	2019	2018
Revenues:		
Product sales	$ 5,200	$ 5,001
Royalty, contract and other revenues	81	87
Total revenues	5,281	5,088
Costs and expenses:		
Cost of goods sold	957	1,001
Research and development expenses	1,057	937
Selling, general and administrative expenses	1,030	997
Total costs and expenses	3,044	2,935
Income from operations	2,237	2,153
Interest expense	(254)	(290)
Other income (expense), net	367	170
Income before provision for income taxes	2,350	2,033
Provision for income taxes	382	494
Net income	1,968	1,539
Net income (loss) attributable to noncontrolling interest	(7)	1
Net income attributable to Gilead	$ 1,975	$ 1,538
Net income per share attributable to Gilead common stockholders - basic	$ 1.55	$ 1.18
Shares used in per share calculation - basic	1,276	1,307
Net income per share attributable to Gilead common stockholders - diluted	$ 1.54	$ 1.17
Shares used in per share calculation - diluted	1,283	1,320

See accompanying notes.

GILEAD SCIENCES, INC.
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME
(unaudited)
(in millions)

	Three Months Ended March 31,	
	2019	2018
Net income	$ 1,968	$ 1,539
Other comprehensive income (loss):		
Net foreign currency translation gain, net of tax	21	7
Available-for-sale debt securities:		
Net unrealized gain (loss), net of tax	30	(36)
Reclassifications to net income, net of tax	—	—
Net change	30	(36)
Cash flow hedges:		
Net unrealized gain (loss), net of tax	28	(61)
Reclassifications to net income, net of tax	(29)	48
Net change	(1)	(13)
Other comprehensive income (loss)	50	(42)
Comprehensive income	2,018	1,497
Comprehensive income (loss) attributable to noncontrolling interest	(7)	1
Comprehensive income attributable to Gilead	$ 2,025	$ 1,496

See accompanying notes.

GILEAD SCIENCES, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(unaudited)
(in millions, except per share amounts)

	Three Months Ended March 31, 2019						
	Gilead Stockholders' Equity						
	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Retained Earnings	Noncontrolling Interest	Total Stockholders' Equity
	Shares	Amount					
Balance at December 31, 2018	1,282	$ 1	$ 2,282	$ 80	$ 19,024	$ 147	$ 21,534
Net income (loss)	—	—	—	—	1,975	(7)	1,968
Other comprehensive income, net of tax	—	—	—	50	—	—	50
Issuances under employee stock purchase plan	1	—	63	—	—	—	63
Issuances under equity incentive plans	4	—	41	—	—	—	41
Stock-based compensation	—	—	144	—	—	—	144
Repurchases of common stock	(13)	—	(36)	—	(867)	—	(903)
Dividends declared ($0.63 per share)	—	—	—	—	(814)	—	(814)
Cumulative effect from the adoption of new leases standard (Note 1)	—	—	—	—	8	—	8
Balance at March 31, 2019	1,274	$ 1	$ 2,494	$ 130	$ 19,326	$ 140	$ 22,091

	Three Months Ended March 31, 2018						
	Gilead Stockholders' Equity						
	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Retained Earnings	Noncontrolling Interest	Total Stockholders' Equity
	Shares	Amount					
Balance at December 31, 2017	1,308	$ 1	$ 1,264	$ 165	$ 19,012	$ 59	$ 20,501
Net income	—	—	—	—	1,538	1	1,539
Other comprehensive loss, net of tax	—	—	—	(42)	—	—	(42)
Issuances under employee stock purchase plan	1	—	48	—	—	—	48
Issuances under equity incentive plans	5	—	64	—	—	—	64
Stock-based compensation	—	—	224	—	—	—	224
Repurchases of common stock	(14)	—	(36)	—	(1,085)	—	(1,121)
Dividends declared ($0.57 per share)	—	—	—	—	(752)	—	(752)
Cumulative effect from the adoption of new accounting standards	—	—	—	(293)	483	—	190
Balance at March 31, 2018	1,300	$ 1	$ 1,564	$ (170)	$ 19,196	$ 60	$ 20,651

See accompanying notes.

GILEAD SCIENCES, INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(unaudited)
(in millions)

	Three Months Ended March 31,	
	2019	2018
Operating Activities:		
Net income	$ 1,968	$ 1,539
Adjustments to reconcile net income to net cash provided by operating activities:		
Depreciation expense	60	56
Amortization expense	299	301
Stock-based compensation expense	143	220
Deferred income taxes	24	35
Other	(157)	49
Changes in operating assets and liabilities:		
Accounts receivable, net	32	101
Inventories	(15)	(14)
Prepaid expenses and other	(43)	529
Accounts payable	(201)	(92)
Income taxes payable	(249)	(618)
Accrued liabilities and other	(417)	164
Net cash provided by operating activities	1,444	2,270
Investing Activities:		
Purchases of marketable debt securities	(6,722)	(397)
Proceeds from sales of marketable debt securities	575	221
Proceeds from maturities of marketable debt securities	6,511	4,762
Capital expenditures	(237)	(212)
Other	(238)	(20)
Net cash provided by (used in) investing activities	(111)	4,354
Financing Activities:		
Proceeds from issuances of common stock	103	111
Repurchases of common stock	(834)	(1,039)
Repayments of debt and other obligations	(750)	(4,500)
Payments of dividends	(817)	(753)
Other	(68)	(414)
Net cash used in financing activities	(2,366)	(6,595)
Effect of exchange rate changes on cash and cash equivalents	20	26
Net change in cash and cash equivalents	(1,013)	55
Cash and cash equivalents at beginning of period	17,940	7,588
Cash and cash equivalents at end of period	$ 16,927	$ 7,643

See accompanying notes.

GILEAD SCIENCES, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
(unaudited)

1. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation

The accompanying unaudited Condensed Consolidated Financial Statements have been prepared in accordance with U.S. generally accepted accounting principles for interim financial information. The financial statements include all adjustments, consisting of normal recurring adjustments that the management of Gilead Sciences, Inc. (Gilead, we, our or us) believes are necessary for a fair presentation of the periods presented. These interim financial results are not necessarily indicative of results expected for the full fiscal year or for any subsequent interim period.

The accompanying Condensed Consolidated Financial Statements include the accounts of Gilead, our wholly-owned subsidiaries and certain variable interest entities for which we are the primary beneficiary. All intercompany transactions have been eliminated. For consolidated entities where we own or are exposed to less than 100% of the economics, we record net income (loss) attributable to noncontrolling interest in our Condensed Consolidated Statements of Income equal to the percentage of the economic or ownership interest retained in such entities by the respective noncontrolling parties.

We assess whether we are the primary beneficiary of a variable interest entity (VIE) at the inception of the arrangement and at each reporting date. This assessment is based on our power to direct the activities of the VIE that most significantly impact the VIE's economic performance and our obligation to absorb losses or the right to receive benefits from the VIE that could potentially be significant to the VIE. As of March 31, 2019, we did not have any material VIEs.

The accompanying Condensed Consolidated Financial Statements and related Notes to Condensed Consolidated Financial Statements should be read in conjunction with the audited Consolidated Financial Statements and the related notes thereto for the year ended December 31, 2018, included in our Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC).

Significant Accounting Policies, Estimates and Judgments

The preparation of these Condensed Consolidated Financial Statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses and related disclosures. On an ongoing basis, we evaluate our significant accounting policies and estimates. We base our estimates on historical experience and on various market-specific and other relevant assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Estimates are assessed each period and updated to reflect current information. Actual results may differ significantly from these estimates.

Concentrations of Risk

We are subject to credit risk from our portfolio of cash equivalents and marketable securities. Under our investment policy, we limit amounts invested in such securities by credit rating, maturity, industry group, investment type and issuer, except for securities issued by the U.S. government. We are not exposed to any significant concentrations of credit risk from these financial instruments. The goals of our investment policy, in order of priority, are as follows: safety and preservation of principal and diversification of risk; liquidity of investments sufficient to meet cash flow requirements; and a competitive after-tax rate of return.

We are also subject to credit risk from our accounts receivable related to our product sales. The majority of our trade accounts receivable arises from product sales in the United States and Europe. To date, we have not experienced significant losses with respect to the collection of our accounts receivable. We believe that our allowance for doubtful accounts was adequate as of March 31, 2019.

Recently Adopted Accounting Standards

In February 2016, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update No. 2016-02 "Leases" (ASU 2016-02) and subsequently issued supplemental adoption guidance and clarification (collectively, Topic 842). Topic 842 amends a number of aspects of lease accounting, including requiring lessees to recognize right-of-use assets and lease liabilities for operating leases with a lease term greater than one year. Topic 842 supersedes Topic 840 "Leases."

On January 1, 2019, we adopted Topic 842 using the modified retrospective approach. Results for reporting periods beginning after January 1, 2019 are presented under Topic 842, while prior period amounts are not adjusted and continue to be reported in accordance with our historical accounting under Topic 840. We elected the package of practical expedients permitted under the transition guidance within Topic 842, which allowed us to carry forward the historical lease classification, retain the initial direct costs for any leases that existed prior to the adoption of the standard and not reassess whether any contracts entered into prior to the adoption are leases. We also elected to account for lease and nonlease components in our lease agreements as a single lease component in determining lease assets and liabilities. In addition, we elected not to recognize the right-of-use assets and liabilities for leases with lease terms of one year or less.

Upon adoption of Topic 842, we recorded $441 million of right-of-use assets within Other long-term assets and $490 million of operating lease liabilities, classified primarily within Other long-term obligations on our Condensed Consolidated Balance Sheet, as of January 1, 2019. The adoption did not have a material impact on our Condensed Consolidated Statements of Income or Condensed Consolidated Statements of Cash Flows. See Note 10. Leases for additional information.

Recently Issued Accounting Standards Not Yet Adopted

In June 2016, the FASB issued Accounting Standards Update No. 2016-13 "Financial Instruments-Credit Losses: Measurement of Credit Losses on Financial Instruments" (ASU 2016-13). ASU 2016-13 requires measurement and recognition of expected credit losses for financial assets. In April 2019, the FASB issued clarification to ASU 2016-13 within ASU 2019-04 "Codification Improvements to Topic 326, Financial Instruments-Credit Losses, Topic 815, Derivatives and Hedging, and Topic 825, Financial Instruments." The guidance will become effective for us beginning in the first quarter of 2020 and must be adopted using a modified retrospective approach, with certain exceptions. Early adoption is permitted beginning in the first quarter of 2019. We are evaluating the impact of the adoption of these standards but we currently do not expect a material impact on our Condensed Consolidated Financial Statements.

In November 2018, the FASB issued Accounting Standards Update No. 2018-18 "Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606" (ASU 2018-18). ASU 2018-18 clarifies that certain transactions between participants in a collaborative arrangement should be accounted for under ASC 606 when the counterparty is a customer. In addition, the update precludes an entity from presenting consideration from a transaction in a collaborative arrangement as revenue if the counterparty is not a customer for that transaction. This guidance will become effective for us beginning in the first quarter of 2020 and will be applied retrospectively to January 1, 2018 when we initially adopted Topic 606. Early adoption is permitted. We are evaluating the impact of the adoption of this standard but we currently do not expect a material impact on our revenue.

2. REVENUES

Disaggregation of Revenues

The following table disaggregates our product sales by product and geographic region and disaggregates our royalty, contract and other revenues by geographic region (in millions):

	Three Months Ended March 31, 2019				Three Months Ended March 31, 2018			
	U.S.	Europe	Other International	Total	U.S.	Europe	Other International	Total
Product sales:								
Atripla	$ 133	$ 16	$ 22	$ 171	$ 228	$ 51	$ 35	$ 314
Biktarvy	739	48	6	793	35	—	—	35
Complera/Eviplera	44	62	9	115	67	109	14	190
Descovy	233	68	41	342	274	75	12	361
Genvoya	728	193	94	1,015	853	186	43	1,082
Odefsey	282	106	9	397	279	58	5	342
Stribild	67	18	11	96	133	29	12	174
Truvada	551	33	22	606	507	97	48	652
Other HIV[1]	11	1	5	17	9	1	3	13
Revenue share – Symtuza[2]	42	24	—	66	—	7	—	7
AmBisome	8	57	28	93	17	56	34	107
Ledipasvir/Sofosbuvir[3]	117	27	81	225	234	56	58	348
Letairis	197	—	—	197	204	—	—	204
Ranexa	155	—	—	155	195	—	—	195
Sofosbuvir/Velpatasvir[4]	230	154	107	491	269	198	69	536
Vemlidy	65	4	32	101	47	3	8	58
Viread	12	14	46	72	7	30	60	97
Vosevi	45	16	2	63	86	16	5	107
Yescarta	90	6	—	96	40	—	—	40
Zydelig	11	15	1	27	14	18	1	33
Other[5]	36	20	6	62	29	15	62	106
Total product sales	3,796	882	522	5,200	3,527	1,005	469	5,001
Royalty, contract and other revenues	22	56	3	81	20	52	15	87
Total revenues	$ 3,818	$ 938	$ 525	$ 5,281	$ 3,547	$ 1,057	$ 484	$ 5,088

Notes:

(1) Includes Emtriva and Tybost

(2) Represents our revenue from cobicistat (C), emtricitabine (FTC) and tenofovir alafenamide (TAF) in Symtuza (darunavir/C/FTC/TAF), a fixed dose combination product commercialized by Janssen Sciences Ireland UC (Janssen)

(3) Amounts consist of sales of Harvoni and the authorized generic version of Harvoni sold by our separate subsidiary, Asegua Therapeutics LLC

(4) Amounts consist of sales of Epclusa and the authorized generic version of Epclusa sold by our separate subsidiary, Asegua Therapeutics LLC

(5) Includes Cayston, Hepsera and Sovaldi

Revenues Recognized from Performance Obligations Satisfied in Prior Periods

During the three months ended March 31, 2019 and 2018, revenues recognized from performance obligations satisfied in prior years related to royalties for licenses of our intellectual property were $155 million and $97 million, respectively. Changes in estimates for variable consideration related to sales made in prior years resulted in a $107 million increase and $87 million decrease in revenues during the three months ended March 31, 2019 and 2018, respectively.

Contract Balances

Our contract assets, which consist of unbilled amounts primarily from arrangements where the licensing of intellectual property is the only or predominant performance obligation, totaled $140 million and $125 million as of March 31, 2019 and December 31, 2018, respectively.

Contract liabilities were not material as of March 31, 2019 and December 31, 2018.

3. FAIR VALUE MEASUREMENTS

We determine the fair value of financial and non-financial assets and liabilities using the fair value hierarchy, which establishes three levels of inputs that may be used to measure fair value, as follows:

- Level 1 inputs include quoted prices in active markets for identical assets or liabilities;
- Level 2 inputs include observable inputs other than Level 1 inputs, such as quoted prices for similar assets or liabilities; quoted prices for identical or similar assets or liabilities in markets that are not active; or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the asset or liability. For our marketable securities, we review trading activity and pricing as of the measurement date. When sufficient quoted pricing for identical securities is not available, we use market pricing and other observable market inputs for similar securities obtained from various third-party data providers. These inputs either represent quoted prices for similar assets in active markets or have been derived from observable market data; and
- Level 3 inputs include unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the underlying asset or liability. Our Level 3 assets and liabilities include those whose fair value measurements are determined using pricing models, discounted cash flow methodologies or similar valuation techniques and significant management judgment or estimation.

Our financial instruments consist primarily of cash and cash equivalents, marketable debt securities, accounts receivable, foreign currency exchange contracts, equity securities, accounts payable and short-term and long-term debt. Cash and cash equivalents, marketable debt securities, certain equity securities and foreign currency exchange contracts are reported at their respective fair values on our Condensed Consolidated Balance Sheets. Equity securities with no readily determinable fair values are recorded using the measurement alternative of cost less impairment, if any, adjusted for observable price changes in orderly transactions for identical or similar investments of the same issuer. Short-term and long-term debt are reported at their amortized costs on our Condensed Consolidated Balance Sheets. The remaining financial instruments are reported in our Condensed Consolidated Balance Sheets at amounts that approximate current fair values. There were no transfers between Level 1, Level 2 and Level 3 in the periods presented.

The following table summarizes the types of assets and liabilities measured at fair value on a recurring basis by level within the fair value hierarchy (in millions):

	March 31, 2019				December 31, 2018			
	Level 1	Level 2	Level 3	Total	Level 1	Level 2	Level 3	Total
Assets:								
Available-for-sale debt securities:								
U.S. treasury securities	$ 4,782	$ —	$ —	$ 4,782	$ 3,969	$ —	$ —	$ 3,969
Certificates of deposit	—	4,211	—	4,211	—	4,361	—	4,361
U.S. government agencies securities	—	1,444	—	1,444	—	938	—	938
Municipal debt securities	—	25	—	25	—	—	—	—
Non-U.S. government securities	—	452	—	452	—	305	—	305
Corporate debt securities	—	12,565	—	12,565	—	13,067	—	13,067
Residential mortgage and asset-backed securities	—	1,036	—	1,036	—	1,524	—	1,524
Equity securities:								
Money market funds	3,778	—	—	3,778	5,305	—	—	5,305
Publicly traded equity securities	1,099	18	—	1,117	881	—	—	881
Deferred compensation plan	150		—	150	124	—	—	124
Foreign currency derivative contracts	—	77	—	77	—	78	—	78
Total	$ 9,809	$ 19,828	$ —	$ 29,637	$ 10,279	$ 20,273	$ —	$ 30,552
Liabilities:								
Deferred compensation plan	$ 150	$ —	$ —	$ 150	$ 124	$ —	$ —	$ 124
Foreign currency derivative contracts	—	2	—	2	—	1	—	1
Total	$ 150	$ 2	$ —	$ 152	$ 124	$ 1	$ —	$ 125

For the three months ended March 31, 2019 and 2018, changes in the fair value of equity securities resulted in net unrealized gains of $197 million and $45 million, respectively, which were included in Other income (expense), net on our Condensed

Consolidated Statements of Income. Investments in equity securities without readily determinable fair values were not material for the periods presented.

The following table summarizes the classification of our equity securities in our Condensed Consolidated Balance Sheets (in millions):

	March 31, 2019	December 31, 2018
Cash and cash equivalents	$ 3,778	$ 5,305
Prepaid and other current assets	1,105	863
Other long-term assets	162	142
Total	$ 5,045	$ 6,310

Our available-for-sale debt securities are classified as cash equivalents, short-term marketable securities and long-term marketable securities on our Condensed Consolidated Balance Sheets. See Note 4. Available-for-Sale Debt Securities for additional information.

Level 2 Inputs

We estimate the fair values of Level 2 instruments by taking into consideration valuations obtained from third-party pricing services. The pricing services utilize industry standard valuation models, including both income-based and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include reported trades of and broker/dealer quotes on the same or similar securities, issuer credit spreads, benchmark securities, prepayment/default projections based on historical data and other observable inputs.

Substantially all of our foreign currency derivative contracts have maturities within an 18-month time horizon and all are with counterparties that have a minimum credit rating of A- or equivalent by S&P Global Ratings, Moody's Investors Service, Inc. or Fitch Ratings, Inc. We estimate the fair values of these contracts by taking into consideration valuations obtained from a third-party valuation service that utilizes an income-based industry standard valuation model for which all significant inputs are observable, either directly or indirectly. These inputs include foreign currency exchange rates, London Interbank Offered Rates (LIBOR) and swap rates. These inputs, where applicable, are observable at commonly quoted intervals.

The total estimated fair values of our short-term and long-term debt, determined using Level 2 inputs based on their quoted market values, were approximately $27.3 billion and $27.1 billion as of March 31, 2019 and December 31, 2018, respectively, and the carrying values were $26.6 billion and $27.3 billion as of March 31, 2019 and December 31, 2018, respectively.

4. AVAILABLE-FOR-SALE DEBT SECURITIES

The following table summarizes our available-for-sale debt securities (in millions):

	March 31, 2019				December 31, 2018			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
U.S. treasury securities	$ 4,786	$ —	$ (4)	$ 4,782	$ 3,978	$ —	$ (9)	$ 3,969
Certificates of deposit	4,211	—	—	4,211	4,361	—	—	4,361
U.S. government agencies securities	1,446	—	(2)	1,444	943	—	(5)	938
Municipal debt securities	25	—	—	25	—	—	—	—
Non-U.S. government securities	453	—	(1)	452	307	—	(2)	305
Corporate debt securities	12,576	1	(12)	12,565	13,095	1	(29)	13,067
Residential mortgage and asset-backed securities	1,040	—	(4)	1,036	1,532	—	(8)	1,524
Total	$ 24,537	$ 1	$ (23)	$ 24,515	$ 24,216	$ 1	$ (53)	$ 24,164

The following table summarizes the classification of our available-for-sale debt securities in our Condensed Consolidated Balance Sheets (in millions):

	March 31, 2019	December 31, 2018
Cash and cash equivalents	$ 11,317	$ 10,592
Short-term marketable securities	10,977	12,149
Long-term marketable securities	2,221	1,423
Total	$ 24,515	$ 24,164

The following table summarizes our available-for-sale debt securities by contractual maturity (in millions):

	March 31, 2019	
	Amortized Cost	Fair Value
Within one year	$ 22,313	$ 22,294
After one year through five years	2,175	2,172
After five years through ten years	31	31
After ten years	18	18
Total	$ 24,537	$ 24,515

The following table summarizes our available-for-sale debt securities that were in a continuous unrealized loss position, but were not deemed to be other-than-temporarily impaired (in millions):

	Less Than 12 Months		12 Months or Greater		Total	
	Gross Unrealized Losses	Estimated Fair Value	Gross Unrealized Losses	Estimated Fair Value	Gross Unrealized Losses	Estimated Fair Value
March 31, 2019						
U.S. treasury securities	$ —	$ 2,971	$ (4)	$ 917	$ (4)	$ 3,888
U.S. government agencies securities	—	483	(2)	458	(2)	941
Non-U.S. government securities	—	100	(1)	160	(1)	260
Corporate debt securities	(1)	1,049	(11)	2,938	(12)	3,987
Residential mortgage and asset-backed securities	—	85	(4)	817	(4)	902
Total	$ (1)	$ 4,688	$ (22)	$ 5,290	$ (23)	$ 9,978
December 31, 2018						
U.S. treasury securities	$ —	$ 896	$ (9)	$ 1,383	$ (9)	$ 2,279
U.S. government agencies securities	—	30	(5)	553	(5)	583
Non-U.S. government securities	—	86	(2)	192	(2)	278
Corporate debt securities	(1)	1,600	(28)	4,204	(29)	5,804
Residential mortgage and asset-backed securities	—	192	(8)	1,186	(8)	1,378
Total	$ (1)	$ 2,804	$ (52)	$ 7,518	$ (53)	$ 10,322

We held a total of 915 and 1,348 positions, which were in an unrealized loss position, as of March 31, 2019 and December 31, 2018, respectively.

Based on our review of these securities, we believe we had no other-than-temporary impairments as of March 31, 2019 and December 31, 2018, because we do not intend to sell these securities nor do we believe that we will be required to sell these securities before the recovery of their amortized cost basis. Gross realized gains and gross realized losses were not material for the three months ended March 31, 2019 and 2018.

5. DERIVATIVE FINANCIAL INSTRUMENTS

Our operations in foreign countries expose us to market risk associated with foreign currency exchange rate fluctuations between the U.S. dollar and various foreign currencies, primarily the Euro. To manage this risk, we may hedge a portion of our foreign currency exposures related to outstanding monetary assets and liabilities as well as forecasted product sales using foreign currency exchange forward or option contracts. In general, the market risk related to these contracts is offset by corresponding gains and losses on the hedged transactions. The credit risk associated with these contracts is driven by changes in interest and currency exchange rates and, as a result, varies over time. By working only with major banks and closely monitoring current

market conditions, we seek to limit the risk that counterparties to these contracts may be unable to perform. We also seek to limit our risk of loss by entering into contracts that permit net settlement at maturity. Therefore, our overall risk of loss in the event of a counterparty default is limited to the amount of any unrecognized gains on outstanding contracts (i.e., those contracts that have a positive fair value) at the date of default. We do not enter into derivative contracts for trading purposes.

We hedge our exposure to foreign currency exchange rate fluctuations for certain monetary assets and liabilities of our entities that are denominated in a non-functional currency. The derivative instruments we use to hedge this exposure are not designated as hedges and, as a result, changes in their fair value are recorded in Other income (expense), net on our Condensed Consolidated Statements of Income.

We hedge our exposure to foreign currency exchange rate fluctuations for forecasted product sales that are denominated in a non-functional currency. The derivative instruments we use to hedge this exposure are designated as cash flow hedges and have maturities of 18 months or less. Upon executing a hedging contract and quarterly thereafter, we assess hedge effectiveness using regression analysis. The unrealized gains or losses in Accumulated other comprehensive income (AOCI) are reclassified into product sales when the respective hedged transactions affect earnings. The majority of gains and losses related to the hedged forecasted transactions reported in AOCI at March 31, 2019 are expected to be reclassified to product sales within 12 months.

The cash flow effects of our derivative contracts for the three months ended March 31, 2019 and 2018 were included within Net cash provided by operating activities on our Condensed Consolidated Statements of Cash Flows.

We had notional amounts on foreign currency exchange contracts outstanding of $2.5 billion and $2.2 billion at March 31, 2019 and December 31, 2018, respectively.

While all our derivative contracts allow us the right to offset assets and liabilities, we have presented amounts on a gross basis. The following table summarizes the classification and fair values of derivative instruments in our Condensed Consolidated Balance Sheets (in millions):

	March 31, 2019			
	Asset Derivatives		Liability Derivatives	
	Classification	Fair Value	Classification	Fair Value
Derivatives designated as hedges:				
Foreign currency exchange contracts	Other current assets	$ 74	Other accrued liabilities	$ (1)
Foreign currency exchange contracts	Other long-term assets	3	Other long-term obligations	—
Total derivatives designated as hedges		77		(1)
Derivatives not designated as hedges:				
Foreign currency exchange contracts	Other current assets	—	Other accrued liabilities	(1)
Total derivatives not designated as hedges		—		(1)
Total derivatives		$ 77		$ (2)

	December 31, 2018			
	Asset Derivatives		Liability Derivatives	
	Classification	Fair Value	Classification	Fair Value
Derivatives designated as hedges:				
Foreign currency exchange contracts	Other current assets	$ 73	Other accrued liabilities	$ (1)
Foreign currency exchange contracts	Other long-term assets	5	Other long-term obligations	—
Total derivatives designated as hedges		78		(1)
Derivatives not designated as hedges:				
Foreign currency exchange contracts	Other current assets	—	Other accrued liabilities	—
Total derivatives not designated as hedges		—		—
Total derivatives		$ 78		$ (1)

The following table summarizes the effect of our foreign currency exchange contracts on our Condensed Consolidated Financial Statements (in millions):

	Three Months Ended March 31,	
	2019	2018
Derivatives designated as hedges:		
Gains (losses) recognized in AOCI	$ 28	$ (61)
Gains (losses) reclassified from AOCI into product sales	29	(48)
Derivatives not designated as hedges:		
Losses recognized in Other income (expense), net	$ (6)	$ (14)

From time to time, we may discontinue cash flow hedges and, as a result, record related amounts in Other income (expense), net on our Condensed Consolidated Statements of Income. There were no material amounts recorded in Other income (expense), net on our Condensed Consolidated Statements of Income for the three months ended March 31, 2019 and 2018 as a result of the discontinuance of cash flow hedges.

As of March 31, 2019 and December 31, 2018, we only held foreign currency exchange contracts. The following table summarizes the potential effect of offsetting derivatives by type of financial instrument on our Condensed Consolidated Balance Sheets (in millions):

				Gross Amounts Not Offset on our Condensed Consolidated Balance Sheets		
Description	Gross Amounts of Recognized Assets/Liabilities	Gross Amounts Offset on our Condensed Consolidated Balance Sheets	Amounts of Assets/Liabilities Presented on our Condensed Consolidated Balance Sheets	Derivative Financial Instruments	Cash Collateral Received/ Pledged	Net Amount (Legal Offset)
As of March 31, 2019						
Derivative assets	$ 77	$ —	$ 77	$ (2)	$ —	$ 75
Derivative liabilities	(2)	—	(2)	2	—	—
As of December 31, 2018						
Derivative assets	$ 78	$ —	$ 78	$ (1)	$ —	$ 77
Derivative liabilities	(1)	—	(1)	1	—	—

6. COLLABORATIVE ARRANGEMENTS

We enter into collaborative arrangements with third parties for the development and commercialization of certain products and product candidates. These arrangements involve two or more parties who are active participants in the operating activities of the collaboration and are exposed to significant risks and rewards depending on the commercial success of the activities. These arrangements may include non-refundable up-front payments, payments by us for options to acquire certain rights, contingent obligations by us for potential development and regulatory milestone payments and/or sales-based milestone payments, royalty payments, revenue or profit-sharing arrangements, cost-sharing arrangements, equity investments, or a combination of these terms.

During the three months ended March 31, 2019, we entered into collaboration arrangements that resulted in cash payments of $165 million, of which $126 million was recorded as up-front collaboration expense within Research and development expenses on our Condensed Consolidated Statements of Income and the remaining balance was recorded in Prepaid and other current assets on our Condensed Consolidated Balance Sheets. During the three months ended March 31, 2018, the initial cash consideration related to collaborations and other arrangements was not material. We do not consider any of these collaboration arrangements to be individually material.

Under the financial terms of these arrangements, we may be required to make payments upon achievement of various developmental, regulatory and commercial milestones, which could be significant. In addition, we may be required to pay significant royalties on future sales if products related to these arrangements are commercialized. The payment of these amounts, however, is contingent upon the occurrence of various future events, which have a high degree of uncertainty of occurrence. Future milestone payments and royalties, if any, will be reflected on our Condensed Consolidated Statements of Income when the corresponding events become probable.

7. OTHER FINANCIAL INFORMATION

Inventories

The following table summarizes our inventories (in millions):

	March 31, 2019	December 31, 2018
Raw materials	$ 1,860	$ 1,888
Work in process	267	235
Finished goods	501	507
Total	$ 2,628	$ 2,630
Reported as:		
Inventories	$ 898	$ 814
Other long-term assets	1,730	1,816
Total	$ 2,628	$ 2,630

Amounts reported as other long-term assets primarily consisted of raw materials as of March 31, 2019 and December 31, 2018.

Other Accrued Liabilities

The following table summarizes the components of other accrued liabilities (in millions):

	March 31, 2019	December 31, 2018
Compensation and employee benefits	$ 325	$ 555
Accrued payment for marketing-related rights acquired from Japan Tobacco Inc.	185	365
Other accrued expenses	1,838	2,219
Total	$ 2,348	$ 3,139

8. INTANGIBLE ASSETS

The following table summarizes our intangible assets, net (in millions):

	March 31, 2019				December 31, 2018			
	Gross Carrying Amount	Accumulated Amortization	Foreign Currency Translation Adjustment	Net Carrying Amount	Gross Carrying Amount	Accumulated Amortization	Foreign Currency Translation Adjustment	Net Carrying Amount
Finite-lived assets:								
Intangible asset - sofosbuvir	$ 10,720	$ (3,729)	$ —	$ 6,991	$ 10,720	$ (3,554)	$ —	$ 7,166
Intangible asset - axicabtagene ciloleucel (DLBCL)	6,200	(502)	—	5,698	6,200	(416)	—	5,784
Intangible asset - Ranexa	688	(688)	—	—	688	(678)	—	10
Other	1,098	(387)	(4)	707	1,096	(359)	(3)	734
Total finite-lived assets	18,706	(5,306)	(4)	13,396	18,704	(5,007)	(3)	13,694
Indefinite-lived assets - In Process Research & Development	2,047	—	(5)	2,042	2,047	—	(3)	2,044
Total intangible assets	$ 20,753	$ (5,306)	$ (9)	$ 15,438	$ 20,751	$ (5,007)	$ (6)	$ 15,738

Aggregate amortization expense related to finite-lived intangible assets was $299 million and $301 million for the three months ended March 31, 2019 and 2018, respectively, and was primarily included in Cost of goods sold on our Condensed Consolidated Statements of Income.

The following table summarizes the estimated future amortization expense associated with our finite-lived intangible assets as of March 31, 2019 (in millions):

Fiscal Year	Amount
2019 (remaining nine months)	$ 851
2020	1,125
2021	1,125
2022	1,125
2023	1,125
Thereafter	8,045
Total	$ 13,396

9. DEBT AND CREDIT FACILITIES

The following table summarizes our borrowings under various financing arrangements (in millions):

				Carrying Amount	
Type of Borrowing	Issue Date	Due Date	Interest Rate	March 31, 2019	December 31, 2018
Senior Unsecured	September 2017	March 2019	3-month LIBOR + 0.22%	$ —	$ 750
Senior Unsecured	March 2014	April 2019	2.05%	500	500
Senior Unsecured	September 2017	September 2019	1.85%	999	999
Senior Unsecured	September 2017	September 2019	3-month LIBOR + 0.25%	500	499
Senior Unsecured	November 2014	February 2020	2.35%	499	499
Senior Unsecured	September 2015	September 2020	2.55%	1,997	1,996
Senior Unsecured	March 2011	April 2021	4.50%	997	997
Senior Unsecured	December 2011	December 2021	4.40%	1,247	1,247
Senior Unsecured	September 2016	March 2022	1.95%	498	498
Senior Unsecured	September 2015	September 2022	3.25%	997	997
Senior Unsecured	September 2016	September 2023	2.50%	746	746
Senior Unsecured	March 2014	April 2024	3.70%	1,744	1,744
Senior Unsecured	November 2014	February 2025	3.50%	1,745	1,745
Senior Unsecured	September 2015	March 2026	3.65%	2,732	2,731
Senior Unsecured	September 2016	March 2027	2.95%	1,245	1,245
Senior Unsecured	September 2015	September 2035	4.60%	990	990
Senior Unsecured	September 2016	September 2036	4.00%	740	740
Senior Unsecured	December 2011	December 2041	5.65%	995	995
Senior Unsecured	March 2014	April 2044	4.80%	1,734	1,734
Senior Unsecured	November 2014	February 2045	4.50%	1,731	1,730
Senior Unsecured	September 2015	March 2046	4.75%	2,217	2,216
Senior Unsecured	September 2016	March 2047	4.15%	1,725	1,724
Total debt, net				26,578	27,322
Less current portion				2,498	2,748
Total long-term debt, net				$ 24,080	$ 24,574

In March 2019, we repaid $750 million of our senior unsecured notes upon maturity that were issued in September 2017.

We are required to comply with certain covenants under our credit agreement and note indentures governing our senior notes. As of March 31, 2019, we were not in violation of any covenants. Additionally, as of March 31, 2019 and December 31, 2018, there were no amounts outstanding under our $2.5 billion five-year revolving credit facility agreement maturing in May 2021.

In April 2019, we repaid $500 million of our senior unsecured notes upon maturity that were issued in March 2014.

10. LEASES

We lease facilities and equipment primarily related to administrative, research and development, and sales and marketing activities under various non-cancelable operating leases in the United States and international markets. We determine if an arrangement contains a lease at inception. Right-of-use assets and lease liabilities are recognized at the commencement date based on the present value of the lease payments over the lease term, which is the non-cancelable period stated in the contract adjusted for any options to extend or terminate when it is reasonably certain that we will exercise that option. Some of our leases include options to extend the terms for up to 15 years and some include options to terminate the lease within one year after the lease commencement date. Right-of-use assets include any prepaid lease payments, and exclude lease incentives and initial direct costs incurred.

As of March 31, 2019, we do not have material finance leases. As most of our operating leases do not provide an implicit interest rate, we use a portfolio approach to determine a collateralized incremental borrowing rate based on the information available at the commencement date to determine the lease liability. Operating lease expense is recognized on a straight-line basis over the lease term. Operating lease expense was $36 million for the three months ended March 31, 2019.

The following table summarizes balance sheet and other information related to our operating leases as of March 31, 2019 (in millions, except weighted average data):

	Classification	Amount
Right-of-use assets, net	Other long-term assets	$ 455
Lease liabilities - current	Other accrued liabilities	$ 75
Lease liabilities - noncurrent	Other long-term obligations	$ 429
Weighted average remaining lease term		9.5 years
Weighted average discount rate		3.61%

The following table summarizes other supplemental information related to our operating leases (in millions):

	Three Months Ended March 31, 2019
Cash paid for amounts included in the measurement of lease liabilities	$ 18
Right-of-use assets obtained in exchange for lease liabilities	$ 30

The following table summarizes a maturity analysis of our operating lease liabilities showing the aggregate lease payments as of March 31, 2019 (in millions):

Fiscal Year	Amount
2019 (remaining nine months)	$ 69
2020	84
2021	72
2022	65
2023	57
Thereafter	257
Total undiscounted lease payments	604
Less: imputed interest	(100)
Total discounted lease payments	$ 504

The following table summarizes the aggregate undiscounted non-cancelable future minimum lease payments for operating leases under the prior leases standard as of December 31, 2018 (in millions):

Fiscal Year	Amount
2019	$ 89
2020	78
2021	66
2022	60
2023	52
Thereafter	229
Total minimum lease payments	$ 574

11. COMMITMENTS AND CONTINGENCIES

We are a party to various legal actions. The most significant of these are described below. We recognize accruals for such actions to the extent that we conclude that a loss is both probable and reasonably estimable. We accrue for the best estimate of a loss within a range; however, if no estimate in the range is better than any other, then we accrue the minimum amount in the range. If we determine that a loss is reasonably possible and the loss or range of loss can be estimated, we disclose the possible loss. Unless otherwise noted, it is not possible to determine the outcome of these matters, and we cannot reasonably estimate the maximum potential exposure or the range of possible loss.

We did not recognize any accruals for the actions described below in our Condensed Consolidated Balance Sheets as of March 31, 2019 and December 31, 2018, as we did not believe losses were probable.

Litigation Related to Sofosbuvir

In January 2012, we acquired Pharmasset, Inc. (Pharmasset). Through the acquisition, we acquired sofosbuvir, a nucleotide analog that acts to inhibit the replication of the hepatitis C virus (HCV). In December 2013, we received approval from U.S. Food and Drug Administration (FDA) for sofosbuvir, now known commercially as Sovaldi. Sofosbuvir is also included in all of our marketed HCV products. We have received a number of litigation claims regarding sofosbuvir. While we have carefully considered these claims both prior to and following the acquisition and believe they are without merit, we cannot predict the ultimate outcome of such claims or range of loss.

We are aware of patents and patent applications owned by third parties that have been or may in the future be alleged by such parties to cover the use of our HCV products. If third parties obtain valid and enforceable patents, and successfully prove infringement of those patents by our HCV products, we could be required to pay significant monetary damages. We cannot predict the ultimate outcome of intellectual property claims related to our HCV products. We have spent, and will continue to spend, significant resources defending against these claims.

Litigation with Idenix Pharmaceuticals, Inc. (Idenix), Universita Degli Studi di Cagliari (UDSG), Centre National de la Recherche Scientifique and L'Universite Montpellier II

In 2013, Idenix, UDSG, Centre National de la Recherche Scientifique and L'Université Montpellier II sued us in U.S. District Court for the District of Delaware alleging that the commercialization of sofosbuvir infringes U.S. Patent No. 7,608,600 (the '600 patent). Also in 2013, Idenix and UDSG sued us in the U.S. District Court for the District of Massachusetts alleging that the commercialization of sofosbuvir infringes U.S. Patent Nos. 6,914,054 (the '054 patent) and 7,608,597 (the '597 patent). In 2014, the court transferred the Massachusetts litigation to the U.S. District Court for the District of Delaware.

Prior to trial in 2016, Idenix committed to give us a covenant not to sue with respect to any claims arising out of the '054 patent related to sofosbuvir and withdrew that patent from the trial. A jury trial was held in 2016 on the '597 patent, and the jury found that we willfully infringed the asserted claims of the '597 patent and awarded Idenix $2.54 billion in past damages. In 2018, the judge invalidated Idenix's '597 patent and vacated the jury's award of $2.54 billion in past damages. Idenix appealed this decision to the U.S. Court of Appeals for the Federal Circuit (CAFC), and briefing is now complete. We believe the Delaware court's decision correctly found that, as a matter of law, the '597 patent is invalid, and we remain confident in the merits of our case on appeal. We believe that the possibility of a material adverse outcome on this matter is remote.

In 2014, the European Patent Office (EPO) granted Idenix's European Patent No. 1 523 489 (the '489 patent), which corresponds to the '600 patent. The same day that the '489 patent was granted, we filed an opposition with the EPO seeking to revoke the '489 patent. An opposition hearing was held in 2016, and the EPO ruled in our favor and revoked the '489 patent. Idenix has appealed. In 2014, Idenix also initiated infringement proceedings against us in Germany and France alleging that the

commercialization of Sovaldi would infringe the German and French counterparts of the '489 patent. In 2015, the German court in Düsseldorf determined that the Idenix patent was highly likely to be invalid and stayed the infringement proceedings pending the outcome of the opposition hearing held by the EPO in 2016. Idenix has not appealed this decision of the German court staying the proceedings. Upon Idenix's request, the French proceedings have been stayed.

Litigation with Merck & Co. Inc. (Merck)

In 2013, Merck contacted us requesting that we pay royalties on the sales of sofosbuvir and obtain a license to U.S. Patent No. 7,105,499 (the '499 patent) and U.S. Patent No. 8,481,712 (the '712 patent), which it co-owns with Ionis Pharmaceuticals, Inc. The '499 and '712 patents cover compounds which do not include, but may relate to, sofosbuvir. We filed a lawsuit in 2013 in the U.S. District Court for the Northern District of California seeking a declaratory judgment that the Merck patents are invalid and not infringed. Initially, in 2016, a jury determined that we had not established that Merck's patents are invalid and awarded Merck $200 million in damages. However, in 2016, the court ruled in our favor on our defense of unclean hands and determined that Merck may not recover any damages from us for the '499 and '712 patents.

In 2018, the CAFC affirmed the court's decision on unclean hands. In January 2019, the U.S. Supreme Court denied Merck's petition for review. In March 2019, the parties executed an agreement concerning the total amount that Merck should reimburse us for the court's award of attorney's fees, appellate fees and interest, and Merck paid us the agreed upon amount. Accordingly, this matter is now closed.

Litigation with the University of Minnesota

The University of Minnesota (the University) has obtained Patent No. 8,815,830 (the '830 patent), which purports to broadly cover nucleosides with antiviral and anticancer activity. In 2016, the University filed a lawsuit against us in the U.S. District Court for the District of Minnesota, alleging that the commercialization of sofosbuvir-containing products infringes the '830 patent. We believe the '830 patent is invalid and will not be infringed by the continued commercialization of sofosbuvir. In 2017, the court granted our motion to transfer the case to California. We have also filed four petitions for inter partes review with the USPTO Patent Trial and Appeal Board (PTAB) alleging that all asserted claims are invalid for anticipation and obviousness. In 2018, the District Court stayed the litigation until after the PTAB rules on our petitions for inter partes review.

Litigation Related to Axicabtagene Ciloleucel

We own patents and patent applications that claim axicabtagene ciloleucel chimeric DNA segments. Third parties may have, or may obtain rights to, patents that allegedly could be used to prevent or attempt to prevent us from commercializing axicabtagene ciloleucel or to require us to obtain a license in order to commercialize axicabtagene ciloleucel. For example, we are aware that Juno Therapeutics, Inc. (Juno) has exclusively licensed Patent No. 7,446,190 (the '190 patent), which was issued to Sloan Kettering Cancer Center. In September 2017, Juno and Sloan Kettering Cancer Center filed a lawsuit against Kite in the U.S. District Court for the Central District of California, alleging that the commercialization of axicabtagene ciloleucel infringes the '190 patent. In October 2017, following FDA approval for Yescarta, Juno filed a second complaint alleging that axicabtagene ciloleucel infringes the '190 patent. Juno subsequently moved to dismiss the September 2017 complaint and has maintained the October 2017 complaint. The court has set a trial date of December 2019 for this lawsuit.

We cannot predict the ultimate outcome of intellectual property claims related to axicabtagene ciloleucel. If Juno's patent is upheld as valid and Juno successfully proves infringement of that patent by axicabtagene ciloleucel, we could be required to pay significant monetary damages or we could be prevented from selling Yescarta unless we were able to obtain a license to this patent. Such a license may not be available on commercially reasonable terms or at all.

Litigation Related to Bictegravir

In 2018, ViiV Healthcare Company (ViiV) filed a lawsuit against us in the U.S. District Court of Delaware, alleging that the commercialization of bictegravir, sold commercially in combination with tenofovir alafenamide and emtricitabine as Biktarvy, infringes ViiV's U.S. Patent No. 8,129,385 (the '385 patent), which was issued to Shionogi & Co. Ltd. and GlaxoSmithKline LLC. The '385 patent is the compound patent covering ViiV's dolutegravir. Bictegravir is structurally different from dolutegravir, and we believe that bictegravir does not infringe the claims of the '385 patent. To the extent that ViiV's patent claims are interpreted to cover bictegravir, we believe those claims are invalid. The U.S. Patent and Trademark Office (USPTO) has granted us patents covering bictegravir. The court has set a trial date of September 2020 for this lawsuit.

In 2018, ViiV also filed a lawsuit against us in the Federal Court of Canada, alleging that our activities relating to our bictegravir compound have infringed ViiV's Canadian Patent No. 2,606,282 (the '282 patent), which was issued to Shionogi & Co. Ltd. and ViiV. The '282 patent is the compound patent covering ViiV's dolutegravir. We believe that bictegravir does not infringe the claims of the '282 patent. To the extent that ViiV's patent claims are interpreted to cover bictegravir, we believe those claims are invalid.

We cannot predict the ultimate outcome of intellectual property claims related to bictegravir. If ViiV's patents are upheld as valid and ViiV successfully proves infringement of those patents by bictegravir, we could be required to pay significant monetary damages.

Litigation with Generic Manufacturers

As part of the approval process for some of our products, FDA granted us a New Chemical Entity (NCE) exclusivity period during which other manufacturers' applications for approval of generic versions of our product will not be approved. Generic manufacturers may challenge the patents protecting products that have been granted NCE exclusivity one year prior to the end of the NCE exclusivity period. Generic manufacturers have sought and may continue to seek FDA approval for a similar or identical drug through an abbreviated new drug application (ANDA), the application form typically used by manufacturers seeking approval of a generic drug. The sale of generic versions of our products earlier than their patent expiration would have a significant negative effect on our revenues and results of operations. To seek approval for a generic version of a product having NCE status, a generic company may submit its ANDA to FDA four years after the branded product's approval.

Current legal proceedings of significance with generic manufacturers include:

HIV Products

In 2018, we received notice that Zydus Pharmaceuticals (USA) Inc. (Zydus) submitted an ANDA to FDA requesting permission to manufacture and market generic versions of Truvada at various dosage strengths. In the notice, Zydus alleges that two patents associated with emtricitabine and four patents associated with the emtricitabine and tenofovir disoproxil fumarate fixed-dose combination are invalid, unenforceable and/or will not be infringed by Zydus' manufacture, use or sale of generic versions of Truvada at various dosage strengths. In response, we filed a lawsuit against Zydus in the U.S. District Court for the District of New Jersey for infringement of our patents.

In 2018, we received notice that Mylan Pharmaceuticals Inc. (Mylan) submitted an ANDA to FDA requesting permission to manufacture and market a generic version of Stribild. In the notice, Mylan alleges that one patent owned by Japan Tobacco Inc. (JT) and associated with elvitegravir is invalid, unenforceable and/or will not be infringed by Mylan's manufacture, use or sale of a generic version of Stribild. In 2019, JT filed a lawsuit against Mylan in the U.S. District Court for the Northern District of West Virginia for infringement of its patent.

HCV Products

In 2018, we received notices from Natco Pharma Limited (Natco) and Teva Pharmaceuticals (Teva) that they have each submitted an ANDA to FDA requesting permission to manufacture and market a generic version of Sovaldi. In Teva's notice, it alleges that nine patents associated with sofosbuvir are invalid, unenforceable and/or will not be infringed by Teva's manufacture, use or sale of generic versions of Sovaldi. In response, we filed lawsuits against Teva in the U.S. District Court for the District of New Jersey and the U.S. District Court for the District of Delaware for infringement of these patents. In Natco's notice, it alleges that two patents associated with sofosbuvir are invalid, unenforceable and/or will not be infringed by Natco's manufacture, use or sale of generic versions of Sovaldi. Natco did not challenge all patents listed on the Orange Book for Sovaldi. We also filed lawsuits against Natco in the U.S. District Court for the District of New Jersey and the U.S. District Court for the District of Delaware for infringement of these patents. In 2018, we reached an agreement with Teva to resolve the lawsuit, which has been dismissed. The settlement agreement has been filed with the Federal Trade Commission and Department of Justice as required by law.

European Patent Claims

In 2015, several parties filed oppositions in the EPO requesting revocation of one of our granted European patents covering sofosbuvir that expires in 2028. In 2016, the EPO upheld the validity of certain claims of our sofosbuvir patent. We have appealed this decision, seeking to restore all of the original claims, and several of the original opposing parties have also appealed, requesting full revocation. The appeal process may take several years.

In 2017, several parties filed oppositions in the EPO requesting revocation of our granted European patent relating to sofosbuvir that expires in 2024. The EPO conducted an oral hearing for this opposition in 2018 and upheld the claims. Two of the original opposing parties have appealed, requesting full revocation. The appeal process may take several years.

In 2016, several parties filed oppositions in the EPO requesting revocation of our granted European patent covering TAF that expires in 2021. In 2017, the EPO upheld the validity of the claims of our TAF patent. Three parties have appealed this decision. The appeal process may take several years.

In 2017, several parties filed oppositions in the EPO requesting revocation of our granted European patent relating to TAF hemifumarate that expires in 2032. We responded to these oppositions, and a hearing was held in February 2019. The patent was upheld at this hearing. The opposing parties may choose to appeal this decision, which could take several years to conclude.

In 2016, three parties filed oppositions in the EPO requesting revocation of our granted European patent covering cobicistat that expires in 2027. In 2017, the EPO upheld the validity of the claims of our cobicistat patent. One of the original opposing parties has appealed this decision. The appeal process may take several years.

While we are confident in the strength of our patents, we cannot predict the ultimate outcome of these oppositions. If we are unsuccessful in defending these oppositions, some or all of our patent claims may be narrowed or revoked and the patent protection for sofosbuvir, TAF and cobicistat in the European Union could be substantially shortened or eliminated entirely. If our patents are revoked, and no other European patents are granted covering these compounds, our exclusivity may be based entirely on regulatory exclusivity granted by the European Medicines Agency. If we lose patent protection for any of these compounds, our revenues and results of operations could be negatively impacted for the years including and succeeding the year in which such exclusivity is lost, which may cause our stock price to decline.

Government Investigations and Related Litigation

In 2011, we received a subpoena from the U.S. Attorney's Office for the Northern District of California requesting documents related to the manufacture, and related quality and distribution practices, of Complera, Atripla, Truvada, Viread, Emtriva, Hepsera and Letairis. We cooperated with the government's inquiry. In 2014, the U.S. Department of Justice informed us that, following an investigation, it declined to intervene in a False Claims Act lawsuit filed by two former employees. Also in 2014, the former employees served a First Amended Complaint, and the U.S. District Court for the Northern District of California issued an order granting in its entirety, without prejudice, our motion to dismiss the First Amended Complaint. In 2015, the plaintiffs filed a Second Amended Complaint, and the District Court issued an order granting our motion to dismiss the Second Amended Complaint. The plaintiffs then filed a notice of appeal in the U.S. Court of Appeals for the Ninth Circuit. In 2017, the Ninth Circuit granted our motion to stay the case pending an appeal to the U.S. Supreme Court, and we filed a Petition for a Writ of Certiorari to the U.S. Supreme Court. In 2018, the Solicitor General submitted a brief for the United States to the Supreme Court stating its intention to file a motion to dismiss under the federal False Claims Act. In January 2019, the Supreme Court denied the Petition and the case has been remanded to the District Court. In March 2019, the Department of Justice filed a motion to dismiss the Second Amended Complaint, which the District Court is expected to rule upon later this year.

In 2016, we received a subpoena from the U.S. Attorney's Office for the District of Massachusetts requesting documents related to our support of 501(c)(3) organizations that provide financial assistance to patients and documents concerning our provision of financial assistance to patients for our HCV products. We are cooperating with this inquiry. In 2017, we received a subpoena from the U.S. Attorney's Office for the District of Massachusetts requesting documents related to our copay coupon program and Medicaid price reporting methodology. We are cooperating with this inquiry.

In 2017, we received a voluntary request for information from the U.S. Attorney's Office for the Eastern District of Pennsylvania requesting information related to our reimbursement support offerings, clinical education programs and interactions with specialty pharmacies for Sovaldi and Harvoni. In 2018, we received another voluntary request for information related to our speaker programs and advisory boards for our HCV and hepatitis B virus (HBV) products. We are cooperating with these voluntary requests.

In 2017, we received a subpoena from the California Department of Insurance and the Alameda County District Attorney's Office requesting documents related to our marketing activities, reimbursement support offerings, clinical education programs and interactions with specialty pharmacies for Harvoni and Sovaldi. We are cooperating with this inquiry.

In 2017, we received a subpoena from the U.S. Department of Health and Human Services requesting documents related to our Frontlines of Communities in the United States (FOCUS) program. We cooperated with the inquiry, and in February 2019, the government informed us that it declined to intervene in the False Claims Act qui tam lawsuit related to the inquiry. In March 2019, the relator filed a voluntary dismissal of the qui tam lawsuit without prejudice as to all claims.

In 2017, we also received a subpoena from the U.S. Attorney's Office for the Southern District of New York requesting documents related to our promotional speaker programs for HIV. We are cooperating with this inquiry.

Product Liability

We have been named as a defendant in one class action lawsuit filed in 2018 and various product liability lawsuits related to Viread, Truvada, Atripla, Complera and Stribild. Plaintiffs allege that Viread, Truvada, Atripla, Complera and/or Stribild caused them to suffer kidney and/or bone injuries. The lawsuits, all of which are pending in state or federal court in California, involve hundreds of plaintiffs. Plaintiffs in these cases seek damages and other relief on various grounds for alleged personal injury and economic loss. We intend to vigorously defend ourselves in these actions. While we believe these cases are without merit, we cannot predict the ultimate outcome. If plaintiffs are successful in their claims, we could be required to pay significant monetary damages.

Other Matters

We are a party to various legal actions that arose in the ordinary course of our business. We do not believe that these other legal actions will have a material adverse impact on our consolidated business, financial position or results of operations.

12. STOCKHOLDERS' EQUITY

Stock Repurchase Program

In the first quarter of 2016, our Board of Directors authorized a $12.0 billion stock repurchase program (2016 Program) under which repurchases may be made in the open market or in privately negotiated transactions. We started repurchases under the 2016 Program in April 2016.

During the three months ended March 31, 2019 and 2018, we repurchased and retired 12 million and 13 million shares of our common stock for $834 million and $1.0 billion, respectively, through open market transactions under the 2016 Program. As of March 31, 2019, the remaining authorized repurchase amount under the 2016 Program was $4.3 billion.

Accumulated Other Comprehensive Income (Loss)

The following table summarizes the changes in AOCI by component, net of tax during the three months ended March 31, 2019 and 2018 (in millions):

	Foreign Currency Translation	Unrealized Gains and Losses on Available-for-Sale Debt Securities	Unrealized Gains and Losses on Cash Flow Hedges	Total
Balance at December 31, 2018	$ 47	$ (52)	$ 85	$ 80
Net unrealized gain	21	30	28	79
Reclassifications to net income	—	—	(29)	(29)
Net current period other comprehensive income (loss)	21	30	(1)	50
Balance at March 31, 2019	$ 68	$ (22)	$ 84	$ 130

	Foreign Currency Translation	Unrealized Gains and Losses on Available-for-Sale Debt Securities	Unrealized Gains and Losses on Cash Flow Hedges	Total
Balance at December 31, 2017	$ 85	$ 194	$ (114)	$ 165
Reclassifications to retained earnings as a result of the adoption of new accounting standards	—	(293)	—	(293)
Balance at January 1, 2018	85	(99)	(114)	(128)
Net unrealized gain (loss)	7	(36)	(61)	(90)
Reclassifications to net income	—	—	48	48
Net current period other comprehensive income (loss)	7	(36)	(13)	(42)
Balance at March 31, 2018	$ 92	$ (135)	$ (127)	$ (170)

The amounts reclassified to net income for gains and losses on cash flow hedges are recorded as part of Product sales on our Condensed Consolidated Statements of Income. See Note 5. Derivative Financial Instruments for additional information. The amounts reclassified to net income for gains and losses on available-for-sale debt securities are recorded as part of Other income (expense), net on our Condensed Consolidated Statements of Income. The income tax impact allocated to each component of other comprehensive income was not material for any period presented.

13. NET INCOME PER SHARE ATTRIBUTABLE TO GILEAD COMMON STOCKHOLDERS

Basic net income per share attributable to Gilead common stockholders is calculated based on the weighted-average number of shares of our common stock outstanding during the period. Diluted net income per share attributable to Gilead common stockholders is calculated based on the weighted-average number of shares of our common stock and other dilutive securities outstanding during the period. The potentially dilutive shares of our common stock resulting from the assumed exercise of outstanding stock options and equivalents were determined under the treasury stock method.

Potential shares of common stock excluded from the computation of diluted net income per share attributable to Gilead common stockholders because their effect would have been antidilutive were 16 million and 12 million shares for the three months ended March 31, 2019 and 2018, respectively.

The following table summarizes the calculation of basic and diluted net income per share attributable to Gilead common stockholders (in millions, except per share amounts):

	Three Months Ended March 31,	
	2019	2018
Net income attributable to Gilead	$ 1,975	$ 1,538
Shares used in per share calculation - basic	1,276	1,307
Dilutive effect of stock options and equivalents	7	13
Shares used in per share calculation - diluted	1,283	1,320
Net income per share attributable to Gilead common stockholders - basic	$ 1.55	$ 1.18
Net income per share attributable to Gilead common stockholders - diluted	$ 1.54	$ 1.17

14. SEGMENT INFORMATION

We have one operating segment, which primarily focuses on the discovery, development and commercialization of innovative medicines in areas of unmet medical need. Therefore, our results of operations are reported on a consolidated basis consistent with internal management reporting reviewed by our chief operating decision maker, who is our chief executive officer.

See Note 2. Revenues for a summary of disaggregated revenues by product and geographic region.

The following table summarizes revenues from each of our customers who individually accounted for 10% or more of our total revenues (as a percentage of total revenues):

	Three Months Ended March 31,	
	2019	2018
AmerisourceBergen Corp.	21%	21%
Cardinal Health, Inc.	20%	21%
McKesson Corp.	20%	20%

15. INCOME TAXES

Our effective tax rate of 16.3% for the three months ended March 31, 2019 differed from the U.S. federal statutory rate of 21% primarily due to a $119 million tax benefit related to settlements with taxing authorities and earnings from non-U.S. subsidiaries that operate in jurisdictions with lower tax rates than the United States, partially offset by the tax on Global Intangible Low-Taxed Income, state taxes and our portion of the non-tax deductible branded prescription drug fee.

Our effective tax rate of 24.3% for the three months ended March 31, 2018 differed from the U.S. federal statutory rate of 21% primarily due to a $49 million tax expense related to a settlement of a foreign tax examination, state taxes and our portion of the non-tax deductible branded prescription drug fee, partially offset by earnings from non-U.S. subsidiaries that operate in jurisdictions with lower tax rates than the United States.

We file federal, state and foreign income tax returns in the United States and in many foreign jurisdictions. For federal and California income tax purposes, the statute of limitations is open for 2013 and 2010 onwards, respectively. Our income tax returns are subject to audit by federal, state and foreign tax authorities. We are currently under examination by the IRS for the tax years from 2013 to 2015 and by various state and foreign jurisdictions. There are differing interpretations of tax laws and regulations, and as a result, significant disputes may arise with these tax authorities involving issues of the timing and amount of deductions and allocations of income among various tax jurisdictions. We regularly evaluate our exposures associated with our tax filing positions.

We record liabilities related to uncertain tax positions in accordance with the income tax guidance which clarifies the accounting for uncertainty in income taxes recognized in an enterprise's financial statements by prescribing a minimum recognition threshold and measurement attribute for the financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. Resolution of one or more of these uncertain tax positions in any period may have a material impact on the results of operations for that period.

Our unrecognized tax benefits decreased by $119 million during the three months ended March 31, 2019 due to settlements with taxing authorities. As of March 31, 2019, we do not believe that it is reasonably possible that our unrecognized tax benefits will materially increase or decrease in the next 12 months.

Item 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

This Quarterly Report on Form 10-Q contains forward-looking statements regarding future events and our future results that are subject to the safe harbors created under the Securities Act of 1933, as amended, and the Securities Exchange Act of 1934, as amended. The forward-looking statements are contained principally in this section entitled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Risk Factors." Words such as "expect," "anticipate," "target," "goal," "project," "hope," "intend," "plan," "believe," "seek," "estimate," "continue," "may," "could," "should," "might," variations of such words and similar expressions are intended to identify such forward-looking statements. In addition, any statements other than statements of historical fact are forward-looking statements, including statements regarding overall trends, operating cost and revenue trends, liquidity and capital needs and other statements of expectations, beliefs, future plans and strategies, anticipated events or trends and similar expressions. We have based these forward-looking statements on our current expectations about future events. These statements are not guarantees of future performance and involve risks, uncertainties and assumptions that are difficult to predict. Our actual results may differ materially from those suggested by these forward-looking statements for various reasons, including those identified below under "Risk Factors." Given these risks and uncertainties, you are cautioned not to place undue reliance on forward-looking statements. The forward-looking statements included in this report are made only as of the date hereof. Except as required under federal securities laws and the rules and regulations of the Securities and Exchange Commission (SEC), we do not undertake and specifically decline any obligation to update any of these statements or to publicly announce the results of any revisions to any forward-looking statements after the distribution of this report, whether as a result of new information, future events, changes in assumptions or otherwise. In evaluating our business, you should carefully consider the risks described in the section entitled "Risk Factors" under Part II, Item 1A in addition to the other information in this Quarterly Report on Form 10-Q. Any of the risks contained herein could materially and adversely affect our business, results of operations and financial condition.

You should read the following management's discussion and analysis of our financial condition and results of operations in conjunction with our audited Consolidated Financial Statements and related notes thereto included as part of our Annual Report on Form 10-K for the year ended December 31, 2018 and our unaudited Condensed Consolidated Financial Statements for the three months ended March 31, 2019 and other disclosures (including the disclosures under Part II, Item 1A, "Risk Factors") included in this Quarterly Report on Form 10-Q. Our Condensed Consolidated Financial Statements have been prepared in accordance with U.S. generally accepted accounting principles and are presented in U.S. dollars.

Management Overview

Gilead Sciences, Inc. (Gilead, we, our or us), incorporated in Delaware on June 22, 1987, is a research-based biopharmaceutical company that discovers, develops and commercializes innovative medicines in areas of unmet medical need. With each new discovery and investigational drug candidate, we strive to transform and simplify care for people with life-threatening illnesses around the world. We have operations in more than 35 countries worldwide, with headquarters in Foster City, California. Gilead's primary areas of focus include HIV/AIDS, liver diseases, hematology/oncology and inflammation/respiratory diseases. We seek to add to our existing portfolio of products through our internal discovery and clinical development programs, product acquisition, in-licensing and strategic collaborations.

Our portfolio of marketed products includes AmBisome®, Atripla®, Biktarvy®, Cayston®, Complera®/Eviplera®, Descovy®, Emtriva®, Epclusa®, Genvoya®, Harvoni®, Hepsera®, Letairis®, Odefsey®, Ranexa®, Sovaldi®, Stribild®, Truvada®, Tybost®, Vemlidy®, Viread®, Vosevi®, Yescarta® and Zydelig®. We sell and distribute authorized generic versions of Epclusa and Harvoni in the United States through our separate subsidiary, Asegua Therapeutics LLC. In addition, we sell and distribute certain products through our corporate partners under collaborative agreements.

Business Highlights

During the first quarter of 2019, we continued to advance our product pipeline across our therapeutic areas with the goal of delivering best-in-class drugs that advance the current standard of care and/or address unmet medical need. Recent key announcements include:

HIV and Liver Diseases Programs

- We announced that STELLAR-3, a Phase 3 study evaluating the safety and efficacy of selonsertib, an investigational, once daily, oral inhibitor of apoptosis signal-regulating kinase 1 (ASK1), for patients with bridging fibrosis (F3) due to nonalcoholic steatohepatitis (NASH), did not meet the pre-specified week 48 primary endpoint of a ≥ 1-stage histologic improvement in fibrosis without worsening of NASH.
- We entered into a strategic collaboration with Insitro, Inc. to discover and develop therapies for patients with NASH.

- We announced the intent to collaborate with Novo Nordisk A/S (Novo Nordisk) on a clinical trial combining compounds from our respective pipelines in NASH. The intended clinical trial will be a proof of concept study combining Novo Nordisk's semaglutide and our cilofexor and firsocostat for the treatment of patients with NASH.
- We submitted a supplemental new drug application to FDA for Descovy for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection among individuals who are HIV-negative and at risk for HIV. A priority review voucher was submitted with the filing, leading to an anticipated review time of six months.
- Japan's Ministry of Health, Labour and Welfare (MHLW) approved Biktarvy for the treatment of HIV-1 infection.
- Japan's MHLW approved Epclusa for adults with chronic HCV infection with decompensated cirrhosis and for patients with chronic HCV infection without cirrhosis or with compensated cirrhosis who have had prior treatment with a direct-acting antiviral therapy.
- We entered into a licensing and collaboration agreement with Yuhan Corporation to co-develop novel therapeutic candidates for the treatment of advanced fibrosis due to NASH.

Oncology and Cell Therapy Programs

- We announced plans for a new facility in Maryland to expand cell therapy production capabilities.

Inflammation Programs

- We announced week 24 results of FINCH 1, an ongoing, randomized, double-blind, placebo- and active-controlled Phase 3 study of filgotinib, an investigational, oral, selective JAK1 inhibitor, in adults with moderately-to-severely active rheumatoid arthritis (RA). FINCH 1 evaluated filgotinib versus adalimumab or placebo, on a stable background dose of methotrexate (MTX) in patients with prior inadequate response to MTX. The study achieved its primary endpoint for both doses of filgotinib in the proportion of patients achieving an American College of Rheumatology 20% response (ACR20) compared to placebo at week 12.
- We announced week 24 results of FINCH 3, an ongoing, randomized, double-blind, active-controlled Phase 3 study of filgotinib in adults with moderately-to-severely active RA. FINCH 3 evaluated filgotinib in combination with MTX and as monotherapy in MTX-naïve patients. The study achieved its primary endpoint in the proportion of patients achieving an ACR20 response at week 24. The proportion of patients achieving the primary endpoint of ACR20 response at week 24 was significantly higher for filgotinib 200 mg plus MTX and filgotinib 100 mg plus MTX compared with MTX alone.
- We announced interim safety information from four studies of filgotinib for the treatment of RA. The data include 24 week results of the ongoing Phase 3 FINCH 1, 2 and 3 trials and updated week 156 safety data from the Phase 2b DARWIN 3 long-term extension study in patients with RA.

Financial Highlights

Total revenues increased by 4% to $5.3 billion for the first quarter of 2019, compared to $5.1 billion for the same period in 2018, primarily due to higher product sales, which were $5.2 billion compared to $5.0 billion for the same period in 2018.

Research and development (R&D) expenses increased by 13% to $1.1 billion for the first quarter of 2019, compared to $937 million for the same period in 2018, primarily due to up-front collaboration expenses and higher investments to support our cell therapy programs partially offset by lower stock-based compensation expense. Stock-based compensation expense was higher for the first quarter of 2018 following the acquisition of Kite Pharma, Inc. (Kite).

Selling, general and administrative (SG&A) expenses increased by 3% to $1,030 million for the first quarter of 2019, compared to $997 million for the same period in 2018, primarily due to higher promotional expenses in the United States and expenses associated with the expansion of our products in Europe and Japan, partially offset by lower stock-based compensation expense. Stock-based compensation expense was higher for the first quarter of 2018 following the acquisition of Kite.

Net income attributable to Gilead was $2.0 billion or $1.54 per diluted share for the first quarter of 2019, compared to $1.5 billion or $1.17 per diluted share for the same period in 2018, primarily due to higher product sales and higher net unrealized gains from changes in the fair value of our equity securities.

As of March 31, 2019, we had $30.1 billion of cash, cash equivalents and marketable debt securities compared to $31.5 billion as of December 31, 2018. During the first quarter of 2019, we generated $1.4 billion in operating cash flow, repaid $750 million of debt, paid cash dividends of $817 million and repurchased 12 million shares of our common stock for $834 million through open market transactions.

Results of Operations

Total Revenues

The following table summarizes the period-over-period changes in our product sales and royalty, contract and other revenues:

(In millions, except percentages)	Three Months Ended March 31, 2019	2018	Change
Revenues:			
Product sales	$ 5,200	$ 5,001	4 %
Royalty, contract and other revenues	81	87	(7)%
Total revenues	$ 5,281	$ 5,088	4 %

Product sales for the three months ended March 31, 2019

Total product sales increased by 4% to $5.2 billion for the three months ended March 31, 2019, compared to $5.0 billion for the same period in 2018, primarily due to higher HIV product sales, partially offset by lower HCV product sales.

HIV product sales increased by 14% to $3.6 billion for the three months ended March 31, 2019, compared to $3.2 billion for the same period in 2018, driven by higher sales volume as a result of the continued uptake of Biktarvy, partially offset by lower average net selling prices and decreases in sales volume of our Truvada (emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF))-based products.

HCV product sales decreased by 24% to $790 million for the three months ended March 31, 2019, compared to $1.0 billion for the same period in 2018, primarily due to lower patient starts and competitive dynamics, including a decline in average net selling price in U.S. Medicare in 2019.

Yescarta, which was approved in the United States in October 2017 and in Europe in August 2018, generated $96 million in sales during the three months ended March 31, 2019, compared to $40 million for the same period in 2018. The increase was driven by an increase in the number of therapies provided to patients.

Other product sales, which include products from our HBV, cardiovascular, oncology and other categories inclusive of Vemlidy, Viread, Letairis, Ranexa, Zydelig and AmBisome, decreased by 7% to $696 million for the three months ended March 31, 2019, compared to $745 million for the same period in 2018. The decrease was primarily due to the expected decline in Ranexa sales after the entry of generic versions of Ranexa in the United States in the first quarter of 2019. Letairis is expected to face competition from generic versions of Letairis in the United States starting in the second quarter of 2019. We expect a decline in our Letairis sales in the United States after the entry of generic versions.

Of our total product sales, 27% and 29% were generated outside the United States during the three months ended March 31, 2019 and 2018, respectively. We faced exposure to movements in foreign currency exchange rates, primarily in the Euro. We used foreign currency exchange contracts to hedge a portion of our foreign currency exposure. Foreign currency exchange, net of hedges, had an immaterial impact on our product sales for the three months ended March 31, 2019, based on a comparison using foreign currency exchange rates from the three months ended March 31, 2018.

Product sales in the United States increased by 8% to $3.8 billion for the three months ended March 31, 2019, compared to $3.5 billion for the same period in 2018. The increase was primarily due to higher sales of our HIV products, partially offset by lower sales of HCV products. The increase in sales of our HIV products was primarily due to the continued uptake of Biktarvy and increased usage of Truvada for PrEP, partially offset by lower average net selling price and decreases in sales volume of Genvoya, Atripla, Stribild, Descovy and Complera. The decrease in sales of our HCV products was due to lower average net selling price, including a decline in average net selling price in U.S. Medicare in 2019, and lower sales volume as a result of fewer patient starts.

Product sales in Europe decreased by 12% to $882 million for the three months ended March 31, 2019, compared to $1.0 billion for the same period in 2018. The decrease was primarily due to lower sales of our HCV products and the broader availability of generic versions of Truvada, Atripla and Viread. The decrease in sales of our HCV products was primarily due to lower average net selling price as a result of increased competition and lower patient starts. The decrease was partially offset by the continued uptake of Biktarvy and Odefsey. Foreign currency exchange, net of hedges, had an immaterial impact on our product sales in Europe for the three months ended March 31, 2019.

Product sales in other locations increased by 11% to $522 million for the three months ended March 31, 2019, compared to $469 million for the same period in 2018, primarily due to higher HIV product sales in Japan as a result of acquiring the rights to certain products in our HIV portfolio in Japan effective January 1, 2019.

The following table summarizes the period-over-period changes in our product sales by product:

(In millions, except percentages)	Three Months Ended March 31, 2019	2018	Change
Atripla	$ 171	$ 314	(46)%
Biktarvy	793	35	*
Complera/Eviplera	115	190	(39)%
Descovy	342	361	(5)%
Genvoya	1,015	1,082	(6)%
Odefsey	397	342	16 %
Stribild	96	174	(45)%
Truvada	606	652	(7)%
Other HIV(1)	17	13	31 %
Revenue share - Symtuza(2)	66	7	*
Total HIV	3,618	3,170	14 %
AmBisome	93	107	(13)%
Ledipasvir/Sofosbuvir(3)	225	348	(35)%
Letairis	197	204	(3)%
Ranexa	155	195	(21)%
Sofosbuvir/Velpatasvir(4)	491	536	(8)%
Vemlidy	101	58	74 %
Viread	72	97	(26)%
Vosevi	63	107	(41)%
Yescarta	96	40	*
Zydelig	27	33	(18)%
Other(5)	62	106	(42)%
Total product sales	$ 5,200	$ 5,001	4 %

* Percentage is greater than 100%

(1) Includes Emtriva and Tybost

(2) Represents our revenue from cobicistat (C), FTC and tenofovir alafenamide (TAF) in Symtuza (darunavir/C/FTC/TAF), a fixed dose combination product commercialized by Janssen Sciences Ireland UC

(3) Amounts consist of sales of Harvoni and the authorized generic version of Harvoni sold by our separate subsidiary, Asegua Therapeutics LLC

(4) Amounts consist of sales of Epclusa and the authorized generic version of Epclusa sold by our separate subsidiary, Asegua Therapeutics LLC

(5) Includes Cayston, Hepsera and Sovaldi

The following is additional discussion of our results on certain products:

- *Descovy (FTC/TAF)-based products - Biktarvy, Descovy, Genvoya, Odefsey and Revenue Share - Symtuza*

  Product sales of our Descovy (FTC/TAF)-based products were $2.6 billion and $1.8 billion and were 50% and 37% of our total product sales and were 72% and 58% of total HIV product sales for the three months ended March 31, 2019 and 2018, respectively.

  For the three months ended March 31, 2019, sales of our Descovy (FTC/TAF)-based products were $2.0 billion in the United States, $439 million in Europe and $150 million in other locations, compared to $1.4 billion in the United States, $326 million in Europe and $60 million in other locations for the same period in 2018. In the United States, the increase was primarily due to higher sales volume as a result of the continued uptake of Biktarvy, partially offset by lower average net selling prices. In Europe, the increase was primarily due to higher sales volume as a result of the continued uptake of Odefsey and Biktarvy.

- *Truvada (FTC/TDF)-based products - Atripla, Complera/Eviplera, Stribild and Truvada*

  Product sales of our Truvada (FTC/TDF)-based products were $988 million and $1.3 billion and were 19% and 27% of our total product sales for the three months ended March 31, 2019 and 2018, respectively.

  For the three months ended March 31, 2019, sales of our Truvada (FTC/TDF)-based products were $795 million in the United States, $129 million in Europe and $64 million in other locations, compared to $935 million in the United States, $286 million in Europe and $109 million in other locations for the same period in 2018. In the United States, the decrease was primarily due to lower sales volume as a result of patients switching to newer regimens containing TAF, partially offset by the increased usage of Truvada for PrEP. In Europe, the decrease was primarily due to lower sales volume as a result of the broader availability of generic versions of Truvada and Atripla and patients switching to newer regimens containing TAF.

- *HCV products - Epclusa, Harvoni, Sovaldi, Vosevi and Authorized Generics of Epclusa and Harvoni*

  HCV product sales were $790 million and $1.0 billion, and were 15% and 21% of our total product sales for the three months ended March 31, 2019 and 2018, respectively.

  For the three months ended March 31, 2019, sales of our HCV products were $393 million in the United States, $203 million in Europe and $194 million in other locations. For the three months ended March 31, 2018, sales of our HCV products were $584 million in the United States, $271 million in Europe and $191 million in other locations.

  In the United States, the decrease was due to lower average net selling price, including a decline in average net selling price in U.S. Medicare in 2019, and lower sales volume as a result of a decrease in market share and fewer patient starts. In Europe, the decrease was primarily due to lower average net selling price as a result of increased competition and lower patient starts.

Cost of Goods Sold and Product Gross Margin

The following table summarizes the period-over-period changes in our cost of goods sold and product gross margin:

	Three Months Ended March 31,		
(In millions, except percentages)	**2019**	**2018**	**Change**
Total product sales	$ 5,200	$ 5,001	4 %
Cost of goods sold	$ 957	$ 1,001	(4)%
Product gross margin	82%	80%	2 %

The decrease in cost of goods sold was primarily due to lower fees paid to Bristol-Myers Squibb Company (BMS) for the net sales of Atripla.

The increase in product gross margin was primarily due to Biktarvy growth, overall HIV product mix and the factor noted above.

Research and Development Expenses

The following table summarizes the period-over-period changes in our R&D expenses:

	Three Months Ended March 31,		
(In millions, except percentages)	**2019**	**2018**	**Change**
Research and development expenses	$ 1,057	$ 937	13%

R&D expenses consist primarily of clinical studies performed by contract research organizations, materials and supplies, licenses and fees, up-front and milestone payments under collaboration agreements, personnel costs, including salaries, benefits and stock-based compensation, and overhead allocations consisting of various support and facilities-related costs.

We do not track total R&D expenses by product candidate, therapeutic area or development phase. However, we manage our R&D expenses by identifying the R&D activities we anticipate will be performed during a given period and then prioritizing efforts based on scientific data, probability of successful development, market potential, available human and capital resources and other considerations. We continually review our R&D pipeline and the status of development and, as necessary, reallocate resources among the R&D portfolio that we believe will best support the future growth of our business.

R&D expenses for the three months ended March 31, 2019 increased by $120 million, or 13%, compared to the same period in 2018, primarily due to $126 million of up-front collaboration expenses and higher investments to support our cell therapy

programs, partially offset by lower stock-based compensation expense. Stock-based compensation expense was $42 million higher for the three months ended March 31, 2018 following the acquisition of Kite.

Selling, General and Administrative Expenses

The following table summarizes the period-over-period changes in our SG&A expenses:

	Three Months Ended March 31,		
(In millions, except percentages)	**2019**	**2018**	**Change**
Selling, general and administrative expenses	$ 1,030	$ 997	3%

SG&A expenses relate to sales and marketing, finance, human resources, legal and other administrative activities. Expenses consist primarily of personnel costs, facilities and overhead costs, outside marketing, advertising and legal expenses and other general and administrative costs. SG&A expenses also include the BPD fee. In the United States, we, along with other pharmaceutical manufacturers of branded drug products, are required to pay a portion of the BPD fee, which is estimated based on select government sales during the prior year as a percentage of total industry government sales and is trued-up upon receipt of invoices from the Internal Revenue Service (IRS).

SG&A expenses for the three months ended March 31, 2019 increased by $33 million, or 3%, compared to the same period in 2018, primarily due to higher promotional expenses in the United States and expenses associated with the expansion of our products in Europe and Japan, partially offset by lower stock-based compensation expense. Stock-based compensation expense was $36 million higher for the three months ended March 31, 2018 following the acquisition of Kite. BPD fee expense for the three months ended March 31, 2019 increased to $99 million compared to $79 million for the same period in 2018, primarily due to net adjustments based on IRS invoices.

Other Income (Expense), Net

Other income (expense), net for the three months ended March 31, 2019 increased to $367 million compared to $170 million for the same period in 2018, primarily due to $152 million higher net unrealized gains from changes in the fair value of our equity securities recorded in the three months ended March 31, 2019 compared to the same period in 2018.

Provision for Income Taxes

Our provision for income taxes was $382 million and $494 million for the three months ended March 31, 2019 and 2018, respectively. Our effective tax rate was 16.3% and 24.3% for the three months ended March 31, 2019 and 2018, respectively.

The decrease in the effective tax rate for the three months ended March 31, 2019 compared to the same period in 2018 was primarily due to $119 million of favorable settlements with taxing authorities in the three months ended March 31, 2019 and a $49 million unfavorable settlement of a foreign tax examination in the three months ended March 31, 2018.

We continue to evaluate certain changes to our legal entity structure in response to guidelines and requirements in various international tax jurisdictions where we conduct business. These changes may take multiple reporting periods to implement and may result in certain material, but non-recurring, adjustments to our deferred tax assets and/or liabilities, which will cause an offsetting increase or decrease to our tax provision. Estimates of these adjustments cannot be reasonably determined at this time and are dependent on the changes actually implemented.

Liquidity and Capital Resources

We believe that our existing capital resources, supplemented by our cash flows generated from operating activities, will be adequate to satisfy our capital needs for the foreseeable future.

The following table summarizes our cash, cash equivalents and marketable debt securities and working capital:

(In millions)	**March 31, 2019**	**December 31, 2018**
Cash, cash equivalents and marketable debt securities	$ 30,125	$ 31,512
Working capital	$ 24,627	$ 25,231

Cash, Cash Equivalents and Marketable Debt Securities

Cash, cash equivalents and marketable debt securities decreased by $1.4 billion, or 4%, compared to December 31, 2018. During the three months ended March 31, 2019, we generated $1.4 billion in operating cash flow, repaid $750 million principal amount of debt, paid cash dividends of $817 million and repurchased 12 million shares of our common stock for $834 million through open market transactions.

Working Capital

Working capital decreased by $604 million, or 2%, compared to December 31, 2018, primarily due to a decrease in cash, cash equivalents and short-term marketable debt securities.

Cash Flows

The following table summarizes our cash flow activities:

	Three Months Ended March 31,	
(In millions)	**2019**	**2018**
Cash provided by (used in):		
Operating activities	$ 1,444	$ 2,270
Investing activities	$ (111)	$ 4,354
Financing activities	$ (2,366)	$ (6,595)

Cash Provided by Operating Activities

Cash provided by operating activities represents the cash receipts and disbursements related to all activities other than investing and financing activities. Operating cash flow is derived by adjusting our net income for non-cash items and changes in operating assets and liabilities. Cash provided by operating activities decreased by $826 million to $1.4 billion for the three months ended March 31, 2019 compared to the same period in 2018. The decrease was primarily due to changes in operating assets and liabilities, including a decrease in accrued government and other rebates and the collection of a receivable from BMS during the three months ended March 31, 2018 following the termination of the collaboration pursuant to the terms of the existing agreements. The decrease was partially offset by lower tax payments during the three months ended March 31, 2019.

Cash Provided by (Used in) Investing Activities

Cash provided by (used in) investing activities primarily consists of purchases, sales and maturities of our marketable debt securities, our capital expenditures and other investments. Cash used in investing activities was $111 million for the three months ended March 31, 2019, compared to cash provided by investing activities of $4.4 billion for the same period in 2018. The change in cash provided by (used in) investing activities was primarily due to higher purchases of marketable debt securities, partially offset by higher proceeds from maturities of our marketable debt securities and a $180 million payment to Japan Tobacco Inc. during the three months ended March 31, 2019 in connection with acquiring the rights to market and distribute certain HIV products in Japan.

Cash Used in Financing Activities

Cash used in financing activities was $2.4 billion for the three months ended March 31, 2019, compared to cash used in financing activities of $6.6 billion for the same period in 2018. The decrease in cash used in financing activities was primarily due to lower repayments of debt and lower repurchases of common stock during the three months ended March 31, 2019.

Debt and Credit Facilities

The summary of our borrowings under various financing arrangements is included in Note 9. Debt and Credit Facilities of the Notes to Condensed Consolidated Financial Statements included in Part 1, Item 1 of this Quarterly Report on Form 10-Q.

In March 2019, we repaid $750 million of our senior unsecured notes upon maturity that were issued in September 2017. Other than the aforementioned repayment, there were no material changes to our debt or our credit facility during the three months ended March 31, 2019. As of March 31, 2019, no amounts were outstanding under our $2.5 billion five-year revolving credit facility agreement maturing in May 2021.

In April 2019, we repaid $500 million of our senior unsecured notes upon maturity that were issued in March 2014.

Critical Accounting Policies, Estimates and Judgments

The preparation of our Condensed Consolidated Financial Statements requires us to make estimates and judgments that affect the reported amounts in the financial statements and related disclosures. On an ongoing basis, we evaluate our significant accounting policies and estimates. We base our estimates on historical experience and on various market-specific and other relevant assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ significantly from these estimates. Estimates are assessed each period and updated to reflect current information. A summary of our critical accounting policies and estimates is presented in Part II, Item 7 of our Annual Report on Form 10-K for the year ended

December 31, 2018. There were no material changes to our critical accounting policies and estimates during the three months ended March 31, 2019.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements as defined in Item 303(a)(4)(ii) of Regulation S-K.

Recent Accounting Pronouncements

See Note 1. Summary of Significant Accounting Policies of the Notes to Condensed Consolidated Financial Statements included in Part 1, Item 1 of this Quarterly Report on Form 10-Q for additional information.

Item 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

There have been no material changes in our market risk during the three months ended March 31, 2019 compared to the disclosures in Part II, Item 7A of our Annual Report on Form 10-K for the year ended December 31, 2018.

Item 4. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

An evaluation as of March 31, 2019 was carried out under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of our "disclosure controls and procedures," which are defined in Rule 13a-15(e) under the Securities Exchange Act of 1934, as amended (the Exchange Act), as controls and other procedures of a company that are designed to ensure that the information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the Securities and Exchange Commission's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. Based upon that evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of March 31, 2019.

Changes in Internal Control over Financial Reporting

Our management, including our Chief Executive Officer and Chief Financial Officer, has evaluated any changes in our internal control over financial reporting that occurred during the quarter ended March 31, 2019, and has concluded that there was no change during such quarter that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Limitations on the Effectiveness of Controls

A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues, if any, within a company have been detected. Accordingly, our disclosure controls and procedures are designed to provide reasonable, not absolute, assurance that the objectives of our disclosure control system are met and, as set forth above, our Chief Executive Officer and Chief Financial Officer have concluded, based on their evaluation as of the end of the period covered by this report, that our disclosure controls and procedures were effective to provide reasonable assurance that the objectives of our disclosure control system were met.

PART II. OTHER INFORMATION

Item 1. LEGAL PROCEEDINGS

For a description of our significant pending legal proceedings, please see Note 11. Commitments and Contingencies of the Notes to Condensed Consolidated Financial Statements included in Part I, Item I of this Quarterly Report on Form 10-Q.

Item 1A. RISK FACTORS

In evaluating our business, you should carefully consider the following risks in addition to the other information in this Quarterly Report on Form 10-Q. A manifestation of any of the following risks could materially and adversely affect our business, results of operations and financial condition. We note these factors for investors as permitted by the Private Securities Litigation Reform Act of 1995. It is not possible to predict or identify all such factors and, therefore, you should not consider the following risks to be a complete statement of all the potential risks or uncertainties that we face.

A substantial portion of our revenues is derived from sales of products to treat HIV and HCV. If we are unable to increase HIV sales or if HCV sales decrease more than anticipated, then our results of operations may be adversely affected.

We receive a substantial portion of our revenue from sales of our products for the treatment of HIV infection. During the three months ended March 31, 2019, sales of our HIV products accounted for approximately 70% of our total product sales, and we expect our HIV products to account for a higher percentage of our total product sales in 2019 than in 2018. Most of our HIV products contain tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF) and/or emtricitabine, which belong to the nucleoside class of antiviral therapeutics. If the treatment paradigm for HIV changes, causing nucleoside-based therapeutics to fall out of favor, or if we are unable to maintain or increase our HIV product sales, our results of operations would likely suffer and we would likely need to scale back our operations, including our future drug development and spending on research and development (R&D) efforts.

During the three months ended March 31, 2019, sales of our products for the treatment of chronic hepatitis C virus (HCV) infection accounted for approximately 15% of our total product sales. Our HCV revenues have declined, and we expect a further decline in product sales in 2019, compared to 2018, in major markets. The drivers of our HCV product revenues are patient starts, net pricing, market share and treatment duration. With treatment duration stabilizing and pricing largely stabilizing, we expect to continue to compete for market share across market segments and geographies. We anticipate patient starts to continue to steadily decline and be more predictable. Any unexpected and adverse changes to these drivers, including any larger than anticipated shifts, may adversely impact our HCV product revenues.

In addition, future sales of our HIV and HCV products depend, in part, on the extent of reimbursement of our products by private and public payers. We may continue to experience global pricing pressure that could result in larger discounts or rebates on our products or delayed reimbursement, which negatively impacts our product sales and results of operations. Also, private and public payers can choose to exclude our products from their formulary coverage lists or limit the types of patients for whom coverage will be provided, which would negatively impact the demand for, and revenues of, our products. Any change in the formulary coverage, reimbursement levels or discounts or rebates offered on our products to payers may impact our anticipated revenues. If we are unable to achieve our forecasted HIV and HCV sales, our stock price could be adversely impacted.

We may be unable to sustain or increase sales of our HIV or HCV products for any number of reasons including, but not limited to, the reasons discussed above and the following:

- As our products are used over a longer period of time in many patients and in combination with other products, and additional studies are conducted, new issues with respect to safety, resistance and interactions with other drugs may arise, which could cause us to provide additional warnings or contraindications on our labels, narrow our approved indications or halt sales of a product, each of which could reduce our revenues.
- As our products mature, private insurers and government payers often reduce the amount they will reimburse patients for these products, which increases pressure on us to reduce prices.
- If physicians do not see the benefit of our HIV or HCV products, the sales of our HIV or HCV products will be limited.
- As new branded or generic products are introduced into major markets, our ability to maintain pricing and market share may be affected.

If we fail to develop and commercialize new products or expand the indications for existing products, our prospects for future revenues and our results of operations may be adversely affected.

The success of our business depends on our ability to introduce new products as well as expand the indications for our existing products to address areas of unmet medical need. The launch of commercially successful products is necessary to cover our substantial research and development expenses and to offset revenue losses when our existing products lose market share due to various factors such as competition and loss of patent exclusivity, as well as to provide for the growth of our business. There are

many difficulties and uncertainties inherent in drug development and the introduction of new products. The product development cycle is characterized by significant investments of resources, long lead times and unpredictable outcomes due to the nature of developing medicines for human use. We expend significant time and resources on our product pipeline without any assurance that we will recoup our investments or that our efforts will be commercially successful. A high rate of failure is inherent in the discovery and development of new products, and failure can occur at any point in the process, including late in the process after substantial investment. For example, see "We face risks in our clinical trials, including the potential for unfavorable results, delays in anticipated timelines and disruption, which may adversely affect our prospects for future revenue growth and our results of operations." We cannot state with certainty when or whether any of our product candidates under development will be approved or launched; whether we will be able to develop, license or acquire additional product candidates or products; or whether any products, once launched, will be commercially successful. Failure to launch commercially successful new products or new indications for existing products could have a material adverse effect on our future revenues, results of operations and long-term success.

Our inability to accurately predict demand for our products, uptake of new products or fluctuations in customer inventories makes it difficult for us to accurately forecast sales and may cause our forecasted revenues and earnings to fluctuate, which could adversely affect our financial results and stock price.

We may be unable to accurately predict demand for our products, including the uptake of new products, as demand depends on a number of factors. For example, the non-retail sector in the United States, which includes government institutions, including state AIDS Drug Assistance Programs (ADAPs), the U.S. Department of Veterans Affairs, correctional facilities and large health maintenance organizations, tends to be less consistent in terms of buying patterns and often causes quarter-over-quarter fluctuations that do not necessarily mirror patient demand for our products. Federal and state budget pressures, as well as the annual grant cycles for federal and state funds, may cause purchasing patterns to not reflect patient demand of our products. We expect to continue to experience fluctuations in the purchasing patterns of our non-retail customers which may result in fluctuations in our product sales, revenues and earnings in the future. In light of the budget crises faced by many European countries, we have observed variations in purchasing patterns induced by cost containment measures in Europe. We believe these measures have caused some government agencies and other purchasers to reduce inventory of our products in the distribution channels, which has decreased our revenues and caused fluctuations in our product sales and earnings. We may continue to see this trend in the future.

We sell and distribute most of our products in the United States exclusively through the wholesale channel. During the three months ended March 31, 2019, approximately 86% of our product sales in the United States were to three wholesalers, AmerisourceBergen Corp., Cardinal Health, Inc. and McKesson Corp. The U.S. wholesalers with whom we have entered into inventory management agreements make estimates to determine end user demand and may not be completely effective in matching their inventory levels to actual end user demand. As a result, changes in inventory levels held by those wholesalers can cause our operating results to fluctuate unexpectedly if our sales to these wholesalers do not match end user demand. In addition, inventory is held at retail pharmacies and other non-wholesaler locations with whom we have no inventory management agreements and no control over buying patterns. Adverse changes in economic conditions, increased competition or other factors may cause retail pharmacies to reduce their inventories of our products, which would reduce their orders from wholesalers and, consequently, the wholesalers' orders from us, even if end user demand has not changed. In addition, we have observed that strong wholesaler and sub-wholesaler purchases of our products in the fourth quarter typically results in inventory draw-down by wholesalers and sub-wholesalers in the subsequent first quarter. As inventory in the distribution channel fluctuates from quarter to quarter, we may continue to see fluctuations in our earnings and a mismatch between prescription demand for our products and our revenues.

In addition, we estimate the rebates we will be required to pay in connection with sales during a particular quarter based on claims data from prior quarters. In the United States, actual rebate claims are typically made by payers one to three quarters in arrears. Actual claims may vary significantly from our estimates which can cause an adjustment to our product revenues. To the extent our actual or anticipated product revenues exceed or fall short of investors' expectations, our stock price could be adversely impacted.

Yescarta, a chimeric antigen receptor (CAR) T cell therapy, represents a novel approach to cancer treatment that creates significant challenges for us, which may impact our ability to increase sales of Yescarta.

Yescarta, a CAR T cell therapy, involves (i) harvesting T cells from the patient's blood, (ii) engineering T cells to express cancer-specific receptors, (iii) increasing the number of engineered T cells and (iv) infusing the functional cancer-specific T cells back into the patient. Advancing this novel and personalized therapy creates significant challenges, including:

- educating and certifying medical personnel regarding the procedures and the potential side effect profile of our therapy, such as the potential adverse side effects related to cytokine release syndrome and neurologic toxicities, in compliance with the Risk Evaluation and Mitigation Strategy program required by U.S. Food and Drug Administration (FDA) for Yescarta;

- using medicines to manage adverse side effects of our therapy, such as tocilizumab and corticosteroids, which may not be available in sufficient quantities, may not adequately control the side effects and/or may have a detrimental impact on the efficacy of the treatment;
- developing a robust and reliable process, while limiting contamination risks, for engineering a patient's T cells ex vivo and infusing the engineered T cells back into the patient; and
- conditioning patients with chemotherapy in advance of administering our therapy, which may increase the risk of adverse side effects.

The use of engineered T cells as a potential cancer treatment is a recent development and may not be broadly accepted by physicians, patients, hospitals, cancer treatment centers, payers and others in the medical community. We may not be able to establish or demonstrate to the medical community or commercial or governmental payers the safety and efficacy of Yescarta and the potential advantages compared to existing and future therapeutics. If we fail to overcome these significant challenges, our sales of Yescarta, results of operations and stock price could be adversely affected.

We face significant competition.

We face significant competition from global pharmaceutical and biotechnology companies, specialized pharmaceutical firms and generic drug manufacturers. Our products compete with other available products based primarily on efficacy, safety, tolerability, acceptance by doctors, ease of patient compliance, ease of use, price, insurance and other reimbursement coverage, distribution and marketing.

Our TAF-containing HIV products compete primarily with products from ViiV Healthcare Company (ViiV). We also face competition from generic HIV products. Generic versions of efavirenz, a component of Atripla, are available in the United States, Canada and Europe. We have observed some pricing pressure related to the efavirenz component of our Atripla sales. TDF, one of the active pharmaceutical ingredients in Truvada, Atripla, Complera/Eviplera and Stribild, faces generic competition in the European Union, the United States and certain other countries. In addition, because emtricitabine, the other active pharmaceutical ingredient of Truvada, faces generic competition in the European Union, Truvada also faces generic competition in the European Union and certain other countries outside of the United States. Pursuant to a settlement agreement relating to patents that protect Truvada and Atripla, Teva Pharmaceuticals will be able to launch generic fixed-dose combinations of emtricitabine and TDF and generic fixed-dose combinations of emtricitabine, TDF and efavirenz in the United States on September 30, 2020.

Our HCV products compete primarily with products marketed by AbbVie and Merck.

Our HBV products face competition from existing therapies for treating patients with HBV as well as generic versions of TDF. Our HBV products also compete with products marketed by Bristol-Myers Squibb Company and Novartis Pharmaceuticals Corporation (Novartis).

Yescarta competes with a CAR T cell therapy marketed by Novartis and is expected to compete with products from other companies developing advanced T cell therapies.

Letairis competes with products marketed by Actelion Pharmaceuticals US, Inc., United Therapeutics Corporation and Pfizer Inc. Because the U.S. patent for ambrisentan, the active pharmaceutical ingredient in Letairis, expired in July 2018, Letairis is expected to face competition from manufacturers of generic versions of Letairis in the United States starting in the second quarter of 2019.

Ranexa competes predominantly with generic compounds from three distinct classes of drugs for the treatment of chronic angina in the United States, including generic and/or branded beta-blockers, calcium channel blockers and long-acting nitrates. Ranexa also faces competition from manufacturers of generic versions of Ranexa in the United States.

In addition, a number of companies are pursuing the development of technologies which are competitive with our existing products or research programs. These competing companies include specialized pharmaceutical firms and large pharmaceutical companies acting either independently or together with other pharmaceutical companies. Furthermore, academic institutions, government agencies and other public and private organizations conducting research may seek patent protection and may establish collaborative arrangements for competitive products or programs. If any of these competitors gain market share as a result of new technologies, commercialization strategies or otherwise, it could adversely affect our results of operations and stock price.

Our results of operations may be adversely affected by current and potential future healthcare legislative and regulatory actions.

Legislative and regulatory actions affecting government prescription drug procurement and reimbursement programs occur relatively frequently. In the United States, the Affordable Care Act (the ACA) was enacted in 2010 to expand healthcare coverage. Since then, numerous efforts have been made to repeal, amend or administratively limit the ACA in whole or in part. For example, the Tax Cuts and Jobs Act, signed into law by President Trump in 2017, repealed the individual health insurance mandate, which is considered a key component of the ACA. In December 2018, a Texas federal district court struck down the ACA on the grounds

that the individual health insurance mandate is unconstitutional, although this ruling has been stayed pending appeal. The ongoing challenges to the ACA and new legislative proposals have resulted in uncertainty regarding the ACA's future viability and destabilization of the health insurance market. The resulting impact on our business is uncertain and could be material.

Efforts to control prescription drug prices could also have a material adverse effect on our business. For example, in 2018, President Trump and the Secretary of the U.S. Department of Health and Human Services (HHS) released the "American Patients First Blueprint" and have begun implementing certain portions. The initiative includes proposals to increase generic drug and biosimilar competition, enable the Medicare program to negotiate drug prices more directly and improve transparency regarding drug prices and ways to lower consumers' out-of-pocket costs. The Trump administration also proposed to establish an "international pricing index" that would be used as a benchmark to determine the costs and potentially limit the reimbursement of drugs under Medicare Part B. In addition, many states have proposed or enacted legislation that seeks to indirectly or directly regulate pharmaceutical drug pricing, such as by requiring biopharmaceutical manufacturers to publicly report proprietary pricing information or to place a maximum price ceiling on pharmaceutical products purchased by state agencies. For example, in 2017, California's governor signed a prescription drug price transparency state bill into law, requiring prescription drug manufacturers to provide advance notice and explanation for price increases of certain drugs that exceed a specified threshold. Both Congress and state legislatures are considering various bills that would reform drug purchasing and price negotiations, allow greater use of utilization management tools to limit Medicare Part D coverage, facilitate the import of lower-priced drugs from outside the United States and encourage the use of generic drugs. Such initiatives and legislation may cause added pricing pressures on our products.

Changes to the Medicaid program at the federal or state level could also have a material adverse effect on our business. Proposals that could impact coverage and reimbursement of our products, including giving states more flexibility to manage drugs covered under the Medicaid program and permitting the re-importation of prescription medications from Canada or other countries, could have a material adverse effect by limiting our products' use and coverage. Furthermore, state Medicaid programs could request additional supplemental rebates on our products as a result of an increase in the federal base Medicaid rebate. To the extent that private insurers or managed care programs follow Medicaid coverage and payment developments, they could use the enactment of these increased rebates to exert pricing pressure on our products, and the adverse effects may be magnified by their adoption of lower payment schedules.

Other proposed regulatory actions affecting manufacturers could have a material adverse effect on our business. For example, in December 2018, HHS proposed a rule that would modify the Medicare Part D protected class policy to provide Part D Plan Sponsors broader authority to impose step therapy, prior authorization and other utilization management controls on products in the Part D protected classes, including our HIV products. In January 2019, HHS also proposed a rule that would remove regulatory protection under the Discount Safe Harbor to the Federal Anti-Kickback Statute for manufacturer rebates paid to Part D Plan Sponsors, Medicaid managed care organizations and pharmacy benefit managers under contract with them, and would create new safe harbors for arrangements with these entities. It is difficult to predict the impact, if any, of any such proposed legislative and regulatory actions or resulting state actions on the use and reimbursement of our products in the United States, but our results of operations may be adversely affected.

Our existing products are subject to reimbursement from government agencies and other third parties. Pharmaceutical pricing and reimbursement pressures may reduce profitability.

Successful commercialization of our products depends, in part, on the availability of governmental and third-party payer reimbursement for the cost of such products and related treatments in the markets where we sell our products. Government health authorities, private health insurers and other organizations generally provide reimbursement. In the United States, the European Union and other significant or potentially significant markets for our products and product candidates, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medical products and services. A substantial portion of sales of our products is subject to significant discounts from list price. In addition, standard reimbursement structures may not adequately reimburse for innovative therapies.

For example, effective October 2018, the Centers for Medicare and Medicaid Services (CMS) established inpatient reimbursement for patients receiving Yescarta. The reimbursement includes payment for a severity adjusted diagnosis related group (DRG) 016, a new technology add-on payment (NTAP) for Yescarta that at most will cover one half the cost of Yescarta and may cover less than that, and, in some cases, an outlier payment. Taken together, the total payment may not be sufficient to reimburse hospitals for their cost of care for patients receiving Yescarta. This payment methodology is likely to be in effect until at least September 2020. Limited payments such as this could impact the willingness of some hospitals to offer the therapy and of doctors to recommend the therapy and could lessen the attractiveness of our therapy to patients, which could have an adverse effect on sales of Yescarta and on our results of operations. CMS has also proposed a National Coverage Decision on CAR T cell therapy and would impose certain coverage limitations on that therapy. These coverage limitations would apply to the entire Medicare program and includes, among other things, a requirement for patients to be enrolled in a clinical trial or registry in order for the hospital and physician to be paid for CAR T cell therapy. Further, commercial payers may follow Medicare coverage policies and could impose similar limitations. Additionally, in the European Union, there are barriers to reimbursement in individual countries that could limit the uptake of Yescarta.

Laws and regulations applicable to the health care industry could impose new obligations on us, require us to change our business practices and restrict our operations in the future.

The health care industry is subject to various federal, state and international laws and regulations pertaining to drug reimbursement, rebates, price reporting, health care fraud and abuse, and data privacy and security. In the United States, these laws include anti-kickback and false claims laws, laws and regulations relating to the Medicare and Medicaid programs and other federal and state programs, the Medicaid Rebate Statute, individual state laws relating to pricing and sales and marketing practices, the Health Insurance Portability and Accountability Act (HIPAA) and other federal and state laws relating to the privacy and security of health information.

Violations of these laws or any related regulations may be punishable by criminal and/or civil sanctions, including, in some instances, substantial fines, civil monetary penalties, exclusion from participation in federal and state health care programs, including Medicare, Medicaid, Veterans Administration health programs, and federal employee health benefit programs, actions against executives overseeing our business and burdensome remediation measures. In addition, these laws and regulations are broad in scope and they are subject to change and evolving interpretations, which could require us to incur substantial costs associated with compliance or to alter one or more of our sales or marketing practices. Violations of these laws, or allegations of such violations, could also result in negative publicity or other consequences that could harm our reputation, disrupt our business or adversely affect our results of operations. If any or all of these events occur, our business and stock price could be materially and adversely affected.

Recently, there has been enhanced scrutiny of company-sponsored patient assistance programs, including insurance premium and co-pay assistance programs and donations to third-party charities that provide such assistance. There has also been enhanced scrutiny by governments on reimbursement support offerings, clinical education programs and promotional speaker programs. If we, or our agents, vendors or donation recipients, are deemed to have failed to comply with laws, regulations or government guidance in any of these areas, we could be subject to criminal or civil sanctions. Any similar violations by our competitors could also negatively impact our industry reputation and increase scrutiny over our business and our products.

For a description of our government investigations and related litigation, see Note 11. Commitments and Contingencies of the Notes to Condensed Consolidated Financial Statements included in Part I, Item 1 of this Quarterly Report on Form 10-Q.

We have engaged in, and may in the future engage in, business acquisitions, licensing arrangements, strategic collaborations or disposal of our assets, which could cause us to incur significant expenses and could adversely affect our financial condition and results of operations.

We have engaged in, and may in the future engage in, business acquisitions, licensing arrangements, strategic collaborations or disposal of our assets, as part of our business strategy. We may not identify suitable transactions in the future and, if we do, we may not complete such transactions in a timely manner, on a cost-effective basis, or at all, and may not realize the expected benefits. If we are successful in making an acquisition, the products and technologies that are acquired may not be successful or may require significantly greater resources and investments than originally anticipated. We may not be able to integrate acquisitions successfully into our existing business and could incur or assume significant debt and unknown or contingent liabilities. We also conduct annual impairment testing of our goodwill and other indefinite lived intangible assets in the fourth quarter, or earlier if impairment indicators exist, as required under U.S. generally accepted accounting principles. If we fail to overcome these risks, it could cause us to incur significant expenses and negatively affect profitability, which could have an adverse effect on our results of operations. We could also experience negative effects on our reported results of operations from acquisition or disposition-related charges, amortization of expenses related to intangibles and charges for impairment of long-term assets.

Approximately 27% of our product sales occur outside the United States, and currency fluctuations and hedging expenses may cause our earnings to fluctuate, which could adversely affect our stock price.

Because a significant percentage of our product sales are denominated in foreign currencies, primarily the Euro, we face exposure to adverse movements in foreign currency exchange rates. When the U.S. dollar strengthens against these foreign currencies, the relative value of sales made in the respective foreign currency decreases. Conversely, when the U.S. dollar weakens against these currencies, the relative value of such sales increases. Overall, we are a net receiver of foreign currencies and, therefore, benefit from a weaker U.S. dollar and are adversely affected by a stronger U.S. dollar.

We use foreign currency exchange forward and option contracts to hedge a portion of our forecasted international sales, primarily those denominated in the Euro. We also hedge certain monetary assets and liabilities denominated in foreign currencies, which reduces but does not eliminate our exposure to currency fluctuations between the date a transaction is recorded and the date cash is collected or paid. Foreign currency exchange, net of hedges, had an immaterial impact on our product sales for the three months ended March 31, 2019, compared to the same period in 2018.

We cannot predict future fluctuations in the foreign currency exchange rates of the U.S. dollar. If the U.S. dollar appreciates significantly against certain currencies and our hedging program does not sufficiently offset the effects of such appreciation, our results of operations will be adversely affected and our stock price may decline.

Additionally, the expenses that we recognize in relation to our hedging activities can also cause our earnings to fluctuate. The level of hedging expenses that we recognize in a particular period is impacted by the changes in interest rate spreads between the foreign currencies that we hedge and the U.S. dollar.

If significant safety issues arise for our marketed products or our product candidates, our reputation may be harmed and our future sales may be reduced, which could adversely affect our results of operations.

The data supporting the marketing approvals for our products and forming the basis for the safety warnings in our product labels were obtained in controlled clinical trials of limited duration and, in some cases, from post-approval use. As our products are used over longer periods of time by patients with underlying health problems or other medicines, we expect to continue finding new issues related to safety, resistance or drug interactions. Any such issues may require changes to our product labels, such as additional warnings, contraindications or even narrowed indications. If any of these were to occur, it could reduce the market acceptance and sales of our products.

Regulatory authorities have been moving towards more active and transparent pharmacovigilance and are making greater amounts of stand-alone safety information and clinical trial data directly available to the public through websites and other means, such as periodic safety update report summaries, risk management plan summaries and various adverse event data. Safety information, without the appropriate context and expertise, may be misinterpreted and lead to misperception or legal action which may potentially cause our product sales or stock price to decline.

Further, if serious safety, resistance or drug interaction issues arise with our marketed products, sales of these products could be limited or halted by us or by regulatory authorities and our results of operations could be adversely affected.

Our operations depend on compliance with complex FDA and comparable international regulations. Failure to obtain broad approvals on a timely basis or to maintain compliance could delay or halt commercialization of our products.

The products we develop must be approved for marketing and sale by regulatory authorities and, once approved, are subject to extensive regulation by FDA, the European Medicines Agency (EMA) and comparable regulatory agencies in other countries. We are continuing clinical trials for many of our products for currently approved and additional uses. We anticipate that we will file for marketing approval in additional countries and for additional indications and products over the next several years. These products may fail to receive such marketing approvals on a timely basis, or at all.

Further, how we manufacture and sell our products is subject to extensive regulation and review. Discovery of previously unknown problems with our marketed products or problems with our manufacturing, safety reporting or promotional activities may result in restrictions on our products, including withdrawal of the products from the market. If we fail to comply with applicable regulatory requirements, including those related to promotion and manufacturing, we could be subject to penalties including fines, suspensions of regulatory approvals, product recalls, seizure of products and criminal prosecution.

For example, under FDA rules, we are often required to conduct post-approval clinical studies to assess a known serious risk, signals of serious risk or to identify an unexpected serious risk. In certain circumstances, we may be required to implement a Risk Evaluation and Mitigation Strategy program for our products, which could include a medication guide, patient package insert, a communication plan to healthcare providers, restrictions on distribution or use of a product and other elements FDA deems necessary to assure safe use of the drug. Failure to comply with these or other requirements imposed by FDA could result in significant civil monetary penalties and our operating results may be adversely affected.

We face risks in our clinical trials, including the potential for unfavorable results, delays in anticipated timelines and disruption, which may adversely affect our prospects for future revenue growth and our results of operations.

We are required to demonstrate the safety and efficacy of products that we develop for each intended use through extensive preclinical studies and clinical trials. The results from preclinical and early clinical studies do not always accurately predict results in later, large-scale clinical trials. Even successfully completed large-scale clinical trials may not result in marketable products. For example, we recently announced that our KITE-585 program, an anti-B cell maturation antigen being evaluated for the treatment of multiple myeloma, will not be moving forward. We also recently announced that STELLAR-3 and STELLAR-4, Phase 3 studies evaluating the safety and efficacy of selonsertib for the treatment of nonalcoholic steatohepatitis (NASH), did not meet the pre-specified week 48 primary endpoints. If any of our product candidates fails to achieve its primary endpoint in clinical trials, if safety issues arise or if the results from our clinical trials are otherwise inadequate to support regulatory approval of our product candidates, commercialization of that product candidate could be delayed or halted. In addition, we may also face challenges in clinical trial protocol design.

If the clinical trials for any of the product candidates in our pipeline are delayed or terminated, our prospects for future revenue growth and our results of operations may be adversely impacted. For example, we face numerous risks and uncertainties with our product candidates, including Descovy for pre-exposure prophylaxis (PrEP); selonsertib for the treatment of NASH; axicabtagene ciloleucel for the treatment of second line diffuse large B-cell lymphoma; and filgotinib for the treatment of rheumatoid arthritis, Crohn's disease and ulcerative colitis, each currently in Phase 3 clinical trials, that could prevent completion of development of these product candidates. These risks include our ability to enroll patients in clinical trials, the possibility of unfavorable results of our clinical trials, the need to modify or delay our clinical trials or to perform additional trials and the risk of failing to obtain FDA and other regulatory body approvals. As a result, our product candidates may never be successfully commercialized. For example, FDA has requested that we conduct a safety study of filgotinib in men with ulcerative colitis (MANTA study), and enrollment in this MANTA study will likely be the rate limiting factor to filing an NDA for filgotinib in the United States. Further, we may make a strategic decision to discontinue development of our product candidates if, for example, we believe commercialization will be difficult relative to other opportunities in our pipeline. If these programs and others in our pipeline cannot be completed on a timely basis or at all, then our prospects for future revenue growth and our results of operations may be adversely impacted. In addition, clinical trials involving our commercial products could raise new safety issues for our existing products, which could in turn adversely affect our results of operations and harm our business.

In addition, we extensively outsource our clinical trial activities and usually perform only a small portion of the start-up activities in-house. We rely on independent third-party contract research organizations (CROs) to perform most of our clinical studies, including document preparation, site identification, screening and preparation, pre-study visits, training, program management, patient enrollment, ongoing monitoring, site management and bioanalytical analysis. Many important aspects of the services performed for us by the CROs are out of our direct control. If there is any dispute or disruption in our relationship with our CROs, our clinical trials may be delayed. Moreover, in our regulatory submissions, we rely on the quality and validity of the clinical work performed by third-party CROs. If any of our CROs' processes, methodologies or results were determined to be invalid or inadequate, our own clinical data and results and related regulatory approvals may be adversely affected.

We depend on relationships with third parties for sales and marketing performance, technology, development, logistics and commercialization of products. Failure to maintain these relationships, poor performance by these companies or disputes with these third parties could negatively impact our business.

We rely on a number of collaborative relationships with third parties for our sales and marketing performance in certain territories. For example, we have collaboration arrangements with Janssen Sciences Ireland UC for Odefsey, Complera/Eviplera and Symtuza. In some countries, we rely on international distributors for sales of certain of our products. Some of these relationships also involve the clinical development of these products by our partners. Reliance on collaborative relationships poses a number of risks, including the risk that:

- we are unable to control the resources our corporate partners devote to our programs or products;
- disputes may arise with respect to the ownership of rights to technology developed with our corporate partners;
- disagreements with our corporate partners could cause delays in, or termination of, the research, development or commercialization of product candidates or result in litigation or arbitration;
- contracts with our corporate partners may fail to provide significant protection or may fail to be effectively enforced if one of these partners fails to perform;
- our corporate partners have considerable discretion in electing whether to pursue the development of any additional products and may pursue alternative technologies or products either on their own or in collaboration with our competitors;
- our corporate partners with marketing rights may choose to pursue competing technologies or to devote fewer resources to the marketing of our products than they do to products of their own development; and
- our distributors and our corporate partners may be unable to pay us.

Given these risks, there is a great deal of uncertainty regarding the success of our current and future collaborative efforts. If these efforts fail, our product development or commercialization of new products could be delayed or revenues from products could decline.

In addition, we rely on third-party sites to collect patients' white blood cells, known as apheresis centers, shippers, couriers, and hospitals for the logistical collection of patients' white blood cells and ultimate delivery of Yescarta to patients. Any disruption or difficulties incurred by any of these vendors could result in product loss and regulatory action and harm our Yescarta business and our reputation. To ensure that any apheresis center is prepared to ship cells to our manufacturing facilities, we plan to conduct quality certifications of each apheresis center. However, apheresis centers may choose not to participate in the certification process or we may be unable to complete certification in a timely manner or at all, which could delay or restrain our manufacturing and commercialization efforts. As a result, our sales of Yescarta may be limited which could harm our results of operations.

Our success depends to a significant degree on our ability to defend our patents and other intellectual property rights both domestically and internationally. We may not be able to obtain effective patents to protect our technologies from use by competitors.

Patents and other proprietary rights are very important to our business. Our success depends to a significant degree on our ability to:

- obtain patents and licenses to patent rights;
- preserve trade secrets and internal know-how;
- defend against infringement of our patents and efforts to invalidate them; and
- operate without infringing on the intellectual property of others.

If we have a properly drafted and enforceable patent, it can be more difficult for our competitors to use our technology to create competitive products and more difficult for our competitors to obtain a patent that prevents us from using technology we create. As part of our business strategy, we actively seek patent protection both in the United States and internationally and file additional patent applications, when appropriate, to cover improvements in our compounds, products and technology.

Patent applications are confidential for a period of time before a patent is issued. As a result, we may not know if our competitors filed patent applications for technology covered by our pending applications or if we were the first to invent or first to file an application directed toward the technology that is the subject of our patent applications. In addition, if competitors file patent applications covering our technology, we may have to participate in litigation, post-grant proceedings before the U.S. Patent and Trademark Office or other proceedings to determine the right to a patent or validity of any patent granted. Litigation, post-grant proceedings before the U.S. Patent and Trademark Office or other proceedings are unpredictable and expensive, and could divert management attention from other operations, such that, even if we are ultimately successful, our results of operations may be adversely affected by such events.

Generic manufacturers have sought, and may continue to seek, FDA approval to market generic versions of our products through an abbreviated new drug application (ANDA), the application process typically used by manufacturers seeking approval of a generic drug. For a description of our ANDA litigation, see Note 11. Commitments and Contingencies of the Notes to Condensed Consolidated Financial Statements included in Part I, Item 1 of this Quarterly Report on Form 10-Q. The entry of generic versions of our products may lead to market share and price erosion and have a negative impact on our business and results of operations.

Our success depends in large part on our ability to operate without infringing upon the patents or other proprietary rights of third parties.

If we infringe the valid patents of third parties, we may be required to pay significant monetary damages or we may be prevented from commercializing products or may be required to obtain licenses from these third parties. We may not be able to obtain alternative technologies or any required license on commercially reasonable terms or at all. If we fail to obtain these licenses or alternative technologies, we may be unable to develop or commercialize some or all of our products. For example, we are aware of patents and patent applications owned by third parties that such parties may claim cover the use of sofosbuvir, axicabtagene ciloleucel and bictegravir. See also a description of our litigation regarding sofosbuvir, axicabtagene ciloleucel and bictegravir in Note 11, Commitments and Contingencies of the Notes to Condensed Consolidated Financial Statements included in Part I, Item 1 of this Quarterly Report on Form 10-Q. We are also aware of U.S. Patent Nos. 9,044,509, 9,579,333 and 9,937,191 assigned to the U.S. Department of Health and Human Services that purport to claim a process of protecting a primate host from infection by an immunodeficiency retrovirus by administering a combination of emtricitabine and tenofovir or TDF prior to exposure of the host to the immunodeficiency retrovirus. We have been in contact with the U.S. Department of Health and Human Services about the scope and relevance of the patents and have explained that we do not believe that these patents are valid because the patent office was not given the most relevant prior art and because physicians and patients were using the claimed methods years before the Centers for Disease Control and Prevention filed the applications for the patents.

Furthermore, we also rely on unpatented trade secrets and improvements, unpatented internal know-how and technological innovation. For example, a great deal of our liposomal manufacturing expertise, which is a key component of our liposomal technology, is not covered by patents but is instead protected as a trade secret. We protect these rights mainly through confidentiality agreements with our corporate partners, employees, consultants and vendors. We cannot be certain that these parties will comply with these confidentiality agreements, that we have adequate remedies for any breach or that our trade secrets, internal know-how or technological innovation will not otherwise become known or be independently discovered by our competitors. Under some of our R&D agreements, inventions become jointly owned by us and our corporate partner and in other cases become the exclusive property of one party. In certain circumstances, it can be difficult to determine who owns a particular invention and disputes could arise regarding those inventions. If our trade secrets, internal know-how, technological innovation or confidential information become known or independently discovered by competitors or if we enter into disputes over ownership of inventions, our business and results of operations could be adversely affected.

Manufacturing problems, including at our third-party manufacturers and corporate partners, could cause inventory shortages and delay product shipments and regulatory approvals, which may adversely affect our results of operations.

In order to generate revenue from our products, we must be able to produce sufficient quantities of our products to satisfy demand. Many of our products are the result of complex manufacturing processes. The manufacturing process for pharmaceutical products is also highly regulated and regulators may shut down manufacturing facilities that they believe do not comply with regulations.

Our products are either manufactured at our own facilities or by third-party manufacturers or corporate partners. We depend on third parties to perform manufacturing activities effectively and on a timely basis for the majority of our solid dose products. We, our third-party manufacturers and our corporate partners are subject to Good Manufacturing Practices (GMP), which are extensive regulations governing manufacturing processes, stability testing, record keeping and quality standards as defined by FDA and EMA. Similar regulations are in effect in other jurisdictions.

Our third-party manufacturers and corporate partners are independent entities subject to their own unique operational and financial risks that are out of our control. If we or any of these third-party manufacturers or corporate partners fail to perform as required, this could impair our ability to deliver our products on a timely basis or receive royalties or could cause delays in our clinical trials and applications for regulatory approval. Further, we may have to write off the costs of manufacturing any batch that fails to pass quality inspection or meet regulatory approval. In addition, we, our third-party manufacturers and our corporate partners may only be able to produce some of our products at one or a limited number of facilities and, therefore, have limited manufacturing capacity for certain products, and we may not be able to locate additional or replacement facilities on a reasonable basis or at all. Our sales of such products could also be adversely impacted by our reliance on such limited number of facilities. To the extent these risks materialize and affect their performance obligations to us, our financial results may be adversely affected.

Our manufacturing operations are subject to routine inspections by regulatory agencies. If we are unable to remedy any deficiencies cited by FDA in these inspections, our currently marketed products and the timing of regulatory approval of products in development could be adversely affected. Further, there is risk that regulatory agencies in other countries where marketing applications are pending will undertake similar additional reviews or apply a heightened standard of review, which could delay the regulatory approvals for products in those countries. If approval of any of our product candidates were delayed or if production of our marketed products was interrupted, our anticipated revenues and our stock price may be adversely affected.

We may not be able to obtain materials or supplies necessary to conduct clinical trials or to manufacture and sell our products, which could limit our ability to generate revenues.

We need access to certain supplies and products to conduct our clinical trials and to manufacture and sell our products. If we are unable to purchase sufficient quantities of these materials or find suitable alternative materials in a timely manner, our development efforts for our product candidates may be delayed or our ability to manufacture our products could be limited, which could limit our ability to generate revenues.

Suppliers of key components and materials must be named in the new drug application or marketing authorization application filed with the regulatory authority for any product candidate for which we are seeking marketing approval, and significant delays can occur if the qualification of a new supplier is required. Even after a manufacturer is qualified by the regulatory authority, the manufacturer must continue to expend time, money and effort in the area of production and quality control to ensure full compliance with GMP. Manufacturers are subject to regular periodic inspections by regulatory authorities following initial approval. If, as a result of these inspections, a regulatory authority determines that the equipment, facilities, laboratories or processes do not comply with applicable regulations and conditions of product approval, the regulatory authority may suspend the manufacturing operations. If the manufacturing operations of any of the single suppliers for our products are suspended, we may be unable to generate sufficient quantities of commercial or clinical supplies of product to meet market demand, which could in turn decrease our revenues and harm our business. In addition, if deliveries of materials from our suppliers were interrupted for any reason, we may be unable to ship certain of our products for commercial supply or to supply our product candidates in development for clinical trials. In addition, some of our products and the materials that we utilize in our operations are manufactured at only one facility, which we may not be able to replace in a timely manner and on commercially reasonable terms, or at all. Problems with any of the single suppliers we depend on, including in the event of a disaster, such as an earthquake, equipment failure or other difficulty, may negatively impact our development and commercialization efforts.

A significant portion of the raw materials and intermediates used to manufacture our antiviral products are supplied by third-party manufacturers and corporate partners outside of the United States. As a result, any political or economic factors in a specific country or region, including any changes in or interpretations of trade regulations, compliance requirements or tax legislation, that would limit or prevent third parties outside of the United States from supplying these materials could adversely affect our ability to manufacture and supply our antiviral products to meet market needs and have a material and adverse effect on our operating results.

If we were to encounter any of these difficulties, our ability to conduct clinical trials on product candidates and to manufacture and sell our products could be impaired, which could have an adverse effect on our business.

Imports from countries where our products are available at lower prices and unapproved generic or counterfeit versions of our products could have a negative impact on our reputation and business.

Prices for our products are based on local market economics and competition and sometimes differ from country to country. Our sales in countries with relatively higher prices may be reduced if products can be imported into those or other countries from lower price markets. If our HIV, HBV and HCV products, which we have agreed to make available at substantially reduced prices to certain low- and middle-income countries participating in our Gilead Access Program, are re-exported from these low- and middle-income countries into the United States, Europe or other higher price markets, our revenues could be adversely affected. In addition, we have entered into voluntary licensing agreements with generic drug companies in India, South Africa and China, as well as a licensing agreement with the Medicines Patent Pool, a United Nations-backed public health organization, which allows generic drug companies to manufacture generic versions of HIV and HBV products incorporating our licensed compounds, TAF, cobicistat, elvitegravir and bictegravir, for distribution in certain low- and middle-income countries. We have also entered into agreements with generic manufacturers in India, Egypt and Pakistan allowing them to produce and/or distribute generic versions of our HCV products in certain low- and middle-income countries. If generic versions of our HIV, HBV and HCV products produced and/or distributed under these agreements are then re-exported to the United States, Europe or other markets outside of these low- and middle-income countries, our revenues could be adversely affected. In addition, purchases of our products in countries where our selling prices are relatively low for resale in countries in which our selling prices are relatively high may adversely impact our revenues and gross margin and may cause our sales to fluctuate from quarter to quarter. Additionally, use of these diverted products could occur in countries where they have not been approved and patients could source the product outside the legitimate supply chain. Therefore, the products may be handled, shipped and stored inappropriately, which may affect the efficacy of the product and could harm patients, our brands or the commercial or scientific reputation of our products.

In the European Union, we are required to permit products purchased in one EU member state to be sold in another EU member state. Purchases of our products in countries where our selling prices are relatively low for resale in countries in which our selling prices are relatively high can affect the inventory level held by our wholesalers and can cause the relative sales levels in the various countries to fluctuate from quarter to quarter and not reflect the actual consumer demand in any given quarter. These quarterly fluctuations may impact our earnings, which could adversely affect our stock price and harm our business.

We are also aware of the existence of various “Buyers Clubs” around the world that promote the personal importation of generic versions of our HCV and HIV products that have not been approved for use in the countries into which they are imported. As a result, patients may be at risk of taking unapproved medications which may not be what they purport to be, may not have the potency they claim to have or may contain harmful substances. To the extent patients take unapproved generic versions of one or more of our medications and are injured by these generic products, our brands or the commercial or scientific reputation of our HCV and HIV products could be harmed.

Further, third parties may illegally distribute and sell counterfeit versions of our products, which do not meet the rigorous quality standards of our manufacturing and supply chain. For example, in 2017 and 2018, there were reports that a product labeled as Epclusa was available in multiple countries, which we determined was not an authentic product based on sample analysis and the lot number. We have cooperated and continue to cooperate with regulatory authorities to investigate this matter. We actively take actions to discourage the distribution and sale of counterfeits of our products around the world, including working with local regulatory and legal authorities to enforce laws against counterfeit drugs, raising public awareness of the dangers of counterfeit drugs and promoting public policies to hinder the sale and availability of counterfeit drugs. Counterfeit drugs pose a serious risk to patient health and safety and may raise the risk of product recalls. Our reputation and business could suffer as a result of counterfeit drugs sold under our brand names.

Expensive litigation and government investigations have increased our expenses which may continue to reduce our earnings.

We are involved in a number of litigation, investigation and other dispute-related matters that require us to expend substantial internal and financial resources. We expect these matters will continue to require a high level of internal and financial resources for the foreseeable future. These matters have reduced and will continue to reduce our earnings and require significant management attention. For a description of our litigation, investigations and other dispute-related matters, see Note 11. Commitments and Contingencies of the Notes to Condensed Consolidated Financial Statements included in Part I, Item 1 of this Quarterly Report on Form 10-Q. The outcome of such legal proceedings or any other legal proceedings that may be brought against us, the investigations or any other investigations that may be initiated and any other dispute-related matters, are inherently uncertain, and adverse developments or outcomes can result in significant expenses, monetary damages, penalties or injunctive relief against us that could significantly reduce our earnings and cash flows and harm our business and reputation.

We may face significant liability resulting from our products and such liability could materially reduce our earnings.

The testing, manufacturing, marketing and use of our commercial products, as well as product candidates in development, involve substantial risk of product liability claims. These claims may be made directly by consumers, healthcare providers, pharmaceutical companies or others. We have limited insurance for product liabilities that may arise. If claims exceed our coverage, our financial condition will be adversely affected. In addition, negative publicity associated with any claims, regardless of their merit, may decrease the future demand for our products and impair our financial condition. For a description of our product liability matters, see Note 11. Commitments and Contingencies of the Notes to Condensed Consolidated Financial Statements included in Part I, Item 1 of this Quarterly Report on Form 10-Q.

If we fail to attract and retain highly qualified personnel, we may be unable to successfully develop new product candidates, conduct our clinical trials and commercialize our product candidates.

Our future success will depend in large part on our continued ability to attract and retain highly qualified scientific, technical and management personnel, as well as personnel with expertise in clinical testing, governmental regulation and commercialization. We face competition for personnel from other companies, universities, public and private research institutions, government entities and other organizations. Competition for qualified personnel in the biopharmaceutical field is intense, and there is a limited pool of qualified potential employees to recruit. We may not be able to attract and retain quality personnel on acceptable terms. Additionally, changes to U.S. immigration and work authorization laws and regulations could make it more difficult for employees to work in or transfer to jurisdictions in which we have operations and could impair our ability to attract and retain qualified personnel. If we are unsuccessful in our recruitment and retention efforts, our business may be harmed.

In April 2019, we announced that Robin L. Washington plans to retire from her position as our Executive Vice President and Chief Financial Officer, effective March 1, 2020, or if earlier, when a successor is named and commences in the role. Should a successor be named and commences in the role prior to March 1, 2020, Ms. Washington has agreed to remain in an advisory capacity through the completion of our reporting of 2019 financial results. If there are delays with the selection of a new Chief Financial Officer or if we do not successfully manage the transition, our business may be negatively impacted.

Business disruptions from natural or man-made disasters may adversely affect our revenues and materially reduce our earnings.

Our worldwide operations, third-party manufacturers or corporate partners could be subject to business interruptions stemming from natural or man-made disasters, including those related to climate change, for which we or they may be uninsured or inadequately insured. Our corporate headquarters in Foster City and our Santa Monica location, which together house a majority of our R&D activities, and our San Dimas, La Verne, Oceanside and El Segundo manufacturing facilities are located in California, a seismically active region. As we may not carry adequate earthquake insurance and significant recovery time could be required to resume operations, our financial condition and operating results could be materially adversely affected in the event of a major earthquake.

We are dependent on information technology systems, infrastructure and data, which may be subject to cyberattacks and security breaches.

We are dependent upon information technology systems, infrastructure and data, including our Kite Konnect platform, which is critical to ensure chain of identity and chain of custody of Yescarta. The multitude and complexity of our computer systems make them inherently vulnerable to service interruption or destruction, malicious intrusion and random attack. Likewise, data privacy or security breaches by employees or others pose a risk that sensitive data, including our intellectual property or trade secrets or the personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyberattacks are increasing in their frequency, sophistication and intensity. Cyberattacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business and technology partners face similar risks and any security breach of their systems could adversely affect our security posture. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts, or the efforts of our partners and vendors, will prevent service interruptions or identify breaches in our systems. Such interruptions or breaches could adversely affect our business and operations and/or cause the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our insurance may not be sufficient in type or amount to cover the financial, legal, business or reputational losses that may result from an interruption or breach of our systems.

Regulators globally are also imposing new data security requirements, including greater monetary fines for privacy violations. For example, the General Data Protection Regulation (GDPR) that became effective in Europe in 2018 established new regulations regarding the handling of personal data, and non-compliance with the GDPR may result in monetary penalties of up to four percent of worldwide revenue. In addition, we may be subject to additional data privacy and security laws, such as the California Consumer Privacy Act of 2018. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types

of sensitive data, including healthcare data or other personal information, could greatly increase our cost of providing our products and services or even prevent us from offering certain services in jurisdictions in which we operate.

Changes in our effective income tax rate could reduce our earnings.

We are subject to income taxes in the United States and various foreign jurisdictions including Ireland. Due to economic and political conditions, various countries are actively considering and have made changes to existing tax laws. We cannot predict the form or timing of potential legislative and regulatory changes that could have a material adverse impact on our results of operations. For example, the United States enacted significant tax reform, and certain provisions of the new law are complex and will continue to significantly affect us.

In addition, significant judgment is required in determining our worldwide provision for income taxes. Various factors may have favorable or unfavorable effects on our income tax rate including, but not limited to, changes in forecasted demand for our HCV products, our portion of the non-tax deductible annual branded prescription drug fee, the accounting for stock options and other share-based awards, mergers and acquisitions, the ability to manufacture product in our Cork, Ireland facility, the amortization of certain acquisition related intangibles for which we receive no tax benefit, future levels of R&D spending, changes in the mix of earnings in the various tax jurisdictions in which we operate, changes in overall levels of pre-tax earnings, resolution of federal, state and foreign income tax audits, and potential changes to our legal entity structure. The impact on our income tax provision resulting from the above mentioned factors may be significant and could have a negative impact on our consolidated results of operations.

Our income tax returns are subject to audit by federal, state and foreign tax authorities. We are currently under examination by the Internal Revenue Service for the tax years from 2013 to 2015 and by various state and foreign jurisdictions. There are differing interpretations of tax laws and regulations and, as a result, significant disputes may arise with these tax authorities involving issues of the timing and amount of deductions and allocations of income among various tax jurisdictions. Resolution of one or more of these exposures in any reporting period could have a material impact on the results of operations for that period.

There can be no assurance that we will pay dividends or continue to repurchase stock.

Our Board of Directors authorized a dividend program under which we intend to pay quarterly dividends of $0.63 per share, subject to quarterly declarations by our Board of Directors. Our Board of Directors also approved the repurchase of up to $12.0 billion of our common stock, of which $4.3 billion is available for repurchase as of March 31, 2019. Any future declarations, amount and timing of any dividends and/or the amount and timing of such stock repurchases are subject to capital availability and determinations by our Board of Directors that cash dividends and/or stock repurchases are in the best interest of our stockholders and are in compliance with all respective laws and our agreements applicable to the declaration and payment of cash dividends and the repurchase of stock. Our ability to pay dividends and/or repurchase stock will depend upon, among other factors, our cash balances and potential future capital requirements for strategic transactions, including acquisitions, debt service requirements, results of operations, financial condition and other factors beyond our control that our Board of Directors may deem relevant. A reduction in or elimination of our dividend payments, our dividend program and/or stock repurchases could have a negative effect on our stock price.

Item 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

Issuer Purchases of Equity Securities

In the first quarter of 2016, our Board of Directors authorized a $12.0 billion share repurchase program (2016 Program) under which repurchases may be made in the open market or in privately negotiated transactions. We started repurchases under the 2016 Program in April 2016.

During the three months ended March 31, 2019, we repurchased and retired 12 million shares of our common stock for $834 million through open market transactions under the 2016 Program. The table below summarizes our stock repurchase activity for the three months ended March 31, 2019:

	Total Number of Shares Purchased (in thousands)		Average Price Paid per Share (in dollars)	Total Number of Shares Purchased as Part of Publicly Announced Program (in thousands)		Maximum Fair Value of Shares that May Yet Be Purchased Under the Program (in millions)
January 1 - January 31, 2019	8,999		$ 68.00	8,973		$ 4,537
February 1 - February 28, 2019	2,334		$ 67.06	1,670		$ 4,425
March 1 - March 31, 2019	2,084		$ 64.28	1,730		$ 4,313
Total	13,417	(1)	$ 67.26	12,373	(1)	

(1) The difference between the total number of shares purchased and the total number of shares purchased as part of a publicly announced program is due to shares of common stock withheld by us from employee restricted stock awards in order to satisfy applicable tax withholding obligations.

Item 3. DEFAULTS UPON SENIOR SECURITIES

Not applicable.

Item 4. MINE SAFETY DISCLOSURES

Not applicable.

Item 5. OTHER INFORMATION

Not applicable.

Item 6. EXHIBITS

Reference is made to the Exhibit Index included herein.

Exhibit Index

Exhibit Footnote	Exhibit Number	Description of Document
(1)	3.1	Restated Certificate of Incorporation of Registrant
(2)	3.2	Amended and Restated Bylaws of Registrant
	4.1	Reference is made to Exhibit 3.1 and Exhibit 3.2
(3)	4.2	Indenture related to Senior Notes, dated as of March 30, 2011, between Registrant and Wells Fargo, National Association, as Trustee
(3)	4.3	First Supplemental Indenture related to Senior Notes, dated as of March 30, 2011, between Registrant and Wells Fargo, National Association, as Trustee (including form of Senior Notes)
(4)	4.4	Second Supplemental Indenture related to Senior Notes, dated as of December 13, 2011, between Registrant and Wells Fargo, National Association, as Trustee (including Form of 2014 Note, Form of 2016 Note, Form of 2021 Note, Form of 2041 Note)
(5)	4.5	Third Supplemental Indenture related to Senior Notes, dated as of March 7, 2014, between Registrant and Wells Fargo, National Association, as Trustee (including Form of 2019 Note, Form of 2024 Note, Form of 2044 Note)
(6)	4.6	Fourth Supplemental Indenture related to Senior Notes, dated as of November 17, 2014, between Registrant and Wells Fargo, National Association, as Trustee (including Form of 2020 Note, Form of 2025 Note, Form of 2045 Note)
(7)	4.7	Fifth Supplemental Indenture, dated as of September 14, 2015, between Registrant and Wells Fargo Bank, National Association, as Trustee (including Form of 2018 Note, Form of 2020 Note, Form of 2022 Note, Form of 2026 Note, Form of 2035 Note and Form of 2046 Note)
(8)	4.8	Sixth Supplemental Indenture, dated as of September 20, 2016, between Registrant and Wells Fargo Bank, National Association, as Trustee (including Form of 2022 Note, Form of 2023 Note, Form of 2027 Note, Form of 2036 Note and Form of 2047 Note)
(9)	4.9	Seventh Supplemental Indenture, dated as of September 21, 2017, between Registrant and Wells Fargo Bank, National Association, as Trustee (including Form of Fixed Rate Note, Form of Form of September 2018 Note, Form of March 2019 Note and Form of September 2019 Note)
*(10)	10.1	Gilead Sciences, Inc. 2004 Equity Incentive Plan, as amended and restated May 10, 2017
*(11)	10.2	Form of employee stock option agreement used under 2004 Equity Incentive Plan (for grants made February 2008 through April 2009)
*(12)	10.3	Form of employee stock option agreement used under 2004 Equity Incentive Plan (for grants commencing in May 2009)
*(13)	10.4	Form of employee stock option agreement used under 2004 Equity Incentive Plan (for grants commencing in February 2010)
*(14)	10.5	Form of employee stock option agreement used under 2004 Equity Incentive Plan (for 2011 and subsequent year grants)
*(12)	10.6	Form of non-employee director option agreement used under 2004 Equity Incentive Plan (for annual grants commencing in May 2009 and through May 2012)
*(15)	10.7	Form of non-employee director option agreement used under 2004 Equity Incentive Plan (for annual grants made in May 2013)
*(15)	10.8	Form of non-employee director option agreement (non-U.S.) used under 2004 Equity Incentive Plan (for annual grants made in May 2013)
*(16)	10.9	Form of non-employee director option agreement used under 2004 Equity Incentive Plan (for annual grants made in and after May 2014)
*(15)	10.10	Form of restricted stock unit issuance agreement (non-U.S.) used under 2004 Equity Incentive Plan (for annual grants to non-employee directors commencing in May 2013)
*(17)	10.11	Form of performance share award agreement used under the 2004 Equity Incentive Plan (for TSR Goals (US) in 2016)
*(17)	10.12	Form of performance share award agreement used under the 2004 Equity Incentive Plan (for TSR Goals (US) with Director Retirement Provisions in 2016)
*(17)	10.13	Form of performance share award agreement used under the 2004 Equity Incentive Plan (for Revenue Goals (US) in 2016)
*(17)	10.14	Form of performance share award agreement used under the 2004 Equity Incentive Plan (for Revenue Goals (US) with Director Retirement Provisions in 2016)
*(18)	10.15	Form of performance share award agreement used under the 2004 Equity Incentive Plan (for TSR Goals - Non-US in 2015)
*(17)	10.16	Form of performance share award agreement used under the 2004 Equity Incentive Plan (for TSR Goals -Non-US in 2016)
*(18)	10.17	Form of performance share award agreement used under the 2004 Equity Incentive Plan (for Revenue Goals - Non-US in 2015)
*(17)	10.18	Form of performance share award agreement used under the 2004 Equity Incentive Plan (for Revenue Goals - Non-US in 2016)
*(14)	10.19	Form of restricted stock unit issuance agreement used under the 2004 Equity Incentive Plan (service-based vesting for certain executive officers commencing in 2011)
*(19)	10.20	Gilead Sciences, Inc. Employee Stock Purchase Plan, restated on January 22, 2015
*(20)	10.21	Gilead Sciences, Inc. Deferred Compensation Plan-Basic Plan Document

*(20)	10.22	Gilead Sciences, Inc. Deferred Compensation Plan-Adoption Agreement

*(20)	10.23	Addendum to the Gilead Sciences, Inc. Deferred Compensation Plan
*(21)	10.24	Gilead Sciences, Inc. 2005 Deferred Compensation Plan, as amended and restated on October 23, 2008
*(22)	10.25	Gilead Sciences, Inc. Severance Plan, as amended on March 8, 2016
*(23)	10.26	Gilead Sciences, Inc. Corporate Bonus Plan, as amended and restated on January 1, 2019
*(24)	10.27	Amended and Restated Gilead Sciences, Inc. Code Section 162(m) Bonus Plan
*(25)	10.28	Gilead Sciences, Inc. Retention Program for Executive Officers
*(26)	10.29	Offer Letter dated April 16, 2008 between Registrant and Robin Washington
*(27)	10.30	Separation Agreement and Release dated August 6, 2018 between Registrant and John F. Milligan, Ph.D.
*(28)	10.31	Offer Letter dated November 30, 2018 between Registrant and Daniel O'Day
*(29)	10.32	Form of Indemnity Agreement entered into between Registrant and its directors and executive officers
*(29)	10.33	Form of Employee Proprietary Information and Invention Agreement entered into between Registrant and certain of its officers and key employees
*(30)	10.34	Form of Employee Proprietary Information and Invention Agreement entered into between Registrant and certain of its officers and key employees (revised in September 2006)
+(31)	10.35	Amendment Agreement, dated October 25, 1993, between Registrant, the Institute of Organic Chemistry and Biochemistry (IOCB) and Rega Stichting v.z.w. (REGA), together with the following exhibits: the License Agreement, dated December 15, 1991, between Registrant, IOCB and REGA (the 1991 License Agreement), the License Agreement, dated October 15, 1992, between Registrant, IOCB and REGA (the October 1992 License Agreement) and the License Agreement, dated December 1, 1992, between Registrant, IOCB and REGA (the December 1992 License Agreement)
+(32)	10.36	Amendment Agreement between Registrant and IOCB/REGA, dated December 27, 2000 amending the 1991 License Agreement and the December 1992 License Agreement
+(33)	10.37	Sixth Amendment Agreement to the License Agreement, between IOCB/REGA and Registrant, dated August 18, 2006 amending the October 1992 License Agreement and the December 1992 License Agreement
+(34)	10.38	Seventh Amendment Agreement to the License Agreement, between IOCB/REGA and Registrant dated July 1, 2013 amending the October 1992 License Agreement and the December 1992 License Agreement
+(35)	10.39	Exclusive License Agreement between Registrant (as successor to Triangle Pharmaceuticals, Inc.), Glaxo Group Limited, The Wellcome Foundation Limited, Glaxo Wellcome Inc. and Emory University, dated May 6, 1999
+(36)	10.40	Royalty Sale Agreement by and among Registrant, Emory University and Investors Trust & Custodial Services (Ireland) Limited, solely in its capacity as Trustee of Royalty Pharma, dated July 18, 2005
+(36)	10.41	Amended and Restated License Agreement between Registrant, Emory University and Investors Trust & Custodial Services (Ireland) Limited, solely in its capacity as Trustee of Royalty Pharma, dated July 21, 2005
++(37)	10.42	Amended and Restated EVG License Agreement between Japan Tobacco Inc., and Registrant, dated November 29, 2018
++(37)	10.43	Master Agreement by and between Registrant, Gilead Sciences K.K. and Japan Tobacco Inc., dated November 29, 2018
+(38)	10.44	Amended and Restated Collaboration Agreement by and among Registrant, Gilead Sciences Ireland UC (formerly Gilead Sciences Limited) and Janssen R&D Ireland, dated December 23, 2014
+(39)	10.45	License Agreement by and among Kite Pharma, Inc., Cabaret Biotech Ltd. and Dr. Zelig Eshhar, dated December 12, 2013
	31.1***	Certification of Chief Executive Officer, as required by Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as amended
	31.2***	Certification of Chief Financial Officer, as required by Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as amended
	32.1**	Certifications of Chief Executive Officer and Chief Financial Officer, as required by Rule 13a-14(b) or Rule 15d-14(b) and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350)
	101.INS***	XBRL Instance Document
	101.SCH***	XBRL Taxonomy Extension Schema Document
	101.CAL***	XBRL Taxonomy Extension Calculation Linkbase Document
	101.DEF***	XBRL Taxonomy Extension Definition Linkbase Document
	101.LAB***	XBRL Taxonomy Extension Label Linkbase Document
	101.PRE***	XBRL Taxonomy Extension Presentation Linkbase Document

(1) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on May 8, 2014, and incorporated herein by reference.
(2) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on December 23, 2015, and incorporated herein by reference.

(3) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on April 1, 2011, and incorporated herein by reference.
(4) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on December 13, 2011, and incorporated herein by reference.
(5) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on March 7, 2014, and incorporated herein by reference.
(6) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on November 17, 2014, and incorporated herein by reference.
(7) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on September 14, 2015, and incorporated herein by reference.

(8) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on September 20, 2016, and incorporated herein by reference.
(9) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on September 21, 2017, and incorporated herein by reference.
(10) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on May 12, 2017, and incorporated herein by reference.
(11) Filed as an exhibit to Registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2007, and incorporated herein by reference.
(12) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2009, and incorporated herein by reference.
(13) Filed as an exhibit to Registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2009, and incorporated herein by reference.
(14) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2011, and incorporated herein by reference.
(15) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2013, and incorporated herein by reference
(16) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014, and incorporated herein by reference.
(17) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016, and incorporated herein by reference.
(18) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015, and incorporated herein by reference.
(19) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on May 8, 2015, and incorporated herein by reference.
(20) Filed as an exhibit to Registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2001, and incorporated herein by reference.
(21) Filed as an exhibit to Registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2008, and incorporated herein by reference.
(22) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on March 11, 2016, and incorporated herein by reference.
(23) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2018, and incorporated herein by reference.
(24) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on May 17, 2016, and incorporated herein by reference.
(25) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2018, and incorporated herein by reference.
(26) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2008, and incorporated herein by reference.
(27) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on August 7, 2018, and incorporated herein by reference.
(28) Filed as an exhibit to Registrant's Current Report on Form 8-K filed on December 10, 2018, and incorporated herein by reference.
(29) Filed as an exhibit to Registrant's Registration Statement on Form S-1 (No. 33-55680), as amended, and incorporated herein by reference.
(30) Filed as an exhibit to Registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2006, and incorporated herein by reference.
(31) Filed as an exhibit to Registrant's Annual Report on Form 10-K for the fiscal year ended March 31, 1994, and incorporated herein by reference.
(32) Filed as an exhibit to Registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2000, and incorporated herein by reference.
(33) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2006, and incorporated herein by reference.
(34) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2013, and incorporated herein by reference.
(35) Filed as an exhibit to Triangle Pharmaceuticals, Inc.'s Quarterly Report on Form 10-Q/A filed on November 3, 1999, and incorporated herein by reference.
(36) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2005, and incorporated herein by reference.
(37) Filed as an exhibit to Registrant's Amendment No. 1 to Annual Report on Form 10-K/A filed on April 18, 2019, and incorporated herein by reference.
(38) Filed as an exhibit to Registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2014, and incorporated herein by reference.
(39) Filed as an exhibit to Kite Pharma, Inc.'s Registration Statement on Form S-1/A (No. 333-196081) filed on June 17, 2014, and incorporated herein by reference.
* Management contract or compensatory plan or arrangement.
** Furnished herewith.
*** Filed herewith.
+ Certain confidential portions of this Exhibit were omitted by means of marking such portions with an asterisk (the Mark). This Exhibit has been filed separately with the Secretary of the Securities and Exchange Commission without the Mark pursuant to Registrant's Application Requesting Confidential Treatment under Rule 24b-2 under the Securities Exchange Act of 1934, as amended.
++ Certain confidential portions of this Exhibit were omitted by means of marking such portions with the Mark because the identified confidential portions are (i) not material and (ii) would be competitively harmful if publicly disclosed.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

GILEAD SCIENCES, INC.
(Registrant)

Date: May 7, 2019

/s/ DANIEL P. O'DAY

Daniel P. O'Day
Chairman and Chief Executive Officer
(Principal Executive Officer)

Date: May 7, 2019

/s/ ROBIN L. WASHINGTON

Robin L. Washington
Executive Vice President and Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 31.1

CERTIFICATION

I, Daniel P. O'Day, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Gilead Sciences, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: May 7, 2019

/s/ DANIEL P. O'DAY

Daniel P. O'Day
Chairman and Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, Robin L. Washington, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Gilead Sciences, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: May 7, 2019

/s/ ROBIN L. WASHINGTON

Robin L. Washington
Executive Vice President and Chief Financial Officer

Exhibit 32.1

CERTIFICATIONS

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (18 U.S.C. § 1350, as adopted), Daniel O'Day, the Chairman and Chief Executive Officer of Gilead Sciences, Inc. (the Company), and Robin L. Washington, the Executive Vice President and Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended March 31, 2019, to which this Certification is attached as Exhibit 32 (the Periodic Report), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the periods covered by the Periodic Report and results of operations of the Company for the periods covered by the Periodic Report.

Dated: May 7, 2019

/s/ DANIEL P. O'DAY

Daniel P. O'Day
Chairman and Chief Executive Officer

/s/ ROBIN L. WASHINGTON

Robin L. Washington
Executive Vice President and Chief Financial Officer

This certification accompanies the Form 10-Q to which it relates, is not deemed filed with the SEC and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-Q), irrespective of any general incorporation language contained in such filing.

EXHIBIT 75

BIOTECH AND PHARMA

Generic HIV prevention drug coming in 2020, Gilead says

PUBLISHED WED, MAY 8 2019•1:53 PM EDT

NBC NEWS Tim Fitzsimons

SHARE

KEY POINTS

Gilead Sciences announced Wednesday that a generic version of Truvada will be available in September 2020, one year earlier than expected.

When taken daily, Truvada prevents HIV transmission.

In the United States a month's supply sells for $1,600 to $2,000, and activists have mounted a pressure campaign to force Gilead to make the drug more widely available in order to curb the global HIV epidemic.

A pharmacist pours Truvada pills

Getty Images

Gilead Sciences announced Wednesday that a generic version of Truvada will be available in September 2020, one year earlier than expected.

Truvada is the pill used for HIV pre-exposure prophylaxis, or PrEP. When taken daily, Truvada prevents HIV transmission.

"Gilead reached an agreement with Teva Pharmaceuticals in 2014 to allow the early launch of a generic version of Truvada into the market in 2020, a year earlier than required," wrote Douglas Brooks, Gilead's executive director for community engagement, in an email shared with NBC News by the advocacy group PrEP4All.

Read more from NBC News:
Marine recruit and other Colorado STEM school students helped disarm gunman
Kentucky teen who sued over school ban for refusing chickenpox vaccination now has chickenpox
Cubs investigate fan's 'offensive' hand gesture, threaten lifetime ban

The information about generic Truvada is also disclosed on page 35 of a Gilead SEC filing released Wednesday morning.

While a month's supply of generic Truvada is available in countries around the world for as little as $70, in the United States a month's supply sells for $1,600 to $2,000, and activists have mounted a pressure campaign to force Gilead to make the drug more widely available in order to curb the global HIV epidemic.

President Donald Trump's "Ending the HIV Epidemic" plan, announced at this year's State of the Union address, will rely heavily on Truvada in order to stem the spread of the virus. But Truvada's high price threatened to make the plan extremely expensive, activists said.

Previously, in a phone call with investors in the second quarter of 2017, then-Gilead CEO John Milligan said, "We don't expect generic Truvada in the United States until 2021."

Activists who have been pushing Gilead to #BreakThePatent hailed the news Wednesday, calling it "a victory for the LGBTQ+ community, for HIV activists, and for U.S. taxpayers," but also tamped down expectations.

In a statement from the PrEP4All Collaboration, Dr. Aaron S. Lord said allowing just one generic manufacturer, Israel-based Teva Pharmaceuticals, to make generic PrEP "will do little to reduce the price in a way that will increase access, and PrEP4All remains suspicious of the terms and lack of transparency surrounding the Teva settlement."

"What's to stop them — other from a desire for profit margins — from releasing the rights now?" Lord asked.

PrEP4All had recently publicized news that Gilead's development and testing of Truvada as PrEP was almost entirely funded by the U.S. government and

therefore the CDC, not Gilead, controls the patent for PrEP. That information was first publicized by the Global Health Justice Partnership at Yale University, which wrote "based on our preliminary review, CDC's Patents for PrEP appear to be valid and enforceable."

The news that the Justice Department and Gilead were negotiating over the Truvada patent issue was first reported by The Washington Post.

An email addressed to "Colleagues" sent Wednesday morning by Douglas Brooks, Gilead's senior director for community engagement, said, "Pursuant to a settlement agreement reached in 2014 ... Teva will be able to launch generic fixed-dose combinations of emtricitabine and TDF ... on September 30, 2020."

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

Gilead did not immediately respond to a request for comment.

KEY POINTS CNBC

- Pharmaceutical companies will be required to disclose the price of its prescription medicines in television commercials, the Trump administration says.
- The requirement is set to take effect as soon as this summer and will apply to drugs that cost more than $35 for a month's supply.

EXHIBIT 76

#BREAKTHEPATENT

OFFICIAL STATEMENT RESPONDING TO GILEAD SCIENCES' ANNOUNCEMENT THAT IT WILL ALLOW TEVA TO MANUFACTURE A GENERIC VERSION OF TRUVADA

Aaron S. Lord, MD issued the following statement to Gilead Sciences' announcement that allow a single generic version of Truvada a year early:

While Gilead's announcement that generic Truvada will be made available in the United States a year early is a victory for the LGBTQ+ community, for HIV activists, and for U.S. taxpayers, this should only be the beginning. Even their announcement today leaves Gilead with exclusive rights to Truvada as PrEP for another 15 months and Teva as the only generic manufacturer on the U.S. market. This will do little to reduce the price in a way that will increase access and PrEP4All remains suspicious of the terms and lack of transparency surrounding the Teva settlement. I have to ask, what's to stop them–other than a desire for profit margins–from releasing the rights now?

Furthermore, Gilead's statement today that the agreement to allow Teva to manufacture a generic a year early was made in 2014 runs afoul of statements made to shareholders by their former CEO John F. Milligan on their Q2 2017 earnings call. In that call, he said, 'we don't expect generic Truvada in the United States until 2021.' If this agreement was made in 2014, why did he lie to shareholders?

U.S. taxpayers paid for the development of this drug, yet it's far too expensive for the people who need it most. Gilead currently prices at between $1,600 and $2,000 for a month's supply of a pill that can be manufactured for a fraction of that amount. We must make sure that every one who needs it can get it.

Finally, the CDC must use the billions of dollars that the American people overpaid to create a national HIV prevention program, aimed at breaking down structural and systemic barriers that prevent the most at-risk communities from accessing the medication. Additionally, the CDC must use its significant leverage to ensure that generic Truvada is available at a price affordable to everyone in this country.

The PREP4ALL Collaboration is a group of activists of diverse backgrounds, dedicated to ensuring wider access to life-saving drugs like PrEP and ending the HIV epidemic. For additional information about the PREP4ALL Collaboration and its campaign to ensure access to PrEP, visit www.breakthepatent.org.

MAY 8, 2019

SHARE

TAKE ACTION

HELP SPREAD THE WORD

SHARE TWEET

ADD YOUR NAME

FIRST NAME* LAST NAME*

EMAIL ADDRESS*

ZIP

ADD YOUR NAME

EXHIBIT 77

Generic PrEP to Arrive in September 2020, but Will Big Savings Follow?

Only one company will sell a version of the HIV prevention pill Truvada. When others go to market, prices will likely drop further.

May 9, 2019 By Trenton Straube

A generic version of the HIV prevention pill Truvada as PrEP, or pre-exposure prophylaxis, will be available in September 2020, a year before expected, according to an announcement by the drug's manufacturer, Gilead Sciences, reports NBC News.

The approval of generic versions of meds is usually met with praise because it means significant cost savings to the consumer—and therefore more access to people who need the medicine. But the case of generic Truvada seems to raise more questions than acclaim.

For starters, only one company, the Israeli-based Teva Pharmaceutical Industries, will be allowed to sell the generic version of Truvada in the U.S. market, starting September 30, 2020.

The agreement with Teva was made in 2014 but only announced now. Why is that, activists want to know. Is it because groups such as ACT UP, Health GAP and the PrEP4ALL Collaboration have been urging the federal government to #BreakThePatent on Truvada, a call that has intensified after the recent revelation that the federal Centers for Disease Control and Prevention holds patents on the drug?

That is not the case, according to a statement from Gilead, which reads: "Gilead reached an agreement with Teva Pharmaceutical in 2014 to allow the early launch of a generic version of Truvada into the market in the United States in 2020, a year earlier than required. This agreement is not related to current discussions with the federal government to determine the best ways to broaden access to Truvada for PrEP for vulnerable populations in the United States and support the federal plan to end the HIV epidemic."

Regardless, Gilead's agreement could give Teva exclusive rights to generic Truvada for about a year. That's because Truvada is made of two different meds: tenofovir disoproxil fumarate (TDF) and emtricitabine. The patent on TDF has already expired (an updated version, tenofovir alafenamide, TAF, is on the market), but the patent for emtricitabine isn't set to expire until September 2021, according to Gilead.

This means Teva will have no competition to force its generic prices much lower than the brand-name version, explains Tim Horn, the director of medication access and pricing at the National Alliance of State & Territorial Directors (NASTAD), in an email exchange with POZ (full disclosure: Horn is a former editor at POZ).

“Historically,” Horn says, “when there’s only one generic manufacturer in the field, the price difference is a miniscule 10% to 15%. The real savings for all purchasers and payers won’t begin until there’s robust generic competition.”

A month’s supply of Truvada in the United States is priced from $1,600 to $2,000 (despite costing only a fraction of that amount to manufacture). This means that Teva’s generic med could still be out of reach for those who need it most, such as young gay Black men and transgender women.

Of course, it must be pointed out that many insurance providers, including Medicaid, cover Truvada and that Gilead offers a copay card. So the oft-repeated price tag of $1,600 shouldn’t deter anyone from trying to access Truvada today.

Other issues will come into play and affect the meds’ costs, says Horn, who raises the possibility that Gilead may discontinue its copay assistance program for Truvada at the end of September 2020 and that Teva may elect not to set up its own program. At this point, it’s impossible to predict the resulting price tags for the meds.

AIDS activist Peter Staley, in a Facebook post about generic Truvada, warned that “Teva can expect to become PrEP4All’s next target if they don’t launch their own patient assistance programs.” Staley’s post, embedded below, also includes text from a correspondence with Douglas Brooks, Gilead’s senior director for community engagement.

What’s more, Gilead’s HIV pill Descovy (made of emtricitabine and the updated tenofovir) will likely be approved for PrEP by the end of 2019, well before the generic Truvada hits the market. If that happens, NASTAD’s Horn says, Descovy will have a robust copay assistance program. “It’s unclear if the end result will be cost savings and improved access with a generic versus mass exodus to high-cost Descovy,” Horn says.

Meanwhile, Aaron S. Lord, MD, with the PrEP4All Collaboration, issued a statement on the announcement of Teva’s generic Truvada. It reads in part:

> “While Gilead’s announcement that generic Truvada will be made available in the United States a year early is a victory for the LGBTQ+ community, for HIV activists and for U.S. taxpayers, this should only be the beginning. Even their announcement today leaves Gilead with exclusive rights to Truvada as PrEP for another 15 months and Teva as the only generic manufacturer on the U.S. market. This will do little to reduce the price in a way that will increase access, and PrEP4All remains suspicious of the terms and lack of transparency surrounding the Teva settlement. I have to ask, what’s to stop them–other than a desire for profit margins–from releasing the rights now?

> "Furthermore, Gilead's statement…that the agreement to allow Teva to manufacture a generic a year early was made in 2014 runs afoul of statements made to shareholders by their former CEO John F. Milligan on their Q2 2017 earnings call. In that call, he said, 'We don't expect generic Truvada in the United States until 2021.' If this agreement was made in 2014, why did he lie to shareholders?"

To read more about Gilead's Descovy as PrEP, click here; to read about efforts to #BreakThePatent, click here; and for news that the CDC owns the patent to Truvada as PrEP, click here.

EXHIBIT 78

From: Prestia, Laura (NIH/OD) [F]
To: Jay.Parrish@gilead.com
Cc: Kirby, Tara (NIH/NIAID) [E]
Subject: RE: Centers for Disease Control NIH Office of Tech Transfer - HIV Technology Licensing Inquiry
Date: Thursday, October 23, 2014 11:39:10 AM

Good morning Dr. Parrish,

In light of your recent and ongoing interest in and success with Truvada, your company appears to be an ideal partner for a technology developed by Dr. Walid Heneine at the Centers for Disease Control and Prevention (CDC).

Dr. Heneine's group has shown that daily pre-exposure prophylaxis (PrEP) with emtricitabine in combination with tenofovir disoproxil fumarate (Truvada) significantly increases the level of protection against HIV transmission. This finding was discovered following repeated virus challenges with macaque monkeys. The CDC is pursuing U.S. and foreign patent protection for this technology.

An abstract with more information can be found in the Federal Register. Also, Dr. Heneine has co-authored publications in PLoS Medicine and Science Translational Medicine, describing the above discovery.

Please contact me if I can be of further assistance.

Best regards,

Laura T. Prestia, Ph.D.
Technology Transfer Fellow-CDC Unit
Office of Technology Transfer
National Institutes of Health
6011 Executive Boulevard, #325
Rockville, MD 20850-3804

Office: 301-594-3283
Email: Laura.prestia@nih.gov
OTT website: http://www.ott.nih.gov

EXHIBIT 79

United States of America
United States Patent and Trademark Office

TRUVADA FOR PREP

Reg. No. 5,358,262

Registered Dec. 19, 2017

Int. Cl.: 5, 44

Service Mark

Trademark

Principal Register

Gilead Sciences Inc. (DELAWARE CORPORATION)
333 Lakeside Drive
Foster City, CALIFORNIA 94404

CLASS 5: Anti-viral pharmaceutical preparations; pharmaceutical preparations for the treatment and prevention of infectious diseases; pharmaceutical preparations for the treatment of immune dysfunction; pharmaceutical preparations for the treatment and prevention of human immunodeficiency virus infection

FIRST USE 2-6-2017; IN COMMERCE 2-6-2017

CLASS 44: Information and advisory services relating to pharmaceuticals, diseases and medical conditions and treatments, namely, pharmaceutical advice, medical and pharmaceutical consultation, medical advisory services, and providing medical information, consultancy and advisory services; information and advisory services relating to pharmaceuticals, diseases and medical conditions and treatments, namely, pharmaceutical advice, medical and pharmaceutical consultation, medical advisory services, and providing medical information, consultancy and advisory services provided on-line over a computer network and the Internet; providing medical information and advisory services regarding HIV infection

FIRST USE 1-11-2016; IN COMMERCE 1-11-2016

THE MARK CONSISTS OF STANDARD CHARACTERS WITHOUT CLAIM TO ANY PARTICULAR FONT STYLE, SIZE OR COLOR

OWNER OF EUROPEAN UNION , REG. NO. 015787484, DATED 12-29-2016, EXPIRES 08-30-2026

OWNER OF U.S. REG. NO. 2915213

No claim is made to the exclusive right to use the following apart from the mark as shown: "FOR PREP"

SER. NO. 87-292,084, FILED 01-06-2017

UNITED STATES PATENT AND TRADEMARK OFFICE · DEPARTMENT OF COMMERCE

Joseph Matal

Performing the Functions and Duties of the
Under Secretary of Commerce for
Intellectual Property and Director of the
United States Patent and Trademark Office

REQUIREMENTS TO MAINTAIN YOUR FEDERAL TRADEMARK REGISTRATION

WARNING: YOUR REGISTRATION WILL BE CANCELLED IF YOU DO NOT FILE THE DOCUMENTS BELOW DURING THE SPECIFIED TIME PERIODS.

Requirements in the First Ten Years*
What and When to File:

- ***First Filing Deadline:*** You must file a Declaration of Use (or Excusable Nonuse) between the 5th and 6th years after the registration date. See 15 U.S.C. §§1058, 1141k. If the declaration is accepted, the registration will continue in force for the remainder of the ten-year period, calculated from the registration date, unless cancelled by an order of the Commissioner for Trademarks or a federal court.

- ***Second Filing Deadline:*** You must file a Declaration of Use (or Excusable Nonuse) and an Application for Renewal between the 9th and 10th years after the registration date.* See 15 U.S.C. §1059.

Requirements in Successive Ten-Year Periods*
What and When to File:

- You must file a Declaration of Use (or Excusable Nonuse) and an Application for Renewal between every 9th and 10th-year period, calculated from the registration date.*

Grace Period Filings*

The above documents will be accepted as timely if filed within six months after the deadlines listed above with the payment of an additional fee.

***ATTENTION MADRID PROTOCOL REGISTRANTS:** The holder of an international registration with an extension of protection to the United States under the Madrid Protocol must timely file the Declarations of Use (or Excusable Nonuse) referenced above directly with the United States Patent and Trademark Office (USPTO). The time periods for filing are based on the U.S. registration date (not the international registration date). The deadlines and grace periods for the Declarations of Use (or Excusable Nonuse) are identical to those for nationally issued registrations. See 15 U.S.C. §§1058, 1141k. However, owners of international registrations do not file renewal applications at the USPTO. Instead, the holder must file a renewal of the underlying international registration at the International Bureau of the World Intellectual Property Organization, under Article 7 of the Madrid Protocol, before the expiration of each ten-year term of protection, calculated from the date of the international registration. See 15 U.S.C. §1141j. For more information and renewal forms for the international registration, see http://www.wipo.int/madrid/en/.

NOTE: Fees and requirements for maintaining registrations are subject to change. Please check the USPTO website for further information. With the exception of renewal applications for registered extensions of protection, you can file the registration maintenance documents referenced above online at http://www.uspto.gov.

NOTE: A courtesy e-mail reminder of USPTO maintenance filing deadlines will be sent to trademark owners/holders who authorize e-mail communication and maintain a current e-mail address with the USPTO. To ensure that e-mail is authorized and your address is current, please use the Trademark Electronic Application System (TEAS) Correspondence Address and Change of Owner Address Forms available at http://www.uspto.gov.

EXHIBIT 80

United States of America
United States Patent and Trademark Office

Truvada
emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg tablets
for PrEP pre-exposure prophylaxis

Reg. No. 5,623,246

Registered Dec. 04, 2018

Int. Cl.: 35, 44

Service Mark

Principal Register

Gilead Sciences, Inc. (DELAWARE CORPORATION)
333 Lakeside Drive
Foster City, CALIFORNIA 94404

CLASS 35: Promoting public awareness on the prevention of HIV infection

FIRST USE 4-00-2018; IN COMMERCE 4-00-2018

CLASS 44: Medical services, namely, providing information regarding the prevention of HIV infection

FIRST USE 4-00-2018; IN COMMERCE 4-00-2018

The color(s) blue, orange, gray and white is/are claimed as a feature of the mark.

The mark consists of a diamond shape divided in two by a horizontally aligned wavy band with the top portion in the color blue and the bottom portion in the color orange, to the right of this design is the wording "TRUVADA" displayed in large letters on a single line in the color gray, the wording "EMTRICITABINE 200 MG / TENOFOVIR" appears below this on a single line in the color gray, "DISOPROXIL FUMARATE 300 MG TABLETS" appears below this on a single line in the color gray and "FOR PREP PRE-EXPOSURE PROPHYLAXIS" appears below this on a single line in the color gray with the wording "FOR PRE-EXPOSURE PROPHYLAXIS" in the color blue and the wording "PREP" in the color white inside a blue oval.

OWNER OF U.S. REG. NO. 4830044, 2915213, 3521014

No claim is made to the exclusive right to use the following apart from the mark as shown: "EMTRICITABINE 200 MG / TENOFOVIR DISOPROXIL FUMARATE 300 MG TABLETS FOR PREP PRE-EXPOSURE PROPHYLAXIS"

SER. NO. 87-227,314, FILED 11-04-2016

UNITED STATES PATENT AND TRADEMARK OFFICE · DEPARTMENT OF COMMERCE

Andrei Iancu

Director of the United States
Patent and Trademark Office

REQUIREMENTS TO MAINTAIN YOUR FEDERAL TRADEMARK REGISTRATION

WARNING: YOUR REGISTRATION WILL BE CANCELLED IF YOU DO NOT FILE THE DOCUMENTS BELOW DURING THE SPECIFIED TIME PERIODS.

Requirements in the First Ten Years*
What and When to File:

- ***First Filing Deadline:*** You must file a Declaration of Use (or Excusable Nonuse) between the 5th and 6th years after the registration date. See 15 U.S.C. §§1058, 1141k. If the declaration is accepted, the registration will continue in force for the remainder of the ten-year period, calculated from the registration date, unless cancelled by an order of the Commissioner for Trademarks or a federal court.

- ***Second Filing Deadline:*** You must file a Declaration of Use (or Excusable Nonuse) and an Application for Renewal between the 9th and 10th years after the registration date.* See 15 U.S.C. §1059.

Requirements in Successive Ten-Year Periods*
What and When to File:

- You must file a Declaration of Use (or Excusable Nonuse) and an Application for Renewal between every 9th and 10th-year period, calculated from the registration date.*

Grace Period Filings*

The above documents will be accepted as timely if filed within six months after the deadlines listed above with the payment of an additional fee.

***ATTENTION MADRID PROTOCOL REGISTRANTS:** The holder of an international registration with an extension of protection to the United States under the Madrid Protocol must timely file the Declarations of Use (or Excusable Nonuse) referenced above directly with the United States Patent and Trademark Office (USPTO). The time periods for filing are based on the U.S. registration date (not the international registration date). The deadlines and grace periods for the Declarations of Use (or Excusable Nonuse) are identical to those for nationally issued registrations. See 15 U.S.C. §§1058, 1141k. However, owners of international registrations do not file renewal applications at the USPTO. Instead, the holder must file a renewal of the underlying international registration at the International Bureau of the World Intellectual Property Organization, under Article 7 of the Madrid Protocol, before the expiration of each ten-year term of protection, calculated from the date of the international registration. See 15 U.S.C. §1141j. For more information and renewal forms for the international registration, see http://www.wipo.int/madrid/en/.

NOTE: Fees and requirements for maintaining registrations are subject to change. Please check the USPTO website for further information. With the exception of renewal applications for registered extensions of protection, you can file the registration maintenance documents referenced above online at http://www.uspto.gov.

NOTE: A courtesy e-mail reminder of USPTO maintenance filing deadlines will be sent to trademark owners/holders who authorize e-mail communication and maintain a current e-mail address with the USPTO. To ensure that e-mail is authorized and your address is current, please use the Trademark Electronic Application System (TEAS) Correspondence Address and Change of Owner Address Forms available at http://www.uspto.gov.

EXHIBIT 81

PTO Form 1478 (Rev 09/2006)
OMB No. 0651-0009 (Exp 02/28/2021)

Trademark/Service Mark Application, Principal Register

Serial Number: 88266226
Filing Date: 01/17/2019

The table below presents the data as entered.

Input Field	Entered
SERIAL NUMBER	88266226
MARK INFORMATION	
***MARK**	DESCOVY FOR PREP
STANDARD CHARACTERS	YES
USPTO-GENERATED IMAGE	YES
LITERAL ELEMENT	DESCOVY FOR PREP
MARK STATEMENT	The mark consists of standard characters, without claim to any particular font style, size, or color.
REGISTER	Principal
APPLICANT INFORMATION	
***OWNER OF MARK**	Gilead Sciences Ireland UC
***STREET**	IDA BUSINESS AND TECHNOLOGY PARK
***CITY**	CARRIGTOHILL, CO. CORK
***COUNTRY**	Ireland
PHONE	650-522-2401
FAX	(650) 522-5575
EMAIL ADDRESS	trademarks@gilead.com
WEBSITE ADDRESS	www.gilead.com
LEGAL ENTITY INFORMATION	
TYPE	UNLIMITED COMPANY
STATE/COUNTRY WHERE LEGALLY ORGANIZED	Ireland
GOODS AND/OR SERVICES AND BASIS INFORMATION	
INTERNATIONAL CLASS	005
***IDENTIFICATION**	Anti-viral pharmaceutical preparations; pharmaceutical preparations for the treatment and prevention of infectious diseases; pharmaceutical preparations for the treatment of immune dysfunction; pharmaceutical preparations for the treatment and prevention of human immunodeficiency virus infection.
FILING BASIS	SECTION 1(b)
FILING BASIS	SECTION 44(d)
FOREIGN APPLICATION NUMBER	018009954

FOREIGN APPLICATION COUNTRY	European Union Trademark - EUTM
FOREIGN FILING DATE	01/14/2019
INTENT TO PERFECT 44(d)	At this time, the applicant intends to rely on Section 44(e) as a basis for registration and requests that the application be suspended to await the submission of the foreign registration. If ultimately the applicant does not rely on §44(e) as a basis for registration, a valid claim of priority may be retained.
INTERNATIONAL CLASS	044
*IDENTIFICATION	Information and advisory services relating to pharmaceuticals, diseases and medical conditions and treatments, namely, pharmaceutical advice, medical and pharmaceutical consultation, medical advisory services, and providing medical information, consultancy and advisory services; information and advisory services relating to pharmaceuticals, diseases and medical conditions and treatments, namely, pharmaceutical advice, medical and pharmaceutical consultation, medical advisory services, and providing medical information, consultancy and advisory services provided on-line over a computer network and the Internet; providing medical information and advisory services regarding HIV infection.
FILING BASIS	SECTION 44(d)
FOREIGN APPLICATION NUMBER	018009954
FOREIGN APPLICATION COUNTRY	European Union Trademark - EUTM
FOREIGN FILING DATE	01/14/2019
INTENT TO PERFECT 44(d)	At this time, the applicant intends to rely on Section 44(e) as a basis for registration and requests that the application be suspended to await the submission of the foreign registration. If ultimately the applicant does not rely on §44(e) as a basis for registration, a valid claim of priority may be retained.
ADDITIONAL STATEMENTS SECTION	
DISCLAIMER	No claim is made to the exclusive right to use FOR PREP apart from the mark as shown.
ACTIVE PRIOR REGISTRATION(S)	The applicant claims ownership of active prior U.S. Registration Number(s) 4876632.
ATTORNEY INFORMATION	
NAME	Gretchen R. Stroud
FIRM NAME	Gilead Sciences, Inc.
STREET	333 LAKESIDE DRIVE
CITY	FOSTER CITY
STATE	California
COUNTRY	United States
ZIP/POSTAL CODE	94404
PHONE	650-522-2401
FAX	(650) 522-5575
EMAIL ADDRESS	trademarks@gilead.com

AUTHORIZED TO COMMUNICATE VIA EMAIL	Yes
OTHER APPOINTED ATTORNEY	Lori Mayall, Jack Wessel, Cynthia Smuzynska and Shelley Lai
CORRESPONDENCE INFORMATION	
NAME	Gretchen R. Stroud
FIRM NAME	Gilead Sciences, Inc.
STREET	333 LAKESIDE DRIVE
CITY	FOSTER CITY
STATE	California
COUNTRY	United States
ZIP/POSTAL CODE	94404
PHONE	650-522-2401
FAX	(650) 522-5575
*EMAIL ADDRESS	trademarks@gilead.com; trademarks@gilead.com
*AUTHORIZED TO COMMUNICATE VIA EMAIL	Yes
FEE INFORMATION	
APPLICATION FILING OPTION	TEAS RF
NUMBER OF CLASSES	2
APPLICATION FOR REGISTRATION PER CLASS	275
*TOTAL FEE DUE	550
*TOTAL FEE PAID	550
SIGNATURE INFORMATION	
SIGNATURE	/Gretchen R. Stroud/
SIGNATORY'S NAME	Gretchen R. Stroud
SIGNATORY'S POSITION	Senior Associate General Counsel
SIGNATORY'S PHONE NUMBER	650-522-2401
DATE SIGNED	01/17/2019

PTO Form 1478 (Rev 09/2006)
OMB No. 0651-0009 (Exp 02/28/2021)

Trademark/Service Mark Application, Principal Register

Serial Number: 88266226
Filing Date: 01/17/2019

To the Commissioner for Trademarks:

MARK: DESCOVY FOR PREP (Standard Characters, see mark)
The literal element of the mark consists of DESCOVY FOR PREP.
The mark consists of standard characters, without claim to any particular font style, size, or color.

The applicant, Gilead Sciences Ireland UC, a UNLIMITED COMPANY legally organized under the laws of Ireland, having an address of
IDA BUSINESS AND TECHNOLOGY PARK
CARRIGTOHILL, CO. CORK
Ireland
650-522-2401(phone)
(650) 522-5575(fax)
trademarks@gilead.com (not authorized)

requests registration of the trademark/service mark identified above in the United States Patent and Trademark Office on the Principal Register established by the Act of July 5, 1946 (15 U.S.C. Section 1051 et seq.), as amended, for the following:

International Class 005: Anti-viral pharmaceutical preparations; pharmaceutical preparations for the treatment and prevention of infectious diseases; pharmaceutical preparations for the treatment of immune dysfunction; pharmaceutical preparations for the treatment and prevention of human immunodeficiency virus infection.
Intent to Use: The applicant has a bona fide intention, and is entitled, to use the mark in commerce on or in connection with the identified goods/services.

Priority based on foreign filing: The applicant has a bona fide intention, and is entitled, to use the mark in commerce on or in connection with the identified goods/services and asserts a claim of priority based on European Union Trademark - EUTM application number 018009954, filed 01/14/2019.
INTENT TO PERFECT 44(d) : At this time, the applicant intends to rely on Section 44(e) as a basis for registration and requests that the application be suspended to await the submission of the foreign registration. If ultimately the applicant does not rely on §44(e) as a basis for registration, a valid claim of priority may be retained.

International Class 044: Information and advisory services relating to pharmaceuticals, diseases and medical conditions and treatments, namely, pharmaceutical advice, medical and pharmaceutical consultation, medical advisory services, and providing medical information, consultancy and advisory services; information and advisory services relating to pharmaceuticals, diseases and medical conditions and treatments, namely, pharmaceutical advice, medical and pharmaceutical consultation, medical advisory services, and providing medical information, consultancy and advisory services provided on-line over a computer network and the Internet; providing medical information and advisory services regarding HIV infection.

Priority based on foreign filing: The applicant has a bona fide intention, and is entitled, to use the mark in commerce on or in connection with the identified goods/services and asserts a claim of priority based on European Union Trademark - EUTM application number 018009954, filed 01/14/2019.
INTENT TO PERFECT 44(d) : At this time, the applicant intends to rely on Section 44(e) as a basis for registration and requests that the application be suspended to await the submission of the foreign registration. If ultimately the applicant does not rely on §44(e) as a basis for registration, a valid claim of priority may be retained.

Disclaimer
No claim is made to the exclusive right to use FOR PREP apart from the mark as shown.

Claim of Active Prior Registration(s)

The applicant claims ownership of active prior U.S. Registration Number(s) 4876632.

For informational purposes only, applicant's website address is: www.gilead.com

The applicant's current Attorney Information:

Gretchen R. Stroud and Lori Mayall, Jack Wessel, Cynthia Smuzynska and Shelley Lai of Gilead Sciences, Inc. 333 LAKESIDE DRIVE
FOSTER CITY, California 94404
United States
650-522-2401(phone)
(650) 522-5575(fax)
trademarks@gilead.com (authorized)

The applicant's current Correspondence Information:

Gretchen R. Stroud
Gilead Sciences, Inc.
333 LAKESIDE DRIVE
FOSTER CITY, California 94404
650-522-2401(phone)
(650) 522-5575(fax)
trademarks@gilead.com;trademarks@gilead.com (authorized)

E-mail Authorization: I authorize the USPTO to send e-mail correspondence concerning the application to the applicant, the applicant's attorney, or the applicant's domestic representative at the e-mail address provided in this application. I understand that a valid e-mail address must be maintained and that the applicant or the applicant's attorney must file the relevant subsequent application-related submissions via the Trademark Electronic Application System (TEAS). Failure to do so will result in the loss of TEAS Reduced Fee status and a requirement to submit an additional processing fee of $125 per international class of goods/services.

A fee payment in the amount of $550 has been submitted with the application, representing payment for 2 class(es).

Declaration

☑ **Basis:**
If the applicant is filing the application based on use in commerce under 15 U.S.C. § 1051(a):

- The signatory believes that the applicant is the owner of the trademark/service mark sought to be registered;
- The mark is in use in commerce on or in connection with the goods/services in the application;
- The specimen(s) shows the mark as used on or in connection with the goods/services in the application; and
- To the best of the signatory's knowledge and belief, the facts recited in the application are accurate.

And/Or
If the applicant is filing the application based on an intent to use the mark in commerce under 15 U.S.C. § 1051(b), § 1126(d), and/or § 1126(e):

- The signatory believes that the applicant is entitled to use the mark in commerce;
- The applicant has a bona fide intention to use the mark in commerce on or in connection with the goods/services in the application; and
- To the best of the signatory's knowledge and belief, the facts recited in the application are accurate.

☑ To the best of the signatory's knowledge and belief, no other persons, except, if applicable, concurrent users, have the right to use the mark in commerce, either in the identical form or in such near resemblance as to be likely, when used on or in connection with the goods/services of such other persons, to cause confusion or mistake, or to deceive.

☑ To the best of the signatory's knowledge, information, and belief, formed after an inquiry reasonable under the circumstances, the allegations and other factual contentions made above have evidentiary support.

☑ The signatory being warned that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements and the like may jeopardize the validity of the application or submission or any registration resulting therefrom, declares that all statements made of his/her own knowledge are true and all statements made on information and belief are believed to be true.

Declaration Signature

Signature: /Gretchen R. Stroud/ Date: 01/17/2019
Signatory's Name: Gretchen R. Stroud
Signatory's Position: Senior Associate General Counsel
Payment Sale Number: 88266226
Payment Accounting Date: 01/18/2019

Serial Number: 88266226
Internet Transmission Date: Thu Jan 17 18:49:47 EST 2019
TEAS Stamp: USPTO/BAS-XXX.XXX.XXX.XX-201901171849473
45865-88266226-620f4a0327399c9ed903a3d62
d4d2f83cc8a64f9d5298c879b4d95a9e067ce6e6
0-DA-19210-20190117123206792919

DESCOVY FOR PREP

EXHIBIT 82

PTO Form 1478 (Rev 09/2006)
OMB No. 0651-0009 (Exp 02/28/2021)

Trademark/Service Mark Application, Principal Register

Serial Number: 88615918
Filing Date: 09/13/2019

The table below presents the data as entered.

Input Field	Entered
SERIAL NUMBER	88615918
MARK INFORMATION	
***MARK**	\\TICRS\EXPORT17\IMAGEOUT 17\886\159\88615918\xml1\ RFA0002.JPG
SPECIAL FORM	YES
USPTO-GENERATED IMAGE	NO
LITERAL ELEMENT	Descovy emtricitabine 200 mg / tenofovir alafenamide 25mg tablets for PrEP pre-exposure prophylaxis
COLOR MARK	YES
COLOR(S) CLAIMED (If applicable)	The color(s) blue, light blue, and black is/are claimed as a feature of the mark.
***DESCRIPTION OF THE MARK (and Color Location, if applicable)**	The mark consists of a blue diamond with an incomplete lighter blue diamond below it along with the word "Descovy" to the right and the words "emtricitabine 200 mg / tenofovir alafenamide 25mg tablets beneath "Descovy". The bottom of the mark consists of a blue oblong shaped pill design with a capital letter "P", lower case "r", capital letter "E" and capital letter "P" within the pill design. The word "for" is to the left of the blue pill design and the words "pre-exposure prophylaxis" are to the right of the blue pill design.
PIXEL COUNT ACCEPTABLE	YES
PIXEL COUNT	944 x 384
REGISTER	Principal
APPLICANT INFORMATION	
***OWNER OF MARK**	Gilead Sciences Ireland UC
***STREET**	IDA Business and Technology Park
***CITY**	Carrigtohill, Co. Cork
***COUNTRY**	Ireland
EMAIL ADDRESS	trademarks@gilead.com
WEBSITE ADDRESS	www.gilead.com
LEGAL ENTITY INFORMATION	
TYPE	Unlimited Company
STATE/COUNTRY WHERE LEGALLY ORGANIZED	Ireland
GOODS AND/OR SERVICES AND BASIS INFORMATION	

INTERNATIONAL CLASS	005
***IDENTIFICATION**	Anti-viral pharmaceutical preparations; pharmaceutical preparations for the treatment and prevention of infectious diseases; pharmaceutical preparations for the treatment of immune dysfunction; pharmaceutical preparations for the treatment and prevention of human immunodeficiency virus infection
FILING BASIS	SECTION 1(b)
FILING BASIS	SECTION 44(d)
FOREIGN APPLICATION NUMBER	2019/01636
FOREIGN APPLICATION COUNTRY	Ireland
FOREIGN FILING DATE	09/06/2019
INTENT TO PERFECT 44(d)	At this time, the applicant intends to rely on Section 44(e) as a basis for registration and requests that the application be suspended to await the submission of the foreign registration. If ultimately the applicant does not rely on §44(e) as a basis for registration, a valid claim of priority may be retained.
INTERNATIONAL CLASS	044
***IDENTIFICATION**	Information and advisory services relating to pharmaceuticals, diseases and medical conditions and treatments, namely, pharmaceutical advice, medical and pharmaceutical consultation, medical advisory services, and providing medical information, consultancy and advisory services; information and advisory services relating to pharmaceuticals, diseases and medical conditions and treatments, namely, pharmaceutical advice, medical and pharmaceutical consultation, medical advisory services, and providing medical information, consultancy and advisory services provided on-line over a computer network and the Internet; providing medical information and advisory services regarding HIV infection
FILING BASIS	SECTION 1(b)
FILING BASIS	SECTION 44(d)
FOREIGN APPLICATION NUMBER	2019/01636
FOREIGN APPLICATION COUNTRY	Ireland
FOREIGN FILING DATE	09/06/2019
INTENT TO PERFECT 44(d)	At this time, the applicant intends to rely on Section 44(e) as a basis for registration and requests that the application be suspended to await the submission of the foreign registration. If ultimately the applicant does not rely on §44(e) as a basis for registration, a valid claim of priority may be retained.
ADDITIONAL STATEMENTS SECTION	
DISCLAIMER	No claim is made to the exclusive right to use emtricitabine 200 mg / tenofovir alafenamide 25mg tablets for PrEP pre-exposure prophylaxis apart from the mark as shown.
ACTIVE PRIOR REGISTRATION(S)	The applicant claims ownership of active prior U.S. Registration Number(s) 4876632 and 5067220.
ATTORNEY INFORMATION	

NAME	Gretchen R. Stroud
ATTORNEY BAR MEMBERSHIP NUMBER	XXX
YEAR OF ADMISSION	XXXX
U.S. STATE/ COMMONWEALTH/ TERRITORY	XX
FIRM NAME	Gilead Sciences, Inc.
STREET	333 Lakeside Drive
CITY	Foster City
STATE	California
COUNTRY	United States
ZIP/POSTAL CODE	94404
PHONE	650-522-2401
FAX	650-522-5575
EMAIL ADDRESS	trademarks@gilead.com
AUTHORIZED TO COMMUNICATE VIA EMAIL	Yes
OTHER APPOINTED ATTORNEY	Lori Mayall; Jack Wessel; Cynthia Smuzynska; Shelley Lai
CORRESPONDENCE INFORMATION	
NAME	Gretchen R. Stroud
FIRM NAME	Gilead Sciences, Inc.
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*AUTHORIZED TO COMMUNICATE VIA EMAIL	Yes
FEE INFORMATION	
APPLICATION FILING OPTION	TEAS RF
NUMBER OF CLASSES	2
APPLICATION FOR REGISTRATION PER CLASS	275
*TOTAL FEE DUE	550
*TOTAL FEE PAID	550
SIGNATURE INFORMATION	
SIGNATURE	/Gretchen R. Stroud/
SIGNATORY'S NAME	Gretchen R. Stroud
SIGNATORY'S POSITION	Attorney of record, California bar member
SIGNATORY'S PHONE NUMBER	650-522-2401

DATE SIGNED	09/12/2019

Trademark/Service Mark Application, Principal Register

Serial Number: 88615918
Filing Date: 09/13/2019

To the Commissioner for Trademarks:

MARK: Descovy emtricitabine 200 mg / tenofovir alafenamide 25mg tablets for PrEP pre-exposure prophylaxis (stylized and/or with design, see mark)
The literal element of the mark consists of Descovy emtricitabine 200 mg / tenofovir alafenamide 25mg tablets for PrEP pre-exposure prophylaxis. The color(s) blue, light blue, and black is/are claimed as a feature of the mark. The mark consists of a blue diamond with an incomplete lighter blue diamond below it along with the word "Descovy" to the right and the words "emtricitabine 200 mg / tenofovir alafenamide 25mg tablets beneath "Descovy". The bottom of the mark consists of a blue oblong shaped pill design with a capital letter "P", lower case "r", capital letter "E" and capital letter "P" within the pill design. The word "for" is to the left of the blue pill design and the words "pre-exposure prophylaxis" are to the right of the blue pill design.
The applicant, Gilead Sciences Ireland UC, a Unlimited Company legally organized under the laws of Ireland, having an address of

IDA Business and Technology Park
Carrigtohill, Co. Cork
Ireland
trademarks@gilead.com

requests registration of the trademark/service mark identified above in the United States Patent and Trademark Office on the Principal Register established by the Act of July 5, 1946 (15 U.S.C. Section 1051 et seq.), as amended, for the following:

International Class 005: Anti-viral pharmaceutical preparations; pharmaceutical preparations for the treatment and prevention of infectious diseases; pharmaceutical preparations for the treatment of immune dysfunction; pharmaceutical preparations for the treatment and prevention of human immunodeficiency virus infection
Intent to Use: The applicant has a bona fide intention, and is entitled, to use the mark in commerce on or in connection with the identified goods/services.

Priority based on foreign filing: The applicant has a bona fide intention, and is entitled, to use the mark in commerce on or in connection with the identified goods/services and asserts a claim of priority based on Ireland application number 2019/01636, filed 09/06/2019.
INTENT TO PERFECT 44(d) : At this time, the applicant intends to rely on Section 44(e) as a basis for registration and requests that the application be suspended to await the submission of the foreign registration. If ultimately the applicant does not rely on §44(e) as a basis for registration, a valid claim of priority may be retained.

International Class 044: Information and advisory services relating to pharmaceuticals, diseases and medical conditions and treatments, namely, pharmaceutical advice, medical and pharmaceutical consultation, medical advisory services, and providing medical information, consultancy and advisory services; information and advisory services relating to pharmaceuticals, diseases and medical conditions and treatments, namely, pharmaceutical advice, medical and pharmaceutical consultation, medical advisory services, and providing medical information, consultancy and advisory services provided on-line over a computer network and the Internet; providing medical information and advisory services regarding HIV infection
Intent to Use: The applicant has a bona fide intention, and is entitled, to use the mark in commerce on or in connection with the identified goods/services.

Priority based on foreign filing: The applicant has a bona fide intention, and is entitled, to use the mark in commerce on or in connection with the identified goods/services and asserts a claim of priority based on Ireland application number 2019/01636, filed 09/06/2019.
INTENT TO PERFECT 44(d) : At this time, the applicant intends to rely on Section 44(e) as a basis for registration and requests that the application be suspended to await the submission of the foreign registration. If ultimately the applicant does not rely on §44(e) as a basis for registration, a valid claim of priority may be retained.

Disclaimer

No claim is made to the exclusive right to use emtricitabine 200 mg / tenofovir alafenamide 25mg tablets for PrEP pre-exposure prophylaxis apart from the mark as shown.

Claim of Active Prior Registration(s)
The applicant claims ownership of active prior U.S. Registration Number(s) 4876632 and 5067220.

For informational purposes only, applicant's website address is: www.gilead.com

The applicant hereby appoints Gretchen R. Stroud. Other appointed attorneys are Lori Mayall; Jack Wessel; Cynthia Smuzynska; Shelley Lai. Gretchen R. Stroud of Gilead Sciences, Inc., is a member of the XX bar, admitted to the bar in XXXX, bar membership no. XXX, and the attorney(s) is located at

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Gretchen R. Stroud submitted the following statement: The attorney of record is an active member in good standing of the bar of the highest court of a U.S. state, the District of Columbia, or any U.S. Commonwealth or territory.

The applicant's current Correspondence Information:

Gretchen R. Stroud
Gilead Sciences, Inc.
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trademarks@gilead.com; trademarks@gilead.com (authorized).

Email Authorization: I authorize the USPTO to send email correspondence concerning the application to the applicant, the applicant's attorney, or the applicant's domestic representative at the email address provided in this application. I understand that a valid email address must be maintained and that the applicant or the applicant's attorney must file the relevant subsequent application-related submissions via the Trademark Electronic Application System (TEAS). Failure to do so will result in the loss of TEAS Reduced Fee status and a requirement to submit an additional processing fee of $125 per international class of goods/services.

A fee payment in the amount of $550 has been submitted with the application, representing payment for 2 class(es).

Declaration

☑ **Basis:**
If the applicant is filing the application based on use in commerce under 15 U.S.C. § 1051(a):

- The signatory believes that the applicant is the owner of the trademark/service mark sought to be registered;
- The mark is in use in commerce on or in connection with the goods/services in the application;
- The specimen(s) shows the mark as used on or in connection with the goods/services in the application; and
- To the best of the signatory's knowledge and belief, the facts recited in the application are accurate.

And/Or
If the applicant is filing the application based on an intent to use the mark in commerce under 15 U.S.C. § 1051(b), § 1126(d), and/or § 1126(e):

- The signatory believes that the applicant is entitled to use the mark in commerce;
- The applicant has a bona fide intention to use the mark in commerce on or in connection with the goods/services in the application; and
- To the best of the signatory's knowledge and belief, the facts recited in the application are accurate.

☑ To the best of the signatory's knowledge and belief, no other persons, except, if applicable, concurrent users, have the right to use the mark in commerce, either in the identical form or in such near resemblance as to be likely, when used on or in connection with the

goods/services of such other persons, to cause confusion or mistake, or to deceive.

- ☑ To the best of the signatory's knowledge, information, and belief, formed after an inquiry reasonable under the circumstances, the allegations and other factual contentions made above have evidentiary support.
- ☑ The signatory being warned that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements and the like may jeopardize the validity of the application or submission or any registration resulting therefrom, declares that all statements made of his/her own knowledge are true and all statements made on information and belief are believed to be true.

Declaration Signature

Signature: /Gretchen R. Stroud/ Date: 09/12/2019
Signatory's Name: Gretchen R. Stroud
Signatory's Position: Attorney of record, California bar member
Payment Sale Number: 88615918
Payment Accounting Date: 09/13/2019

Serial Number: 88615918
Internet Transmission Date: Fri Sep 13 13:25:36 EDT 2019
TEAS Stamp: USPTO/BAS-XXX.XXX.XXX.XX-201909131325362
63356-88615918-6107212cdd48a26e08a7d4288
e7d0b8cc33803fc9a15dfd4a782635943b1c13e5
-DA-25364491-20190909193005314024


Descovy
emtricitabine 200mg/
tenofovir alafenamide 25mg tablets
for PrEP pre-exposure prophylaxis

EXHIBIT 83

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRUVADA safely and effectively. See full prescribing information for TRUVADA.

TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) tablets, for oral use
Initial U.S. Approval: 2004

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION
See full prescribing information for complete boxed warning.

- **Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued TRUVADA. Hepatic function should be monitored closely in HBV-infected patients who discontinue TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.1)**
- **TRUVADA used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initial use and periodically during use. Drug-resistant HIV-1 variants have been identified with the use of TRUVADA for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate TRUVADA for HIV-1 PrEP if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed. (5.2)**

----------RECENT MAJOR CHANGES----------

Indications and Usage		
Treatment of HIV-1 Infection (1.1)		05/2018
HIV-1 Pre-Exposure Prophylaxis (PrEP) (1.2)		05/2018
Dosage and Administration		
Testing Prior to Initiation of TRUVADA for Treatment of HIV-1 Infection or for HIV-1 PrEP (2.1)		05/2018
HIV-1 Screening for Individuals Receiving TRUVADA for HIV-1 PrEP (2.2)		05/2018
Recommended Dosage for HIV-1 PrEP (2.5)		05/2018
Warnings and Precautions		
Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection (5.1)		05/2018
Comprehensive Management to Reduce the Risk of Acquiring HIV-1 and Development of HIV-1 Resistance When TRUVADA Is Used for HIV-1 PrEP (5.2)		05/2018
New Onset or Worsening Renal Impairment (5.3)		05/2018
Risk of Adverse Reactions Due to Drug Interactions (5.7)		05/2018
Early Virologic Failure	*Removed*	05/2018

----------INDICATIONS AND USAGE----------
TRUVADA is a two-drug combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), both HIV-1 nucleoside analog reverse transcriptase inhibitors, and is indicated:
- in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg. (1.1)
- in combination with safer sex practices for HIV-1 pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Testing: Prior to or when initiating TRUVADA test for hepatitis B virus infection. Prior to initiation and during use of TRUVADA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)
- HIV-1 Screening: Screen all patients for HIV-1 infection before initiating TRUVADA for HIV-1 PrEP and at least once every 3 months while taking TRUVADA. (2.2)

Treatment of HIV-1 Infection
- Recommended dosage in adults and pediatric patients weighing at least 35 kg: One TRUVADA tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food. (2.3)
- Recommended dosage in pediatric patients weighing at least 17 kg: One TRUVADA low-strength tablet (100 mg/150 mg, 133 mg/200 mg, or 167 mg/250 mg based on body weight) once daily taken orally with or without food. (2.4)
- Recommended dosage in renally impaired HIV-1 infected adult patients:
  - Creatinine clearance (CrCl) 30–49 mL/min: 1 tablet every 48 hours. (2.6)
  - CrCl below 30 mL/min or hemodialysis: TRUVADA is not recommended. (2.6)

HIV-1 Pre-Exposure Prophylaxis (PrEP)
- Recommended dosage in HIV-1 uninfected adults and adolescents weighing at least 35 kg: One TRUVADA tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food. (2.5)
- Recommended dosage in renally impaired HIV-uninfected individuals: TRUVADA is not recommended in HIV-uninfected individuals if CrCl is below 60 mL/min. (2.6)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 200 mg/300 mg, 167 mg/250 mg, 133 mg/200 mg, and 100 mg/150 mg of emtricitabine and tenofovir disoproxil fumarate, respectively. (3)

----------CONTRAINDICATIONS----------
TRUVADA for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status. (4)

----------WARNINGS AND PRECAUTIONS----------
- Comprehensive management to reduce the risk of acquiring HIV-1: Use as part of a comprehensive prevention strategy including other prevention measures; strictly adhere to dosing schedule. (5.2)
- Management to reduce the risk of acquiring HIV-1 drug resistance: refer to full prescribing information for additional detail. (5.2)
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Avoid administering TRUVADA with concurrent or recent use of nephrotoxic drugs. (5.3)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.4)
- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.5)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.6)

----------ADVERSE REACTIONS----------
- In HIV-1 infected patients, the most common adverse reactions (incidence greater than or equal to 10%) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. (6.1)
- In HIV-1 uninfected adults in PrEP trials, adverse reactions that were reported by more than 2% of TRUVADA subjects and more frequently than by placebo subjects were headache, abdominal pain, and weight decreased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-445-3235 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- Tenofovir disoproxil fumarate increases didanosine concentrations. Dose reduction and close monitoring for didanosine toxicity are warranted. (7.2)
- Coadministration decreases atazanavir concentrations. When coadministered with TRUVADA, use atazanavir given with ritonavir. (7.2)
- Coadministration of TRUVADA with certain HIV-1 protease inhibitors or certain drugs to treat HCV increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.2)
- Consult Full Prescribing Information prior to and during treatment for important drug interactions. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Women infected with HIV-1 or suspected of having acquired HIV-1 infection should be instructed not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued TRUVADA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in HBV-infected patients who discontinue TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

TRUVADA used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and periodically (at least every 3 months) during use. Drug-resistant HIV-1 variants have been identified with use of TRUVADA for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate TRUVADA for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Treatment of HIV-1 Infection

TRUVADA is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg *[see Clinical Studies (14)]*.

1.2 HIV-1 Pre-Exposure Prophylaxis (PrEP)

TRUVADA is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg. Individuals must have a negative HIV-1 test immediately prior to initiating TRUVADA for HIV-1 PrEP *[see Dosage and Administration (2.2)]*.

- If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 status or use a test cleared by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection *[see Warnings and Precautions (5.2), Use in Specific Populations (8.4) and Clinical Studies (14.3, 14.4)]*.

When considering TRUVADA for HIV-1 PrEP, factors that help to identify individuals at risk may include:

- has partner(s) known to be HIV-1 infected, or
- engages in sexual activity within a high prevalence area or social network and has additional risk factors for HIV-1 acquisition, such as:
    - inconsistent or no condom use
    - diagnosis of sexually transmitted infections
    - exchange of sex for commodities (such as money, food, shelter, or drugs)
    - use of illicit drugs or alcohol dependence
    - incarceration
    - partner(s) of unknown HIV-1 status with any of the factors listed above

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of TRUVADA for Treatment of HIV-1 Infection or for HIV-1 PrEP

Prior to or when initiating TRUVADA, test patients for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to initiation and during use of TRUVADA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.3)].*

2.2 HIV-1 Screening for Individuals Receiving TRUVADA for HIV-1 PrEP

Screen all patients for HIV-1 infection before initiating TRUVADA for HIV-1 PrEP and at least once every 3 months while taking TRUVADA *[see Indications and Usage (1.2), Contraindications (4) and Warnings and Precautions (5.2)].*

2.3 Recommended Dosage for Treatment of HIV-1 Infection in Adults and Pediatric Patients Weighing at Least 35 kg

TRUVADA is a two-drug fixed dose combination product containing emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). The recommended dosage of TRUVADA in adults and in pediatric patients weighing at least 35 kg is one tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food *[see Clinical Pharmacology (12.3)]*.

2.4 Recommended Dosage for Treatment of HIV-1 Infection in Pediatric Patients Weighing at Least 17 kg and Able to Swallow a Tablet

The recommended oral dosage of TRUVADA for pediatric patients weighing at least 17 kg and who can swallow a tablet is presented in Table 1. Tablets should be taken once daily with or without food. Weight should be monitored periodically and the TRUVADA dose adjusted accordingly.

Table 1 Dosing for Treatment of HIV-1 Infection in Pediatric Patients Weighing 17 kg to less than 35 kg

Body Weight (kg)	Dosing of TRUVADA (FTC/TDF)
17 to less than 22	one 100 mg /150 mg tablet once daily
22 to less than 28	one 133 mg /200 mg tablet once daily
28 to less than 35	one 167 mg /250 mg tablet once daily

2.5 Recommended Dosage for HIV-1 PrEP

The dosage of TRUVADA in HIV-1 uninfected adults and adolescents weighing at least 35 kg is one tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food *[see Clinical Pharmacology (12.3)]*.

2.6 Dosage Adjustment in Patients with Renal Impairment

Treatment of HIV-1 Infection

Table 2 provides dosage interval adjustment for patients with renal impairment. No dosage adjustment is necessary for HIV-1 infected patients with mild renal impairment (creatinine clearance 50–80 mL/min). The safety and effectiveness of the dosing interval adjustment recommendations in patients with moderate renal impairment (creatinine clearance 30–49 mL/min) have not been clinically evaluated; therefore, clinical response to treatment and renal function should be closely monitored in these patients *[see Warnings and Precautions (5.3)]*.

No data are available to make dosage recommendations in pediatric patients with renal impairment.

Table 2 Dosage Interval Adjustment for HIV-1 Infected Adult Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]		
	≥50	30–49	<30 (Including Patients Requiring Hemodialysis)
Recommended Dosing Interval	Every 24 hours	Every 48 hours	TRUVADA is not recommended.

a. Calculated using ideal (lean) body weight

HIV-1 PrEP

TRUVADA for HIV-1 PrEP is not recommended in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min *[see Warnings and Precautions (5.3)]*.

If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TRUVADA for HIV-1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use *[see Warnings and Precautions (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

TRUVADA tablets are available in four dose strengths.

- 100 mg/150 mg Tablets: 100 mg of emtricitabine (FTC) and 150 mg of tenofovir disoproxil fumarate (TDF) (equivalent to 123 mg of tenofovir disoproxil): blue, oval shaped, film coated, debossed with “GSI” on one side and with “703” on the other side.
- 133 mg/200 mg Tablets: 133 mg of FTC and 200 mg of TDF (equivalent to 163 mg of tenofovir disoproxil): blue, rectangular shaped, film coated, debossed with “GSI” on one side and with “704” on the other side.
- 167 mg/250 mg Tablets: 167 mg of FTC and 250 mg of TDF (equivalent to 204 mg of tenofovir disoproxil): blue, modified capsule shaped, film coated, debossed with “GSI” on one side and with “705” on the other side.
- 200 mg/300 mg Tablets: 200 mg of FTC and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil): blue, capsule shaped, film coated, debossed with “GILEAD” on one side and with “701” on the other side.

4 CONTRAINDICATIONS

TRUVADA for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection

All patients should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating TRUVADA *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in HBV-infected patients who have discontinued TRUVADA. Patients infected with HBV who discontinue TRUVADA should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of anti-hepatitis B therapy may

be warranted, especially in patients with advanced liver disease or cirrhosis, since posttreatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. HBV-uninfected individuals should be offered vaccination.

5.2 Comprehensive Management to Reduce the Risk of Acquiring HIV-1 and Development of HIV-1 Resistance When TRUVADA Is Used for HIV-1 PrEP

Use TRUVADA for HIV-1 PrEP only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because TRUVADA is not always effective in preventing acquisition of HIV-1 *[see Clinical Studies (14.3 and 14.4)]*.

- Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), the importance of virologic suppression in their partner(s) with HIV-1, and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis, chlamydia, and gonorrhea).
- Inform uninfected individuals about and support their efforts in reducing sexual risk behavior.

Use TRUVADA to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-negative**.** HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only TRUVADA, because TRUVADA alone does not constitute a complete regimen for HIV-1 treatment *[see Microbiology (12.4)];* therefore, care should be taken to minimize drug exposure in HIV-infected individuals.

- Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating TRUVADA for HIV-1 PrEP, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (e.g., fever, fatigue, myalgia, skin rash) and ask about potential exposure events (e.g., unprotected, or condom broke during, sex with an HIV-1 infected partner) that may have occurred within the last month.
- If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting HIV-1 PrEP for at least one month and reconfirm HIV-1 status or use a test approved or cleared by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.

While using TRUVADA for HIV-1 PrEP, HIV-1 screening tests should be repeated at least every 3 months, and upon diagnosis of any sexually transmitted infections. Some individuals, such as adolescents, may benefit from more frequent visits and counseling *[see Use in Specific Populations (8.4)]*.

- If a screening test indicates possible HIV-1 infection, or if symptoms consistent with acute HIV-1 infection develop following a potential exposure event, convert the HIV-1 PrEP regimen to an HIV treatment regimen until negative infection status is confirmed using a test approved or cleared by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.

Counsel uninfected individuals to strictly adhere to the recommended TRUVADA dosing schedule. The effectiveness of TRUVADA in reducing the risk of acquiring HIV-1 is strongly correlated with adherence, as demonstrated by measurable drug levels in clinical trials *[see Use in Specific Populations (8.4), Microbiology (12.4), and Clinical Studies (14.3 and 14.4)]*.

5.3 New Onset or Worsening Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of TDF, a component of TRUVADA *[see Adverse Reactions (6.2)]*.

Prior to initiation and during use of TRUVADA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs [NSAIDs]) *[see Drug Interactions (7.1)]*. Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on TDF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures, and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in patients at risk of renal dysfunction.

Treatment of HIV-1 Infection

Dosing interval adjustment of TRUVADA and close monitoring of renal function are recommended in all patients with estimated creatinine clearance 30–49 mL/min *[see Dosage and Administration (2.6)]*. No safety or efficacy data are available in patients with renal impairment who received TRUVADA using these dosing guidelines, so the potential benefit of TRUVADA therapy should be assessed against the potential risk of renal toxicity. TRUVADA is not recommended in patients with estimated creatinine clearance below 30 mL/min or patients requiring hemodialysis.

HIV-1 PrEP

TRUVADA for HIV-1 PrEP is not recommended in uninfected individuals with estimated creatinine clearance less than 60 mL/min. If a decrease in estimated creatinine clearance is observed while using TRUVADA for HIV-1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use *[see Dosage and Administration (2.6)]*.

5.4 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including TRUVADA. During the initial phase of combination antiretroviral treatment, HIV-1 infected patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

5.5 Bone Loss and Mineralization Defects

Bone Mineral Density

In clinical trials in HIV-1 infected adults and in a clinical trial of HIV-1 uninfected individuals, TDF (a component of TRUVADA) was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators *[see Adverse Reactions (6.1)]*. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving TDF.

Clinical trials evaluating TDF in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the TDF-treated HIV-1 infected pediatric

subjects as compared to the control groups. Similar trends were observed in adolescent subjects aged 12 years to less than 18 years treated for chronic hepatitis B. In all pediatric trials, skeletal growth (height) appeared to be unaffected.

The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial. If bone abnormalities are suspected, appropriate consultation should be obtained.

Mineralization Defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with TDF use *[see Adverse Reactions (6.1)]*. Arthralgia and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving TDF-containing products *[see Warnings and Precautions (5.3)].*

5.6 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including FTC and TDF, components of TRUVADA, alone or in combination with other antiretrovirals. Treatment with TRUVADA should be suspended in any patient or uninfected individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.7 Risk of Adverse Reactions Due to Drug Interactions

The concomitant use of TRUVADA and other drugs may result in known or potentially significant drug interactions, some of which may lead to possible clinically significant adverse reactions from greater exposures of concomitant drugs *[see Drug Interactions (7.2)].*

See Table 7 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with TRUVADA; review concomitant medications during therapy with TRUVADA; and monitor for adverse reactions associated with the concomitant drugs.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Severe Acute Exacerbations of Hepatitis B in Patients with HBV Infection *[see Warnings and Precautions (5.1)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.3)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.4)]*.
- Bone Loss and Mineralization Defects *[see Warnings and Precautions (5.5)]*.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.6)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions from Clinical Trials Experience in HIV-1 Infected Subjects

Clinical Trials in Adult Subjects

In Study 934, 511 antiretroviral-naïve subjects received efavirenz (EFV) administered in combination with either FTC+TDF (N=257) or zidovudine (AZT)/lamivudine (3TC) (N=254) for 144 weeks. The most common adverse reactions (incidence greater than or equal to 10%, all grades) included diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. Table 3 provides the treatment-emergent adverse reactions (Grades 2–4) occurring in greater than or equal to 5% of subjects treated in any treatment group.

Skin discoloration, manifested by hyperpigmentation, occurred in 3% of subjects taking FTC+TDF, and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Table 3 Selected Adverse Reactions[a] (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 934 (0–144 Weeks)

	FTC+TDF+EFV[b]	AZT/3TC+EFV
	N=257	N=254
Fatigue	9%	8%
Depression	9%	7%
Nausea	9%	7%
Diarrhea	9%	5%
Dizziness	8%	7%
Upper respiratory tract infections	8%	5%
Sinusitis	8%	4%
Rash event[c]	7%	9%
Headache	6%	5%
Insomnia	5%	7%
Nasopharyngitis	5%	3%
Vomiting	2%	5%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
b. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of FTC+TDF with efavirenz.
c. Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash vesicular.

Laboratory Abnormalities: Laboratory abnormalities observed in this trial were generally consistent with those seen in other trials of TDF and/or FTC (Table 4).

Table 4 Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0–144 Weeks)

	FTC+TDF+EFV[a]	AZT/3TC+EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm^3)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

a. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of FTC+TDF with efavirenz.

Clinical Trials in Pediatric Subjects

Emtricitabine: In addition to the adverse reactions reported in adults, anemia and hyperpigmentation were observed in 7% and 32%, respectively, of pediatric subjects (3 months to less than 18 years of age) who received treatment with FTC in the larger of two open-label, uncontrolled pediatric trials (N=116).

Tenofovir Disoproxil Fumarate: In pediatric clinical trials (Studies 352 and 321) conducted in 184 HIV-1 infected subjects 2 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with TDF were consistent with those observed in clinical trials of TDF in adults.

In Study 352 (2 to less than 12 years of age), 89 pediatric subjects received TDF for a median exposure of 104 weeks. Of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these 4 subjects presented with hypophosphatemia and had decreases in total body or spine BMD Z-score *[see Warnings and Precautions (5.5)].* Total body BMD gain at Week 48 was less in the TDF group compared to the stavudine (d4T) or zidovudine (AZT) treatment groups. The mean rate of BMD gain in lumbar spine was similar between treatment groups. One TDF-treated subject and none of the d4T- or AZT-treated subjects experienced significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline in BMD Z-scores were −0.012 for lumbar spine and −0.338 for total body in the 64 subjects who were treated with TDF for 96 weeks.

In Study 321 (12 to less than 18 years of age), the mean rate of BMD gain at Week 48 was less in the TDF compared to the placebo treatment group. Six TDF-treated subjects and one placebo-treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were −0.341 for lumbar spine and −0.458 for total body in the 28 subjects who were treated with TDF for 96 weeks.

In both trials, skeletal growth (height) appeared to be unaffected.

Adverse Reactions from Clinical Trial Experience in Uninfected Subjects Taking TRUVADA for HIV-1 PrEP

Clinical Trials in Adult Subjects

The safety profile of TRUVADA for HIV-1 PrEP was comparable to that observed in clinical trials of HIV-infected subjects based on two randomized placebo-controlled clinical trials (iPrEx, Partners PrEP) in which 2,830 HIV-1 uninfected adults received TRUVADA once daily for HIV-1 PrEP. Subjects were followed for a median of 71 weeks and 87 weeks, respectively. Table 5 provides a list of selected adverse events that occurred in 2% or more of subjects in any treatment group in the iPrEx trial, with an incidence greater than placebo.

Table 5 Selected Adverse Events (All Grades) Reported in ≥2% in Any Treatment Group in the iPrEx Trial and Greater than Placebo

	FTC/TDF (N=1251)	Placebo (N=1248)
Headache	7%	6%
Abdominal pain	4%	2%
Weight decreased	3%	2%

In the Partners PrEP trial, the frequency of adverse events in the TRUVADA treatment group was generally either less than or the same as in the placebo group.

Laboratory Abnormalities: Table 6 provides a list of Grade 2-4 laboratory abnormalities observed in the iPrEx and Partners PrEP trials. Six subjects in the TDF-containing arms of the Partners PrEP trial discontinued from the trial due to an increase in serum creatinine compared with no discontinuations in the placebo group. One subject in the TRUVADA arm of the iPrEx trial discontinued from the trial due to an increase in serum creatinine and another subject discontinued due to low serum phosphorus. Grades 2−3 proteinuria (2-4+) and/or glycosuria (3+) occurred in less than 1% of subjects treated with TRUVADA in the iPrEx trial and Partners PrEP trial.

Table 6 Laboratory Abnormalities (Highest Toxicity Grade Reported for Each Subject) in the iPrEx Trial and Partners PrEP Trial

Grade 2-4[a]	iPrEx Trial		Partners PrEP Trial	
	FTC/TDF (N=1251)	Placebo (N=1248)	FTC/TDF (N=1579)	Placebo (N=1584)
Creatinine (>1.4 × ULN)	<1%	<1%	<1%	<1%
Phosphorus (<2.0 mg/dL)	10%	8%	9%	9%
AST (>2.6 × ULN)	5%	5%	<1%	<1%
ALT (>2.6 × ULN)	7%	7%	<1%	<1%
Hemoglobin (<9.4 mg/dL)	1%	2%	2%	2%
Neutrophils (<750/mm^3)	<1%	<1%	5%	3%

a. Grading is per DAIDS criteria.

Changes in Bone Mineral Density: In clinical trials of HIV-1 uninfected individuals, decreases in BMD were observed. In the iPrEx trial, a substudy of 503 subjects found mean changes from baseline in BMD ranging from –0.4% to –1.0% across total hip, spine, femoral neck, and trochanter in the TRUVADA group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of TRUVADA-treated subjects versus 6% of placebo-treated subjects lost at least 5% of BMD at the spine during treatment. Bone fractures were reported in 1.7% of the TRUVADA group compared with 1.4% in the placebo group. No correlation between BMD and fractures was noted *[see Clinical Studies (14.3)]*. The Partners PrEP trial found similar fracture rates between the treatment and placebo groups (0.8% and 0.6%, respectively); no BMD evaluations were performed in this trial *[see Clinical Studies (14.4)]*.

Clinical Trials in Adolescent Subjects

In a single-arm, open-label clinical trial (ATN113), in which 67 HIV-1 uninfected adolescent (15 to 18 years of age) men who have sex with men received TRUVADA once daily for HIV-1 PrEP, the safety profile of TRUVADA was similar to that observed in adults. Median duration to exposure of TRUVADA was 47 weeks *[see Use in Specific Populations (8.4)].*

In the ATN113 trial, median BMD increased from baseline to Week 48, +2.58% for lumbar spine and +0.72% for total body. One subject had significant (greater than or equal to 4%) total body BMD loss at Week 24. Median changes from baseline BMD Z-scores were 0.0 for lumbar spine and −0.2 for total body at Week 48. Three subjects showed a worsening (change from > −2 to ≤ −2) from baseline in their lumbar spine or total body BMD Z-scores at Week 24 or 48. Interpretation of these data, however, may be limited by the low rate of adherence to TRUVADA by Week 48.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TDF. No additional adverse reactions have been identified during postapproval use of FTC. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders
allergic reaction, including angioedema

Metabolism and Nutrition Disorders
lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders
dyspnea

Gastrointestinal Disorders
pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders
hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders
rash

Musculoskeletal and Connective Tissue Disorders
rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders
acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions
asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

7 DRUG INTERACTIONS

7.1 Drugs Affecting Renal Function

FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion *[see Clinical Pharmacology (12.3)]*. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of TRUVADA with drugs that are eliminated by active tubular secretion may increase concentrations of FTC, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.3)]*. Drugs that decrease renal function may increase concentrations of FTC and/or tenofovir.

7.2 Established and Significant Interactions

Table 7 provides a listing of established or clinically significant drug interactions. The drug interactions described are based on studies conducted with either TRUVADA, the components of TRUVADA (FTC and TDF) as individual agents and/or in combination, or are predicted drug interactions that may occur with TRUVADA *[see Clinical Pharmacology (12.3)].*

Table 7 Established and Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
NRTI: didanosine[c]	↑ didanosine	Patients receiving TRUVADA and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse reactions. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving TDF with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with TRUVADA. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing less than 60 kg. When coadministered, TRUVADA and Videx EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).
HIV-1 Protease Inhibitors: atazanavir[c]	↓ atazanavir	When coadministered with TRUVADA, atazanavir 300 mg should be given with ritonavir 100 mg.
lopinavir/ritonavir[c] atazanavir/ritonavir[c] darunavir/ritonavir[c]	↑ tenofovir	Monitor patients receiving TRUVADA concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir for TDF-associated adverse reactions. Discontinue TRUVADA in patients who develop TDF-associated adverse reactions.
Hepatitis C Antiviral Agents: sofosbuvir/velpatasvir[c] sofosbuvir/velpatasvir/voxilaprevir[c]	↑ tenofovir	Monitor patients receiving TRUVADA concomitantly with EPCLUSA® (sofosbuvir/velpatasvir) or VOSEVI® (sofosbuvir/velpatasvir/voxilaprevir) for adverse reactions associated with TDF.
ledipasvir/sofosbuvir[c]		Monitor patients receiving TRUVADA concomitantly with HARVONI® (ledipasvir/sofosbuvir) without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination for adverse reactions associated with TDF. In patients receiving TRUVADA concomitantly with HARVONI and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with TDF.

a. This table is not all inclusive.
b. ↑=Increase, ↓=Decrease
c. Indicates that a drug-drug interaction trial was conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TRUVADA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Data on the use of TRUVADA during pregnancy from observational studies have shown no increased risk of major birth defects. Available data from the APR show no increase in the overall risk of major birth defects with first trimester exposure for emtricitabine (FTC) (2.3%) or tenofovir disoproxil fumarate (TDF) (2.1%) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage for individual drugs is not reported in the APR. In the U.S. general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15–20%.

In animal reproduction studies, no adverse developmental effects were observed when the components of TRUVADA were administered separately at doses/exposures ≥60 (FTC), ≥14 (TDF) and 2.7 (tenofovir) times those of the recommended daily dose of TRUVADA (*see Data*).

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

HIV-1 PrEP: Published studies indicate an increased risk of HIV-1 infection during pregnancy and an increased risk of mother to child transmission during acute HIV-1 infection. In women at risk of acquiring HIV-1, consideration should be given to methods to prevent acquisition of HIV, including continuing or initiating TRUVADA for HIV-1 PrEP, during pregnancy.

Data

Human Data

TRUVADA for HIV-1 PrEP: In an observational study based on prospective reports to the APR, 78 HIV-seronegative women exposed to TRUVADA during pregnancy delivered live-born infants with no major malformations. All except for one were first trimester exposures, and the median duration of exposure was 10.5 weeks. There were no new safety findings in the women receiving TRUVADA for HIV-1 PrEP compared with HIV-1 infected women treated with other antiretroviral medications.

Emtricitabine: Based on prospective reports to the APR of 3,749 exposures to FTC-containing regimens during pregnancy resulting in live births (including 2,614 exposed in the first trimester and 1,135 exposed in the second/third trimester), there was no increase in overall major birth defects with FTC compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of major birth defects in live births was 2.3% (95% CI: 1.8% to 2.9%) with first trimester exposure to FTC-containing regimens and 2.1% (95% CI: 1.4% to 3.1%) with the second/third trimester exposure to FTC-containing regimens.

Tenofovir Disoproxil Fumarate: Based on prospective reports from the APR of 4,817 exposures to TDF-containing regimens during pregnancy resulting in live births (including 3,342 exposed in the first trimester and 1,475 exposed in the second/third trimester), there was no increase in overall major birth defects with TDF compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of major birth defects in live births was 2.3% (95% CI: 1.8% to 2.8%) with first trimester exposure to TDF-containing regimens, and 2.1% (95% CI: 1.4% to 3.0%) with the second/third trimester exposure to TDF-containing regimens.

Methodologic limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

Additionally, published observational studies on emtricitabine and tenofovir exposure in pregnancy have not shown an increased risk for major malformations.

Animal Data

Emtricitabine: FTC was administered orally to pregnant mice (at 0, 250, 500, or 1,000 mg/kg/day), and rabbits (at 0, 100, 300, or 1,000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 120 times higher than human exposures at the recommended daily dose. In a pre/postnatal development study in mice, FTC was administered orally at doses up to 1,000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended daily dose.

Tenofovir Disoproxil Fumarate: TDF was administered orally to pregnant rats (at 0, 50, 150, or 450 mg/kg/day) and rabbits (at 0, 30, 100, or 300 mg/kg/day) through organogenesis (on gestation days 7 through 17, and 6 through 18, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with TDF in rats at doses up to 14 times the human dose based on body surface area comparisons and in rabbits at doses up to 19 times the human dose based on body surface area comparisons. In a pre/postnatal development study in rats, TDF was administered orally through lactation at doses up to 600 mg/kg/day; no adverse effects were observed in the offspring at tenofovir exposures of approximately 2.7 times higher than human exposures at the recommended daily dose of TRUVADA.

8.2 Lactation

Risk Summary

Based on published data, FTC and tenofovir have been shown to be present in human breast milk *(see Data).* It is not known if the components of TRUVADA affect milk production or have effects on the breastfed child.

Treatment of HIV-1 Infection:

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1.

Because of the potential for: (1) HIV transmission (in HIV-negative infants); (2) developing viral resistance (in HIV-positive infants); and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are taking TRUVADA for the treatment of HIV-1.

HIV-1 PrEP:

In HIV-uninfected women, the developmental and health benefits of breastfeeding and the mother's clinical need for TRUVADA for HIV-1 PrEP should be considered along with any potential adverse effects on the breastfed child from TRUVADA and the risk of HIV-1 acquisition due to nonadherence and subsequent mother to child transmission.

Women should not breastfeed if acute HIV-1 infection is suspected because of the risk of HIV-1 transmission to the infant.

Data

HIV-1 PrEP: In a study of 50 breastfeeding women who received TRUVADA for HIV-1 PrEP between 1 and 24 weeks postpartum (median 13 weeks), after 7 days of treatment, tenofovir was undetectable but FTC was detectable in the plasma of most infants. In these infants, the average FTC plasma concentration was less than 1% of the FTC C_{max} observed in HIV-infected infants (up to 3 months of age) receiving the therapeutic dose of FTC (3 mg/kg/day). There were no serious adverse events. Two infants (4%) had an adverse event of mild diarrhea which resolved.

8.4 Pediatric Use

Treatment of HIV-1 Infection

No pediatric clinical trial was conducted to evaluate the safety and efficacy of TRUVADA in patients with HIV-1 infection. Data from previously conducted trials with the individual drug products, FTC and TDF, were relied upon to support dosage recommendations for TRUVADA. For additional information, consult the prescribing information for EMTRIVA and VIREAD.

TRUVADA should only be administered to HIV-1 infected pediatric patients with body weight greater than or equal to 17 kg and who are able to swallow a tablet. Because it is a fixed-dose combination tablet, TRUVADA cannot be adjusted for patients of lower weight *[see Warnings and Precautions (5.5), Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. TRUVADA is not approved for use in pediatric patients weighing less than 17 kg.

HIV-1 PrEP

The safety and effectiveness of TRUVADA for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg is supported by data from adequate and well-controlled studies of TRUVADA for HIV-1 PrEP in adults with additional data from safety and pharmacokinetic studies in previously conducted trials with the individual drug products, FTC and TDF, in HIV-1 infected adults and pediatric subjects *[see Dosage and Administration (2.5), Adverse Reactions (6.1), Clinical Pharmacology (12.3 and 12.4), and Clinical Studies (14.3 and 14.4)].*

Safety, adherence, and resistance were evaluated in a single-arm, open-label clinical trial (ATN113) in which 67 HIV-1 uninfected at-risk adolescent men who have sex with men received TRUVADA once daily for HIV-1 PrEP. The mean age of subjects was 17 years (range 15 to 18 years); 46% were Hispanic, 52% Black, and 37% White. The safety profile of TRUVADA in ATN113 was similar to that observed in the adult HIV-1 PrEP trials *[see Adverse Reactions (6.1)]*.

In the ATN113 trial, HIV-1 seroconversion occurred in 3 subjects. Tenofovir diphosphate levels in dried blood spot assays indicate that these subjects had poor adherence. No tenofovir- or FTC-associated HIV-1 resistance substitutions were detected in virus isolated from the 3 subjects who seroconverted *[see Microbiology (12.4)].*

Adherence to study drug, as demonstrated by tenofovir diphosphate levels in dried blood spot assays, declined markedly after Week 12 once subjects switched from monthly to quarterly visits, suggesting that adolescents may benefit from more frequent visits and counseling.

8.5 Geriatric Use

Clinical trials of FTC, TDF, or TRUVADA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Renal Impairment

Treatment of HIV-1 Infection

The dosing interval for TRUVADA should be modified in HIV-infected adult patients with estimated creatinine clearance of 30–49 mL/min. TRUVADA is not recommended in patients with estimated

creatinine clearance below 30 mL/min and in patients with end-stage renal disease requiring dialysis *[see Dosage and Administration (2.6)]*.

HIV-1 PrEP

TRUVADA for HIV-1 PrEP is not recommended in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TRUVADA for HIV-1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use *[see Dosage and Administration (2.6)]*.

10 OVERDOSAGE

If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Emtricitabine: Hemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether FTC can be removed by peritoneal dialysis.

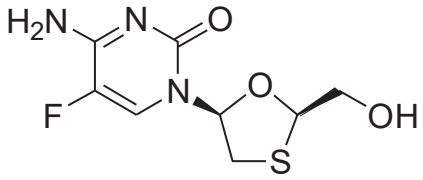
Tenofovir Disoproxil Fumarate: Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of TDF, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

TRUVADA tablets are fixed-dose combination tablets containing emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). FTC is a synthetic nucleoside analog of cytidine. TDF is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. Both FTC and tenofovir exhibit inhibitory activity against HIV-1 reverse transcriptase.

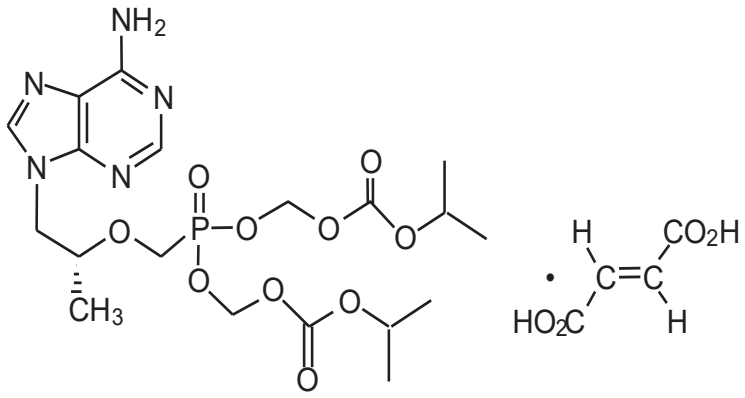
Emtricitabine: The chemical name of FTC is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. FTC is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



FTC is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25 °C. The partition coefficient (log p) for emtricitabine is −0.43 and the pKa is 2.65.

Tenofovir Disoproxil Fumarate: TDF is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir DF is 9-[(*R*)-2 [[bis[[(isopropoxycarbonyl)oxy]- methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25 °C. The partition coefficient (log p) for tenofovir disoproxil is 1.25 and the pKa is 3.75. All dosages are expressed in terms of TDF except where otherwise noted.

TRUVADA tablets are for oral administration, and are available in the following strengths:

- Film-coated tablet containing 200 mg of FTC and 300 mg of TDF (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients
- Film-coated tablet containing 167 mg of FTC and 250 mg of TDF (which is equivalent to 204 mg of tenofovir disoproxil) as active ingredients
- Film-coated tablet containing 133 mg of FTC and 200 mg of TDF (which is equivalent to 163 mg of tenofovir disoproxil) as active ingredients
- Film-coated tablet containing 100 mg of FTC and 150 mg of TDF (which is equivalent to 123 mg of tenofovir disoproxil) as active ingredients

All strengths of TRUVADA tablets also include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch (gluten free). The 200 mg/300 mg strength tablets are coated with Opadry II Blue Y-30-10701, which contains FD&C Blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin. The 167 mg/250 mg, 133 mg/200 mg, and 100 mg/150 mg strength tablets are coated with Opadry II Blue, which contains FD&C Blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TRUVADA is a fixed-dose combination of antiviral drugs FTC and TDF *[see Microbiology (12.4)].*

12.3 Pharmacokinetics

TRUVADA: One TRUVADA tablet was comparable to one FTC capsule (200 mg) plus one TDF tablet (300 mg) following single-dose administration to fasting healthy subjects (N=39).

Emtricitabine: The pharmacokinetic properties of FTC are summarized in Table 8. Following oral administration of FTC, FTC is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours postdose. Less than 4% of FTC binds to human plasma proteins in vitro, and the binding is independent of concentration over the range of 0.02–200 µg/mL. Following administration of radiolabelled FTC, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of FTC include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of FTC, the plasma FTC half-life is approximately 10 hours.

Tenofovir Disoproxil Fumarate: The pharmacokinetic properties of TDF are summarized in Table 8. Following oral administration of TDF, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. Less than 0.7% of tenofovir binds to human plasma proteins in vitro, and the binding is independent of concentration over the range of 0.01–25 μg/mL. Approximately 70–80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of TDF, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 8 Single Dose Pharmacokinetic Parameters for FTC and Tenofovir in Adults[a]

	FTC	Tenofovir
Fasted Oral Bioavailability[b] (%)	92 (83.1–106.4)	25 (NC–45.0)
Plasma Terminal Elimination Half-Life[b] (hr)	10 (7.4–18.0)	17 (12.0–25.7)
C_{max}[c] (μg/mL)	1.8±0.72[d]	0.30±0.09
AUC[c] (μg·hr/mL)	10.0±3.12[d]	2.29±0.69
CL/F[c] (mL/min)	302±94	1043±115
CL_{renal}[c] (mL/min)	213±89	243±33

a. NC=Not calculated
b. Median (range)
c. Mean (± SD)
d. Data presented as steady state values

Effects of Food on Oral Absorption

TRUVADA may be administered with or without food. Administration of TRUVADA following a high fat meal (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0.75 hour. The mean increases in tenofovir AUC and C_{max} were approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy trials, TDF (tenofovir) was taken under fed conditions. FTC systemic exposures (AUC and C_{max}) were unaffected when TRUVADA was administered with either a high fat or a light meal.

Specific Populations

Race

Emtricitabine: No pharmacokinetic differences due to race have been identified following the administration of FTC.

Tenofovir Disoproxil Fumarate: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of TDF.

Gender

Emtricitabine and Tenofovir Disoproxil Fumarate: FTC and tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric Patients

Treatment of HIV-1 Infection: The pharmacokinetic data for tenofovir and FTC following administration of TRUVADA in pediatric subjects weighing 17 kg and above are not available. The dosage recommendations of TRUVADA in this population are based on the dosage recommendations of FTC and TDF in this population. Refer to the EMTRIVA and VIREAD prescribing information for pharmacokinetic information on the individual products in pediatric patients.

HIV-1 PrEP: The pharmacokinetic data for tenofovir and FTC following administration of TRUVADA in HIV-1 uninfected adolescents weighing 35 kg and above are not available. The dosage recommendations of TRUVADA for HIV-1 PrEP in this population are based on safety and adherence data from the ATN113 trial *[see Use in Specific Populations (8.4)]* and known pharmacokinetic information in HIV-infected adolescents taking TDF and FTC for treatment.

Geriatric Patients

Pharmacokinetics of FTC and tenofovir have not been fully evaluated in the elderly (65 years of age and older).

Patients with Renal Impairment

The pharmacokinetics of FTC and tenofovir are altered in subjects with renal impairment *[see Warnings and Precautions (5.3)]*. In adult subjects with creatinine clearance below 50 mL/min, C_{max} and $AUC_{0-\infty}$ of FTC and tenofovir were increased. No data are available to make dosage recommendations in pediatric patients with renal impairment.

Patients with Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg dose of TDF have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. The pharmacokinetics of TRUVADA or FTC have not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Assessment of Drug Interactions

The steady state pharmacokinetics of FTC and tenofovir were unaffected when FTC and TDF were administered together versus each agent dosed alone.

In vitro studies and clinical pharmacokinetic drug-drug interaction trials have shown that the potential for CYP mediated interactions involving FTC and tenofovir with other medicinal products is low.

TDF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. When TDF is coadministered with an inhibitor of these transporters, an increase in absorption may be observed.

No clinically significant drug interactions have been observed between FTC and famciclovir, indinavir, stavudine, TDF, and zidovudine (Tables 9 and 10). Similarly, no clinically significant drug interactions have been observed between TDF and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin, or sofosbuvir in trials conducted in healthy volunteers (Tables 11 and 12).

Table 9 Drug Interactions: Changes in Pharmacokinetic Parameters for FTC in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	FTC Dose (mg)	N	% Change of FTC Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
TDF	300 once daily × 7 days	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Zidovudine	300 twice daily × 7 days	200 once daily × 7 days	27	⇔	⇔	⇔
Indinavir	800 × 1	200 × 1	12	⇔	⇔	NA
Famciclovir	500 × 1	200 × 1	12	⇔	⇔	NA
Stavudine	40 × 1	200 × 1	6	⇔	⇔	NA

a. All interaction trials conducted in healthy volunteers
b. ↑ = Increase; ⇔ = No Effect; NA = Not Applicable

Table 10 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of FTC[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	FTC Dose (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
TDF	300 once daily × 7 days	200 once daily × 7 days	17	⇔	⇔	⇔
Zidovudine	300 twice daily × 7 days	200 once daily × 7 days	27	↑ 17 (↑ 0 to ↑ 38)	↑ 13 (↑ 5 to ↑ 20)	⇔
Indinavir	800 × 1	200 × 1	12	⇔	⇔	NA
Famciclovir	500 × 1	200 × 1	12	⇔	⇔	NA
Stavudine	40 × 1	200 × 1	6	⇔	⇔	NA

a. All interaction trials conducted in healthy volunteers
b. ↑ = Increase; ⇔ = No Effect; NA = Not Applicable

Table 11 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[a] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)		
			C_{max}	AUC	C_{min}
Atazanavir[c]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ Ritonavir[c]	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/ Ritonavir[d]	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Ledipasvir/ Sofosbuvir[e,f]	90/400 once daily × 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir[e,g]		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir[h]	90/400 once daily × 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to ↑ 197)
Ledipasvir/ Sofosbuvir[i]	90/400 once daily × 10 days	14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)
Ledipasvir/ Sofosbuvir[j]	90/400 once daily × 10 days	29	↑ 61 (↑ 51 to ↑ 72)	↑ 65 (↑ 59 to ↑ 71)	↑ 115 (↑ 105 to ↑ 126)
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir[k]	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	⇔	⇔
Sofosbuvir/ Velpatasvir[l]	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir[m]	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir[n]	400/100/100 + Voxilaprevir[o] 100 once daily	29	↑ 48 (↑ 36 to ↑ 61)	↑ 39 (↑ 32 to ↑ 46)	↑ 47 (↑ 38 to ↑ 56)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔
Tipranavir/ Ritonavir[p]	500/100 twice daily	22	↓ 23 (↓ 32 to ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	750/200 twice daily (23 doses)	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

a. Subjects received VIREAD 300 mg once daily.
b. Increase = ↑; Decrease = ↓; No Effect = ⇔
c. Reyataz Prescribing Information.
d. Prezista Prescribing Information.
e. Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provided similar results.
f. Comparison based on exposures when administered as atazanavir/ritonavir + FTC/TDF.
g. Comparison based on exposures when administered as darunavir/ritonavir + FTC/TDF.
h. Study conducted with ATRIPLA (efavirenz/FTC/TDF) coadministered with HARVONI.
i. Study conducted with COMPLERA (FTC/rilpivirine/TDF) coadministered with HARVONI.
j. Study conducted with TRUVADA (FTC/TDF) + dolutegravir coadministered with HARVONI.
k. Study conducted with ATRIPLA coadministered with SOVALDI® (sofosbuvir).
l. Study conducted with COMPLERA coadministered with EPCLUSA; coadministration with EPCLUSA also results in comparable increases in tenofovir exposures when TDF is administered as ATRIPLA, STRIBILD, TRUVADA + atazanavir/ritonavir, or TRUVADA + darunavir/ritonavir.
m. Administered as raltegravir + FTC/TDF.
n. Comparison based on exposures when administered as darunavir + ritonavir + FTC/TDF.
o. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients
p. Aptivus Prescribing Information.

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with TRUVADA: abacavir, didanosine (buffered tablets), FTC, entecavir, and lamivudine.

Table 12 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Atazanavir[b]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[b]	Atazanavir/Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[c] (↓ 42 to ↓ 3)	↓ 23[c] (↓ 46 to ↑ 10)
Darunavir[d]	Darunavir/Ritonavir 300/100 once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine[e]	250 once, simultaneously with TDF and a light meal[f]	33	↓ 20[g] (↓ 32 to ↓ 7)	⇔[g]	NA
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Entecavir	1 once daily × 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑41) ⇔	↑ 29[h] (↑ 12 to ↑ 48) ⇔	↑ 47[h] (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	⇔	⇔	⇔
Tipranavir[i]	Tipranavir/Ritonavir 500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

a. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable
b. Reyataz Prescribing Information.
c. In HIV-infected subjects, addition of TDF to atazanavir 300 mg plus ritonavir 100 mg resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
d. Prezista Prescribing Information.
e. Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules. When didanosine 250 mg enteric-coated capsules were administered with TDF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.
f. 373 kcal, 8.2 g fat

g. Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.
h. Increases in AUC and C_{min} are not expected to be clinically relevant; hence, no dose adjustments are required when TDF and ritonavir-boosted saquinavir are coadministered.
i. Aptivus Prescribing Information.

12.4 Microbiology

Mechanism of Action

Emtricitabine: FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate (FTC-TP), which inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. FTC-TP is a weak inhibitor of mammalian DNA polymerases α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir Disoproxil Fumarate: TDF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. TDF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate (TFV-DP), which inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination. TFV-DP is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity

Emtricitabine and Tenofovir Disoproxil Fumarate: No antagonism was observed in combination studies evaluating the cell culture antiviral activity of FTC and tenofovir together.

Emtricitabine: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC_{50}) values for FTC were in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL). In drug combination studies of FTC with nucleoside RT inhibitors (abacavir, lamivudine, stavudine, zidovudine), non-nucleoside RT inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), no antagonism was observed. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 μM) and showed strain-specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 μM).

Tenofovir Disoproxil Fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells, and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04–8.5 μM. In drug combination studies of tenofovir with nucleoside RT inhibitors (abacavir, didanosine, lamivudine, stavudine, zidovudine), non-nucleoside RT inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), no antagonism was observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5–2.2 μM) and showed strain-specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM).

Prophylactic Activity in a Nonhuman Primate Model of HIV-1 Transmission

Emtricitabine and Tenofovir Disoproxil Fumarate: The prophylactic activity of the combination of daily oral FTC and TDF was evaluated in a controlled study of macaques inoculated once weekly for 14 weeks with SIV/HIV-1 chimeric virus (SHIV) applied to the rectal surface. Of the 18 control animals, 17 became infected after a median of 2 weeks. In contrast, 4 of the 6 animals treated daily with oral FTC and TDF remained uninfected and the two infections that did occur were significantly delayed until 9 and 12 weeks and exhibited reduced viremia. An M184I-expressing FTC-resistant variant emerged in 1 of the 2 macaques after 3 weeks of continued drug exposure.

Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to the combination of FTC and tenofovir have been selected in cell culture. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT. In addition, a K70E substitution in the HIV-1 RT has been selected by tenofovir and results in reduced susceptibility to tenofovir.

In Study 934, a clinical trial of treatment-naïve subjects *[see Clinical Studies (14.2)]*, resistance analysis was performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation. Development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the treatment arms. The M184V amino acid substitution, associated with resistance to FTC and lamivudine, was observed in 2/19 analyzed subject isolates in the FTC+TDF group and in 10/29 analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R or K70E substitution in their HIV-1 as analyzed through standard genotypic analysis.

Emtricitabine: FTC-resistant isolates of HIV-1 have been selected in cell culture and in vivo. Genotypic analysis of these isolates showed that the reduced susceptibility to FTC was associated with a substitution in the HIV-1 RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in RT and showed a 2- to 4-fold reduction in susceptibility to tenofovir.

In treatment-naïve subjects, isolates from 8/47 (17%) analyzed subjects developed the K65R substitution in the TDF arm through 144 weeks; 7 occurred in the first 48 weeks of treatment and 1 at Week 96. In treatment-experienced subjects, 14/304 (5%) isolates from subjects failing TDF through Week 96 showed greater than 1.4-fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a K65R amino acid substitution in the HIV-1 RT.

iPrEx Trial: In the iPrEx trial, a clinical trial of HIV-1 seronegative adult subjects *[see Clinical Studies (14.3)]*, no amino acid substitutions associated with resistance to FTC or TDF were detected at the time of seroconversion among 48 subjects in the TRUVADA group and 83 subjects in the placebo group who became infected with HIV-1 during the trial. Ten subjects were observed to be HIV-1 infected at time of enrollment. The M184V/I substitutions associated with resistance to FTC were observed in 3 of the 10 subjects (2 of 2 in the TRUVADA group and 1 of 8 in the placebo group). One of the two subjects in the TRUVADA group harbored wild type virus at enrollment and developed the M184V substitution 4 weeks after enrollment. The other subject had indeterminate resistance at enrollment but was found to have the M184I substitution 4 weeks after enrollment.

Partners PrEP Trial: In the Partners PrEP trial, a clinical trial of HIV-1 seronegative adult subjects *[see Clinical Studies (14.4)],* no variants expressing amino acid substitutions associated with resistance to FTC or TDF were detected at the time of seroconversion among 12 subjects in the TRUVADA group, 15 subjects in the TDF group, and 51 subjects in the placebo group. Fourteen subjects were observed to be HIV-1 infected at the time of enrollment (3 in the TRUVADA group, 5 in the TDF group, and 6 in the placebo group). One of the three subjects in the TRUVADA group who was infected with wild type virus at enrollment selected an M184V expressing virus by Week 12. Two of the five subjects in the TDF group had tenofovir-resistant viruses at the time of seroconversion; one subject infected with wild type virus at enrollment developed a K65R substitution by Week 16, while the second subject had virus expressing the combination of D67N and K70R substitutions upon seroconversion at Week 60, although baseline virus was not genotyped and it is unclear if the

resistance emerged or was transmitted. Following enrollment, 4 subjects (2 in the TDF group, 1 in the TRUVADA group, and 1 in the placebo group) had virus expressing K103N or V106A substitutions, which confer high-level resistance to NNRTIs but have not been associated with FTC or TDF and may have been present in the infecting virus.

ATN113 Trial: In ATN113, a clinical trial of HIV-1 seronegative adolescent subjects *[see Use in Specific Populations (8.4)],* no amino acid substitutions associated with resistance to FTC or TDF were detected at the time of seroconversion from any of the 3 subjects who became infected with HIV-1 during the trial. All 3 subjects who seroconverted were nonadherent to the recommended TRUVADA dosage.

Cross Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: Cross-resistance among certain NRTIs has been recognized. The M184V/I and/or K65R substitutions selected in cell culture by the combination of FTC and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either FTC or lamivudine, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

Emtricitabine: FTC-resistant isolates (M184V/I) were cross-resistant to lamivudine but retained susceptibility in cell culture to the NRTIs didanosine, stavudine, tenofovir, and zidovudine, and to NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R substitution, selected in vivo by abacavir, didanosine, and tenofovir, demonstrated reduced susceptibility to inhibition by FTC. Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to FTC.

Tenofovir Disoproxil Fumarate: The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected patients treated with abacavir or didanosine. HIV-1 isolates with the K65R and K70E substitutions also showed reduced susceptibility to FTC and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbors the K65R or K70E substitutions. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V substitution without zidovudine resistance-associated substitutions (N=8) had reduced response to TDF. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine: In long-term oral carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

FTC was not genotoxic in the reverse mutation bacterial test (Ames test), or the mouse lymphoma or mouse micronucleus assays.

FTC did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through

sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

TDF was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, TDF was negative when administered to male mice.

There were no effects on fertility, mating performance, or early embryonic development when TDF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

Tenofovir and TDF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in four animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

The efficacy and safety of TRUVADA have been evaluated in the studies summarized in Table 13.

Table 13 Trials Conducted with TRUVADA for HIV-1 Treatment and HIV-1 PrEP

Trial	Population	Study Arms (N)[a]	Timepoint
Study 934[b] (NCT00112047)	HIV-infected, treatment-naïve adults	FTC+TDF + efavirenz (257) zidovudine/lamivudine + efavirenz (254)	48 Weeks
iPrEx[c] (NCT00458393)	HIV-seronegative men or transgender women who have sex with men	TRUVADA (1,251) Placebo (1,248)	4,237 person-years
Partners PrEP[c] (NCT00557245)	HIV serodiscordant heterosexual couples	TRUVADA (1,583) Placebo (1,586)	7,827 person-years

a. Randomized and dosed.
b. Randomized, open label, active-controlled trial.
c. Randomized, double-blind, placebo-controlled trial.

14.2 Clinical Trial Results for Treatment of HIV-1: Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter trial comparing FTC+TDF administered in combination with efavirenz (EFV) versus

zidovudine (AZT)/lamivudine (3TC) fixed-dose combination administered in combination with EFV in 511 antiretroviral-naïve adult subjects. From Weeks 96 to 144 of the trial, subjects received TRUVADA with EFV in place of FTC+TDF with EFV. Subjects had a mean age of 38 years (range 18–80); 86% were male, 59% were Caucasian, and 23% were Black. The mean baseline CD4+ cell count was 245 cells/mm^3 (range 2–1,191) and median baseline plasma HIV-1 RNA was 5.01 $\log_{10}$ copies/mL (range 3.56–6.54). Subjects were stratified by baseline CD4+ cell count (< or ≥200 cells/mm^3); 41% had CD4+ cell counts <200 cells/mm^3 and 51% of subjects had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did not have EFV resistance at baseline are presented in Table 14.

Table 14 Virologic Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144	
	FTC+TDF +EFV (N=244)	AZT/3TC +EFV (N=243)	FTC+TDF +EFV (N=227)[a]	AZT/3TC +EFV (N=229)[a]
Responder[b]	84%	73%	71%	58%
Virologic failure[c]	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death	<1%	1%	1%	1%
Discontinued due to adverse event	4%	9%	5%	12%
Discontinued for other reasons[d]	10%	14%	20%	22%

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue trial after Week 48 or Week 96 were excluded from analysis.
b. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.
c. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.
d. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation, and other reasons.

Through Week 48, 84% and 73% of subjects in the FTC+TDF group and the AZT/3TC group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in the proportion of subjects who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks is largely due to the higher number of discontinuations due to adverse events and other reasons in the AZT/3TC group in this open-label trial. In addition, 80% and 70% of subjects in the FTC+TDF group and the AZT/3TC group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in CD4+ cell count was 190 cells/mm^3 in the FTC+TDF group and 158 cells/mm^3 in the AZT/3TC group at Week 48 (312 and 271 cells/mm^3 at Week 144).

Through 48 weeks, 7 subjects in the FTC+TDF group and 5 subjects in the AZT/3TC group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

14.3 Clinical Trial Results for HIV-1 PrEP: iPrEx

The iPrEx trial was a randomized, double-blind, placebo-controlled multinational study evaluating TRUVADA in 2,499 HIV-seronegative men or transgender women who have sex with men and with evidence of high-risk behavior for HIV-1 infection. Evidence of high-risk behavior included any one of the following reported to have occurred up to six months prior to study screening: no condom use during anal intercourse with an HIV-1 positive partner or a partner of unknown HIV status; anal intercourse with more than 3 sex partners; exchange of money, gifts, shelter, or drugs for anal sex;

sex with male partner and diagnosis of sexually transmitted infection; no consistent use of condoms with sex partner known to be HIV-1 positive.

All subjects received monthly HIV-1 testing, risk-reduction counseling, condoms, and management of sexually transmitted infections. Of the 2,499 enrolled subjects, 1,251 received TRUVADA and 1,248 received placebo. The mean age of subjects was 27 years; 5% were Asian, 9% Black, 18% White, and 72% Hispanic/Latino.

Subjects were followed for 4,237 person-years. The primary outcome measure was the incidence of documented HIV seroconversion. At the end of treatment, emergent HIV-1 seroconversion was observed in 131 subjects, of which 48 occurred in the TRUVADA group and 83 occurred in the placebo group, indicating a 42% (95% CI: 18–60%) reduction in risk. Risk reduction was found to be higher (53%; 95% CI: 34–72%) among subjects who reported previous unprotected anal intercourse (URAI) at screening (732 and 753 subjects reported URAI within the last 12 weeks at screening in the TRUVADA and placebo groups, respectively). In a post-hoc case control study of plasma and intracellular drug levels in about 10% of study subjects, risk reduction appeared to be greatest in subjects with detectable intracellular tenofovir diphosphate concentrations. Efficacy was therefore strongly correlated with adherence.

14.4 Clinical Trial Results for HIV-1 PrEP: Partners PrEP

The Partners PrEP trial was a randomized, double-blind, placebo-controlled 3-arm trial conducted in 4,758 HIV-1 serodiscordant heterosexual couples in Kenya and Uganda to evaluate the efficacy and safety of TDF (N=1,589) and FTC/TDF (N=1,583) versus (parallel comparison) placebo (N=1,586) in preventing HIV-1 acquisition by the uninfected partner.

All uninfected partner subjects received monthly HIV-1 testing, evaluation of adherence, assessment of sexual behavior, and safety evaluations. Women were also tested monthly for pregnancy. Women who became pregnant during the trial had study drug interrupted for the duration of the pregnancy and while breastfeeding. The uninfected partner subjects were predominantly male (61–64% across study drug groups) and had a mean age of 33–34 years.

Following 7,827 person-years of follow-up, 82 emergent HIV-1 seroconversions were reported, with an overall observed seroincidence rate of 1.05 per 100 person-years. Of the 82 seroconversions, 13 and 52 occurred in partner subjects randomized to TRUVADA and placebo, respectively. Two of the 13 seroconversions in the TRUVADA arm and 3 of the 52 seroconversions in the placebo arm occurred in women during treatment interruptions for pregnancy. The risk reduction for TRUVADA relative to placebo was 75% (95% CI: 55–87%). In a post-hoc case control study of plasma drug levels in about 10% of study subjects, risk reduction appeared to be greatest in subjects with detectable plasma tenofovir concentrations. Efficacy was therefore strongly correlated with adherence.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRUVADA tablets are available in bottles containing 30 tablets with child-resistant closure as follows:

- 100 mg of FTC and 150 mg of TDF (equivalent to 123 mg of tenofovir disoproxil) tablets are blue, oval shaped, film coated, debossed with “GSI” on one side and with “703” on the other side (NDC 61958-0703-1).
- 133 mg of FTC and 200 mg of TDF (equivalent to 163 mg of tenofovir disoproxil) tablets are blue, rectangular shaped, film coated, debossed with “GSI” on one side and with “704” on the other side (NDC 61958-0704-1).

- 167 mg of FTC and 250 mg of TDF (equivalent to 204 mg of tenofovir disoproxil) tablets are blue, modified capsule shaped, film coated, debossed with “GSI” on one side and with “705” on the other side (NDC 61958-0705-1).
- 200 mg of FTC and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil) tablets are blue, capsule shaped, film coated, debossed with “GILEAD” on one side and with “701” on the other side (NDC 61958-0701-1).

Store at 25 °C (77 °F), excursions permitted to 15 °C–30 °C (59 °F–86 °F) (see USP Controlled Room Temperature).

- Keep container tightly closed
- Dispense only in original container

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Important Information for Uninfected Individuals Taking TRUVADA for HIV-1 PrEP

Encourage use of the Agreement Form for Initiating TRUVADA for PrEP of Sexually Acquired HIV-1 Infection.

In addition, advise HIV-uninfected individuals about the following *[see Warnings and Precautions (5.2)]*:

- The need to confirm that they are HIV-negative before starting to take TRUVADA to reduce the risk of acquiring HIV-1.
- That HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking TRUVADA, because TRUVADA alone does not constitute a complete regimen for HIV-1 treatment.
- The importance of taking TRUVADA on a regular dosing schedule and to strictly adhere to the recommended dosing schedule to reduce the risk of acquiring HIV-1. Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses.
- That TRUVADA should only be used as part of a complete prevention strategy including other prevention measures.
- To use condoms consistently and correctly to lower the chances of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- The importance of knowing their HIV status and the status of their partner(s).
- The importance of virologic suppression in their partner(s) with HIV-1.
- The need to get tested regularly for HIV-1 (at least every 3 months, or more frequently for some individuals such as adolescents) and to ask their partner(s) to get tested as well.
- To report any symptoms of acute HIV-1 infection (flu-like symptoms) to their healthcare provider immediately.
- That the signs and symptoms of acute infection include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- To get tested for other sexually transmitted infections, such as syphilis, chlamydia, and gonorrhea, that may facilitate HIV-1 transmission.

- To assess their sexual risk behavior and get support to help reduce sexual risk behavior.

Severe Acute Exacerbation of Hepatitis B in Patients Infected with HBV

Inform patients that severe acute exacerbations of hepatitis B have been reported in patients infected with hepatitis B virus (HBV) who have discontinued TRUVADA. Advise patients not to discontinue TRUVADA without first informing their healthcare provider. All patients should be tested for HBV infection before or when starting TRUVADA and those who are infected with HBV need close medical follow-up for several months after stopping TRUVADA to monitor for exacerbations of hepatitis *[see Warnings and Precautions (5.1)]*.

New Onset or Worsening Renal Impairment

Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of TDF, a component of TRUVADA. Advise patients to avoid TRUVADA with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) *[see Warnings and Precautions (5.3)]*. The dosing interval of TRUVADA may need adjustment in HIV-1 infected patients with renal impairment. TRUVADA for HIV-1 PrEP should not be used in HIV-1 uninfected individuals if estimated creatinine clearance is less than 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TRUVADA for HIV-1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use *[see Dosage and Administration (2.6)]*.

Immune Reconstitution Syndrome

Inform patients that in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[see Warnings and Precautions (5.4)].*

Bone Loss and Mineralization Defects

Inform patients that decreases in bone mineral density have been observed with the use of TDF or TRUVADA. Consider bone monitoring in patients and uninfected individuals who have a history of pathologic bone fracture or at risk for osteopenia *[see Warnings and Precautions (5.5)].*

Lactic Acidosis and Severe Hepatomegaly

Inform patients and uninfected individuals that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with TRUVADA should be suspended in any person who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.6)]*.

Drug Interactions

Advise patients that TRUVADA may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other medication, including other HIV drugs and drugs for treatment of hepatitis C virus *[see Warnings and Precautions (5.7) and Drug Interactions (7)].*

Dosage Recommendations for Treatment of HIV-1 Infection

Inform patients that it is important to take TRUVADA with other antiretroviral drugs for the treatment of HIV-1 on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance.

Pregnancy Registry

Inform patients using TRUVADA for HIV-1 treatment or HIV-1 PrEP that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to TRUVADA *[see Use in Specific Populations (8.1)].*

Lactation

Instruct mothers not to breastfeed if they are taking TRUVADA for the treatment of HIV-1 infection or if acute HIV-1 infection is suspected in a mother taking TRUVADA for HIV-1 PrEP because of the risk of passing the HIV-1 virus to the baby. In HIV-uninfected women, the benefits and risks of TRUVADA while breastfeeding should be evaluated, including the risk of HIV-1 acquisition due to medication nonadherence and subsequent mother to child transmission *[see Use in Specific Populations (8.2)].*

Manufactured for and distributed by:

Gilead Sciences, Inc.
Foster City, CA 94404

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Medication Guide
TRUVADA® (tru-VAH-dah)
(emtricitabine and tenofovir disoproxil fumarate)
tablets

Read this Medication Guide before you start taking TRUVADA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

This Medication Guide provides information about **two different ways** that TRUVADA may be used. See the section **"What is TRUVADA?"** for detailed information about how TRUVADA may be used.

What is the most important information I should know about TRUVADA?

TRUVADA can cause serious side effects, including:

- **Worsening of Hepatitis B virus infection (HBV). Your healthcare provider will test you for HBV before starting treatment with TRUVADA. If you have HBV infection and take TRUVADA, your HBV may get worse (flare-up) if you stop taking TRUVADA. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - Do not stop taking TRUVADA without first talking to your healthcare provider.
  - Do not run out of TRUVADA. Refill your prescription or talk to your healthcare provider before your TRUVADA is all gone.
  - If you stop taking TRUVADA, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection, or give you a medication to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking TRUVADA.

For more information about side effects, see the section "What are the possible side effects of TRUVADA?".

Other important information for people who take TRUVADA to help reduce their risk of getting HIV-1 infection:

Before taking TRUVADA to reduce your risk of getting HIV-1 infection:

- **You must be HIV-negative to start TRUVADA. You must get tested to make sure that you do not already have HIV-1 infection.**
- **Do not take TRUVADA to reduce the risk of getting HIV-1 unless you are confirmed to be HIV-negative.**
- Many HIV-1 tests can miss HIV-1 infection in a person who has recently become infected. If you have flu-like symptoms, you could have recently become infected with HIV-1. Tell your healthcare provider if you had a flu-like illness within the last month before starting TRUVADA or at any time while taking TRUVADA. Symptoms of new HIV-1 infection include:
  - tiredness
  - fever
  - joint or muscle aches
  - headache
  - sore throat
  - vomiting or diarrhea
  - rash
  - night sweats
  - enlarged lymph nodes in the neck or groin

While you are taking TRUVADA to reduce your risk of getting HIV-1:

- **Just taking TRUVADA may not keep you from getting HIV-1.**
- **You must continue using safer sex practices while you are taking TRUVADA to reduce your risk of getting HIV-1.**
- **You must stay HIV-negative to keep taking TRUVADA to reduce your risk of infection.**
  - Know your HIV-1 status and the HIV-1 status of your partners.
  - Practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal fluids, or blood.
  - Ask your partners with HIV-1 if they are taking anti-HIV-1 medicine and have an undetectable viral load. An undetectable viral load is when the amount of virus in the blood is too low to be measured in a lab test. To maintain an undetectable viral load, your partners must keep taking anti-HIV-1 medicine every day. Your risk of getting HIV-1 is lower if your partners with HIV-1 are taking effective treatment.
  - Get tested for HIV-1 at least every 3 months or when your healthcare provider tells you.
  - Get tested for other sexually transmitted infections such as syphilis, chlamydia, and gonorrhea. These infections make it easier for HIV-1 to infect you.
  - If you think you were exposed to HIV-1, tell your healthcare provider right away. They may want to do more tests to be sure you are still HIV-negative.

- Get information and support to help reduce risky sexual behavior.
- Have fewer sex partners.
- Do not miss any doses of TRUVADA. Missing doses may increase your risk of getting HIV-1 infection.

- If you do become HIV-positive, you need more medicine than TRUVADA alone to treat HIV-1. TRUVADA by itself is not a complete treatment for HIV-1.
- If you have HIV-1 and take only TRUVADA, over time your HIV-1 may become harder to treat.

What is TRUVADA?

TRUVADA is a prescription medicine that is used to:

- treat HIV-1 infection when used with other anti-HIV-1 medicines in adults and children who weigh at least 37 pounds (at least 17 kg).
- help reduce the risk of getting HIV-1 infection when used with safer sex practices in adults and adolescents who weigh at least 77 pounds (at least 35 kg).

TRUVADA works better to reduce the risk of getting HIV-1 when the medicines are in your bloodstream before you are exposed to HIV-1.

HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

TRUVADA contains the medicines emtricitabine and tenofovir disoproxil fumarate.

It is not known if TRUVADA is safe and effective in children with HIV-1 infection who weigh less than 37 pounds (less than 17 kg).

For people taking TRUVADA to reduce the risk of getting HIV-1 infection:

Do not take TRUVADA to help reduce your risk of getting HIV-1 if:

- **you already have HIV-1 infection.** If you are HIV-positive, you need to take other medicines with TRUVADA to treat HIV-1. TRUVADA by itself is not a complete treatment for HIV-1.
- **you do not know your HIV-1 infection status.** You may already be HIV-positive. You need to take other HIV-1 medicines with TRUVADA to treat HIV-1.

TRUVADA can only help reduce your risk of getting HIV-1 **before** you are infected.

What should I tell my healthcare provider before taking TRUVADA?

Before taking TRUVADA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, including HBV infection
- have kidney problems or receive kidney dialysis treatment
- have bone problems
- are pregnant or plan to become pregnant. It is not known if TRUVADA can harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with TRUVADA.

  Pregnancy Registry: There is a pregnancy registry for women who take TRUVADA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. TRUVADA can pass to your baby in your breast milk.
  - Do not breastfeed if you have HIV-1 or if you think you have recently become infected with HIV-1 because of the risk of passing HIV-1 to your baby.
  - If you take TRUVADA to reduce the risk of getting HIV-1, talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines may interact with TRUVADA. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with TRUVADA.
- Do not start a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take TRUVADA with other medicines.

How should I take TRUVADA?

- Take TRUVADA exactly as your healthcare provider tells you to take it.
- If you take TRUVADA to treat HIV-1 infection, you need to take other HIV-1 medicines. Your healthcare provider will tell you what medicines to take and how to take them.
- Take TRUVADA 1 time each day with or without food.
- Children who take TRUVADA are prescribed a lower strength tablet than adults. Children should swallow the

TRUVADA tablet**.** Tell your healthcare provider if your child cannot swallow the tablet, because they may need a different HIV-1 medicine.

- Your healthcare provider will change the dose of TRUVADA as needed based on your child's weight.

- Take TRUVADA at the same time each day to help keep TRUVADA blood levels constant.
- **Do not miss a dose of TRUVADA.** Missing a dose lowers the amount of medicine in your blood. Refill your TRUVADA prescription before you run out of medicine.
- Do not change your dose or stop taking TRUVADA without first talking with your healthcare provider. Stay under a healthcare provider's care when taking TRUVADA.
- If you take too much TRUVADA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of TRUVADA?

TRUVADA may cause serious side effects, including:

- **See "What is the most important information I should know about TRUVADA?"**
- **New or worse kidney problems**, **including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and during treatment with TRUVADA. Your healthcare provider may tell you to take TRUVADA less often, or to stop taking TRUVADA if you get new or worse kidney problems.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when **an HIV-1 infected person starts taking HIV-1 medicines.** Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting TRUVADA for treatment of HIV-1 infection.
- **Bone problems** can happen in some people who take TRUVADA. Bone problems include bone pain, or softening or thinning of bones, which may lead to fractures. Your healthcare provider may need to do tests to check your bones.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. **Tell your healthcare provider right away if you get these symptoms:** weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. **Tell your healthcare provider right away if you get these symptoms:** skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effects of TRUVADA in people taking TRUVADA to treat HIV-1 infection include:

- diarrhea
- nausea
- tiredness
- headache
- dizziness
- depression
- problems sleeping
- abnormal dreams
- rash

Common side effects in people who take TRUVADA to reduce the risk of getting HIV-1 infection include:

- headache
- stomach-area (abdomen) pain
- decreased weight

These are not all the possible side effects of TRUVADA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TRUVADA?

- Store TRUVADA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep TRUVADA in its original container.
- Keep the container tightly closed.
- Do not use TRUVADA if seal over bottle opening is broken or missing.

Keep TRUVADA and all other medicines out of reach of children.

General information about TRUVADA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRUVADA for a condition for which it was not prescribed. Do not give TRUVADA to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about TRUVADA that is written for health professionals.

What are the ingredients in TRUVADA?

Active ingredients: emtricitabine and tenofovir disoproxil fumarate.

Inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and

pregelatinized starch (gluten free). The 200 mg/300 mg strength tablets are coated with Opadry II Blue Y-30-10701, which contains FD&C Blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin. The 167 mg/250 mg, 133 mg/200 mg, and 100 mg/150 mg strength tablets are coated with Opadry II Blue, which contains FD&C Blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

Manufactured for and distributed by:
Gilead Sciences, Inc.
Foster City, CA 94404

For more information, call 1-800-445-3235 or go to www.TRUVADA.com.

21752-GS-032

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: May 2018

EXHIBIT 84

Truvada®

200 mg emtricitabine-tenofovir disoproxil fumarate 300 mg

TRUVADA for a Pre-exposure Prophylaxis (PrEP) Indication

Training Guide for Healthcare Providers

About TRUVADA for a PrEP indication to reduce the risk of sexually acquired HIV-1 infection in high-risk adults

INDICATION

TRUVADA (emtricitabine/tenofovir disoproxil fumarate) is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.* This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

PRESCRIBING CONSIDERATIONS: When prescribing TRUVADA for pre-exposure prophylaxis:

- Only prescribe TRUVADA as part of a comprehensive prevention strategy because TRUVADA is not always effective in preventing the acquisition of HIV-1
- Counsel all uninfected individuals to strictly adhere to their TRUVADA daily dosing schedule because the effectiveness of TRUVADA in reducing the risk of acquiring HIV-1 is strongly correlated with adherence and measurable drug levels
- Confirm a negative HIV-1 test immediately prior to initiating TRUVADA for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
- Screen for HIV-1 infection at least once every 3 months while taking TRUVADA for PrEP
- Do not prescribe TRUVADA for a PrEP indication if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed

*Factors that may help to identify individuals at high risk include individuals having partner(s) known to be HIV-1 infected or engaging in sexual activity within a high prevalence area or social network and one or more of the following: inconsistent or no condom use, diagnosis of sexually transmitted infections, exchange of sex for commodities (such as money, food, shelter, or drugs), use of illicit drugs or alcohol dependence, incarceration, or partner(s) of unknown HIV-1 status with any of the factors listed above.

BOXED WARNINGS: Use of TRUVADA for a PrEP Indication

- **TRUVADA used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-1 negative immediately prior to initial use and periodically (at least every 3 months) during use. Drug-resistant HIV-1 variants have been identified with the use of TRUVADA for a PrEP indication following undetected acute HIV-1 infection. Do not initiate TRUVADA for a PrEP indication if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed**
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, a component of TRUVADA**
- **TRUVADA is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV who have discontinued TRUVADA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue TRUVADA. If appropriate, initiation of anti–hepatitis B therapy may be warranted**

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Why Use TRUVADA for a PrEP Indication?

By inhibiting HIV-1 from replicating as it enters the body, TRUVADA for a PrEP indication works to prevent the virus from establishing permanent infection. However, TRUVADA should not be seen as the first line of defense against HIV-1. Because TRUVADA is not always effective in preventing the acquisition of HIV-1, TRUVADA for a PrEP indication must be used in combination with a comprehensive prevention strategy that includes safer sex practices, such as regular and correct condom use, regular HIV-1 testing for themselves (and their sexual partners), and other proven HIV-1 prevention methods to safely and effectively reduce the risk of acquiring HIV-1.

- TRUVADA for a PrEP indication must only be prescribed to uninfected individuals at high risk who are confirmed to be HIV-1 negative
- Uninfected individuals who are prescribed TRUVADA for a PrEP indication should not miss any doses. Missing doses raises the risk of acquiring HIV-1

TRUVADA is also indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. TRUVADA should never be used alone in an individual infected with HIV-1 because of the increased risk of resistance. Therefore, it is critical to confirm negative HIV-1 status. Confirm a negative HIV-1 test immediately prior to initiating TRUVADA for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection. Screen for HIV-1 infection at least once every 3 months while taking TRUVADA for PrEP.

Key Findings of the TRUVADA for a PrEP Indication Trials

The iPrEx Trial

- In one clinical trial of TRUVADA for a PrEP indication, TRUVADA was shown to reduce the risk of HIV-1 acquisition by 42% for high risk men who have sex with men who also received comprehensive prevention services, including monthly HIV-1 testing, condom provision, counseling, and management of other sexually transmitted infections
- In a post hoc case control study of plasma and intracellular drug levels in about 10% of clinical trial subjects, risk reduction appeared to be the greatest in subjects with detectable intracellular tenofovir. Efficacy was therefore strongly correlated with adherence
- Because of the intensive risk reduction counseling provided as part of the trial, self-reported risk behavior among the subjects in this clinical trial declined overall during the trial, both in terms of decreases in the number of sexual partners and increases in condom use

The Partners PrEP Trial

- In another clinical trial of TRUVADA for a PrEP indication in serodiscordant couples, TRUVADA was shown to reduce HIV-1 acquisition by 75% for the uninfected individuals exposed to the virus through heterosexual sex
- In a post hoc case control study of plasma drug levels in about 10% of clinical trial subjects, risk reduction appeared to be the greatest in subjects with detectable plasma tenofovir. Efficacy was therefore strongly correlated with adherence

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TRUVADA Safety Profile

IMPORTANT SAFETY INFORMATION

Contraindication: TRUVADA for a PrEP indication is contraindicated in individuals with positive or unknown HIV-1 status.

Warnings and Precautions Relating to the Use of TRUVADA for a PrEP Indication

- **Comprehensive management to reduce the risk of acquiring HIV-1:** TRUVADA for a PrEP indication should only be used as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because TRUVADA is not always effective in preventing the acquisition of HIV-1
  - Counsel uninfected individuals at high risk about safer sex practices, including:
    - Using condoms consistently and correctly
    - Knowing their HIV-1 status and that of their partner(s)
    - Being tested for other sexually transmitted infections
    - Informing individuals about the importance of reducing sexually risky behaviors and supporting their efforts to do so
  - **Use TRUVADA to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-1 negative.** HIV resistance substitutions may emerge with individuals with undetected HIV-1 infection who are taking only TRUVADA because TRUVADA alone does not constitute a complete treatment regimen for HIV-1 infection. Therefore:
    - Confirm a negative HIV-1 test immediately prior to initiating TRUVADA for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
    - Screen for HIV-1 infection at least once every 3 months while taking TRUVADA for PrEP
    - Evaluate for signs or symptoms of acute HIV-1 infection prior to and while prescribing TRUVADA for a PrEP indication. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection
  - Counsel all uninfected individuals to strictly adhere to their TRUVADA daily dosing schedule. The effectiveness of TRUVADA in reducing the risk of acquiring HIV-1 is strongly correlated with adherence and measurable drug levels
- **New onset or worsening renal impairment:** Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before prescribing TRUVADA. Monitor CrCl and serum phosphorus in individuals at risk for renal impairment. Avoid administering TRUVADA with concurrent or recent use of nephrotoxic drugs
  - **Do not prescribe TRUVADA for a PrEP indication for uninfected individuals with a creatinine clearance below 60 mL/min. If a decrease in CrCl is observed in uninfected individuals while using TRUVADA for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use**
- **HBV infection:** It is recommended that all individuals be tested for the presence of chronic hepatitis B virus (HBV) before initiating TRUVADA
  - HBV-uninfected individuals should be offered vaccination
- **Decreases in bone mineral density (BMD):** Consider assessment of BMD in individuals with a history of pathologic fracture or other risk factors for osteoporosis or bone loss
- **Redistribution/accumulation of body fat:** Observed in patients receiving antiretroviral therapy
- **Immune reconstitution syndrome:** May necessitate further evaluation and treatment in HIV-1–infected patients

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Important Safety Information About the Use of TRUVADA for a PrEP Indication in Specific Populations

- **Pregnancy:** There are no adequate and well-controlled trials in pregnant women. TRUVADA should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking TRUVADA for a PrEP indication, careful consideration should be given to whether use of TRUVADA should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy
  - A pregnancy registry is available. Enroll women taking TRUVADA for a PrEP indication by calling 1-800-258-4263
- **Nursing mothers:** Women infected with HIV-1 or taking TRUVADA for a PrEP indication should be instructed not to breast-feed. The components of TRUVADA (emtricitabine and tenofovir disoproxil fumarate) are excreted in breast milk, and it is not known if these can harm the infant
- **Pediatrics:** The TRUVADA for a PrEP indication is based on trials in adults

Reminder about the use of TRUVADA for a PrEP indication: It is important to confirm and regularly reconfirm negative HIV-1 status before and while the individual is taking TRUVADA for a PrEP indication.

- Confirm a negative HIV-1 test immediately prior to initiating TRUVADA for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
- Screen for HIV-1 infection at least once every 3 months while taking TRUVADA for PrEP
- It is important to be alert to the signs of potential acute HIV-1 infection when prescribing TRUVADA for a PrEP indication. These include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and cervical and inguinal adenopathy
- If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection
- HIV-1 resistance mutations may emerge in individuals with undetected HIV-1 infection who are taking TRUVADA for a PrEP indication

Use the Checklist for Prescribers and the Agreement Form to help manage and counsel individuals about the correct and safe use of TRUVADA for a PrEP indication.

Important Safety Information

Drug Interactions

- **Coadministration with other products**
  - Do not use TRUVADA with drugs containing emtricitabine or tenofovir disoproxil fumarate, or with drugs containing lamivudine. Do not administer in combination with HEPSERA® (adefovir dipivoxil)
  - Caution should be exercised when co-administering TRUVADA with didanosine, atazanavir, or lopinavir/ritonavir due to the potential for toxicities

For further details about TRUVADA drug interactions, please see Full Prescribing Information for TRUVADA in back pocket.

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Common Adverse Events

- In HIV-1–uninfected individuals in PrEP trials, adverse reactions that were reported by more than 2% of TRUVADA subjects and more frequently than by placebo subjects were headache, abdominal pain, and weight decreased
- The most common adverse events (incidence ≥10%) reported by HIV-1–infected subjects in clinical trials (in combination with efavirenz) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash

For more information about TRUVADA and its indication for PrEP, please see the Full Prescribing Information, including Boxed WARNINGS and Medication Guide. For more information about the REMS program for TRUVADA for a PrEP indication, please log on to www.TRUVADApreprems.com. You may also obtain additional information and educational materials about the use of TRUVADA for a PrEP indication at 1-800-445-3235.

Post-Training Review Questions

1. TRUVADA for a PrEP indication should be used only:

a. As part of a comprehensive HIV-1 prevention strategy that includes other preventive measures since TRUVADA is not always effective in preventing the acquisition of HIV-1

b. In individuals who have been counseled to strictly adhere to their TRUVADA daily dosing schedule since the effectiveness of TRUVADA in reducing the risk of acquiring HIV-1 is strongly correlated with adherence and measurable drug levels

c. In individuals who have a confirmed negative HIV-1 test prior to initiating and routinely while taking TRUVADA for a PrEP indication

d. All of the above

2. Which of the following statements is false?

a. TRUVADA should be used for a PrEP indication only in individuals confirmed to be HIV-1 negative

b. TRUVADA has been found to be safe and effective for pre-exposure prophylaxis to reduce the risk of acquiring HIV-1 through injection drug use

c. Women taking TRUVADA for a PrEP indication should not breast-feed their babies

d. TRUVADA for a PrEP indication is not always effective in preventing HIV-1

3. Which of the following items are not included on the Checklist for Prescribers for initiating TRUVADA for a PrEP indication?

a. Perform HBV screening test

b. Perform testing for TB

c. Confirm negative HIV-1 status of the individual

d. Confirm creatinine clearance is ≥60 mL/min

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4. Hepatic function should be monitored closely in:

a. HBV-infected individuals who discontinue TRUVADA

b. All people taking TRUVADA

c. All people who discontinue TRUVADA

d. None of the above

5. In clinical trials evaluating TRUVADA for a PrEP indication, which of the following adverse reactions was not common?

a. Abdominal pain

b. Headache

c. Dizziness

d. Decreased weight

6. TRUVADA for a PrEP indication is indicated only for:

a. Men who are at high risk for sexually acquired HIV-1 infection

b. Adults who are at high risk of acquiring HIV-1 infection by any means

c. Adults who are at high risk of acquiring HIV-1 infection through injection drug use

d. Adults who are at high risk for sexually acquired HIV-1 infection

7. The Agreement Form for Initiating TRUVADA for PrEP of Sexually Acquired HIV-1 Infection provides which of the following information:

a. A list of activities that put individuals at risk for sexually acquired HIV-1

b. A confirmation that the prescriber has discussed the risks and benefits of using TRUVADA for a PrEP indication with the uninfected individual

c. A signature from the individual asserting that the prescriber has explained the risks and benefits of taking TRUVADA for a PrEP indication, including the need for adherence and a comprehensive prevention strategy, which includes safer sex practices

d. All of the above

Answer key: 1–d; 2-b; 3–b; 4–a; 5–c; 6–d; 7-d

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Help uninfected individuals learn more about TRUVADA for a pre-exposure prophylaxis (PrEP) indication

GILEAD SCIENCES
565 SINCLAIR FRONTAGE RD
MILPITAS CA 95035-9905

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 19 MILPITAS, CA
POSTAGE WILL BE PAID BY ADDRESSEE

NO POSTAGE NECESSARY IF MAILED UNITED STATES

VOID

((POCKET))

If you would like additional educational materials about TRUVADA for a PrEP indication, please select which ones you want and how many you would like us to send to you.

	Quantity:		
☐ Important Safety Information for Uninfected Individuals	☐ 10	☐ 25	☐ 50
☐ Important Safety Information for Healthcare Providers	☐ 10	☐ 25	☐ 50
☐ TRUVADA Medication Guide	☐ 10	☐ 25	☐ 50
☐ Safety Information Fact Sheet	☐ 10	☐ 25	☐ 50
☐ Checklist for Prescribers	☐ 10	☐ 25	☐ 50
☐ Agreement Form	☐ 10	☐ 25	☐ 50

Your full name and degree: _____

Street address: _____

City: _____ State: _____ ZIP: _____

Your practice or clinic name: _____

Your specialty: _____

Telephone: _____ E-mail: _____

Terms and Conditions

Gilead Sciences, Inc., and its authorized agents agree only to use the above information for purposes of fulfilling your request for additional materials regarding TRUVADA for a PrEP indication and will not transfer your information to any other party unless required to do so for the sole purpose of completing your request.

GILEAD

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MOISTEN GLUE STRIP AND FOLD TO SEAL.

Notes

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Reference: TRUVADA [package insert]. Foster City, CA: Gilead Sciences, Inc; 2012.

GILEAD

EXHIBIT 85

Agreement Form

for Initiating Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg for HIV-1 Pre-exposure Prophylaxis (PrEP)

Individual Label

Instructions: Review form with an HIV-negative person who is about to start or is taking emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP at each visit. File form in the person's medical record.

Emtricitabine/tenofovir disoproxil fumarate is indicated in combination with safer sex practices for HIV-1 pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg. Individuals must have a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP.

- **If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting HIV-1 PrEP for at least 1 month and reconfirm HIV-1 status or use a test cleared by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection**

The following factors may help to identify at-risk individuals:

- Has partner(s) known to be HIV-1 infected, or
- Engages in sexual activity within a high prevalence area or social network and has additional risk factors for HIV-1 acquisition, such as:
  - Inconsistent or no condom use
  - Diagnosis of sexually transmitted infections
  - Exchange of sex for commodities (such as money, shelter, food, or drugs)
  - Use of illicit drugs, alcohol dependence
  - Incarceration
  - Partner(s) of unknown HIV-1 status with any of the factors listed above

Healthcare Provider Agreement

By signing below, I signify my understanding of the risks and benefits of emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP and my obligation as a prescriber to educate the HIV-negative person about these risks, counsel the person on risk reduction, monitor the person appropriately, and report adverse events. Specifically, I attest to having done the following:

- Confirmed the negative HIV-1 status of this person prior to starting emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP
- Read the Prescribing Information, including the BOXED WARNING
- Discussed with the HIV-negative person the known safety risks with use of emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP
- Reviewed the importance of adherence with a comprehensive prevention strategy, including practicing safer sex
- Discussed the importance of virologic suppression in their partner(s) with HIV
- Discussed the importance of regular HIV-1 testing (at least every 3 months) while taking emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP, noting that some individuals, such as adolescents, may benefit from more frequent visits and counseling
- Reviewed the emtricitabine/tenofovir disoproxil fumarate Medication Guide with the HIV-negative person at risk prior to prescribing emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP
- Completed the items on the Checklist for Prescribers: Initiation of Emtricitabine/Tenofovir Disoproxil Fumarate for HIV-1 Pre-exposure Prophylaxis (PrEP)

Healthcare Provider's Signature Date

HIV-Negative Person Agreement

By signing below, I acknowledge that I have talked with my healthcare provider about the risks and benefits of emtricitabine/tenofovir disoproxil fumarate to reduce the risk of getting HIV-1 infection, and I understand them clearly. Specifically, I attest to the following:

- My healthcare provider talked with me about the importance of follow-up HIV-1 testing, and I agree to have repeat HIV-1 screening tests (at least every 3 months) as scheduled by my healthcare provider
- My healthcare provider talked with me about the safety risks involved with using emtricitabine/tenofovir disoproxil fumarate to reduce the risk of getting HIV-1 infection
- My healthcare provider talked with me about a complete prevention strategy and always practicing safer sex by using condoms correctly
- I will talk with my healthcare provider if I have any questions
- I have read the emtricitabine/tenofovir disoproxil fumarate Medication Guide

HIV-Negative Person's Signature

Date

EXHIBIT 86

PTO Form 1478 (Rev 09/2006)
OMB No. 0651-0009 (Exp 02/28/2021)

Trademark/Service Mark Application, Principal Register

TEAS Plus Application

Serial Number: 88504395
Filing Date: 07/08/2019

NOTE: Data fields with the * are mandatory under TEAS Plus. The wording "(if applicable)" appears where the field is only mandatory under the facts of the particular application.

The table below presents the data as entered.

Input Field	Entered
TEAS Plus	**YES**
MARK INFORMATION	
***MARK**	STEP UP. PREP UP.
***STANDARD CHARACTERS**	YES
USPTO-GENERATED IMAGE	YES
LITERAL ELEMENT	STEP UP. PREP UP.
***MARK STATEMENT**	The mark consists of standard characters, without claim to any particular font style, size, or color.
REGISTER	Principal
APPLICANT INFORMATION	
***OWNER OF MARK**	Gilead Sciences, Inc.
***STREET**	333 Lakeside Drive
***CITY**	Foster City
***STATE** **(Required for U.S. applicants)**	California
***COUNTRY**	United States
***ZIP/POSTAL CODE** **(Required for U.S. and certain international addresses)**	94404
EMAIL ADDRESS	trademarks@gilead.com
LEGAL ENTITY INFORMATION	
***TYPE**	CORPORATION
*** STATE/COUNTRY OF INCORPORATION**	Delaware
GOODS AND/OR SERVICES AND BASIS INFORMATION	
***INTERNATIONAL CLASS**	035
***IDENTIFICATION**	Promoting public awareness of **prevention, treatment, and diagnosis of HIV and AIDS**
***FILING BASIS**	SECTION 1(b)

*INTERNATIONAL CLASS	044
*IDENTIFICATION	Providing medical information in the field of **prevention, treatment, and diagnosis of HIV and AIDS**
*FILING BASIS	SECTION 1(b)
ADDITIONAL STATEMENTS SECTION	
*TRANSLATION (if applicable)	
*TRANSLITERATION (if applicable)	
*CLAIMED PRIOR REGISTRATION (if applicable)	
*CONSENT (NAME/LIKENESS) (if applicable)	
*CONCURRENT USE CLAIM (if applicable)	
DISCLAIMER	No claim is made to the exclusive right to use PREP apart from the mark as shown.
ATTORNEY INFORMATION	
NAME	Gretchen R. Stroud
STREET	333 Lakeside Drive
CITY	Foster City
STATE	California
COUNTRY	United States
ZIP/POSTAL CODE	94404
EMAIL ADDRESS	trademarks@gilead.com
AUTHORIZED TO COMMUNICATE VIA EMAIL	Yes
OTHER APPOINTED ATTORNEY	Lori Mayall, Jack Wessel, Cynthia Smuzynska, Shelley Lai
CORRESPONDENCE INFORMATION	
*NAME	Gretchen R. Stroud
*STREET	333 Lakeside Drive
*CITY	Foster City
*STATE (Required for U.S. addresses)	California
*COUNTRY	United States
*ZIP/POSTAL CODE	94404
*EMAIL ADDRESS	trademarks@gilead.com; jack.wessel@gilead.com
*AUTHORIZED TO COMMUNICATE VIA EMAIL	Yes
FEE INFORMATION	
APPLICATION FILING OPTION	TEAS Plus
NUMBER OF CLASSES	2
FEE PER CLASS	225
*TOTAL FEE PAID	450

SIGNATURE INFORMATION	
* SIGNATURE	/Gretchen R. Stroud/
* SIGNATORY'S NAME	Gretchen R. Stroud
* SIGNATORY'S POSITION	Sr. Associate General Counsel, IP, California Bar Member
* DATE SIGNED	07/08/2019

PTO Form 1478 (Rev 09/2006)
OMB No. 0651-0009 (Exp 02/28/2021)

Trademark/Service Mark Application, Principal Register

TEAS Plus Application

Serial Number: 88504395
Filing Date: 07/08/2019

To the Commissioner for Trademarks:

MARK: STEP UP. PREP UP. (Standard Characters, see mark)
The mark in your application is STEP UP. PREP UP..

The applicant, Gilead Sciences, Inc., a corporation of Delaware, having an address of
333 Lakeside Drive
Foster City, California 94404
United States
trademarks@gilead.com (not authorized)

requests registration of the trademark/service mark identified above in the United States Patent and Trademark Office on the Principal Register established by the Act of July 5, 1946 (15 U.S.C. Section 1051 et seq.), as amended, for the following:

For specific filing basis information for each item, you must view the display within the Input Table.
International Class 035: Promoting public awareness of prevention, treatment, and diagnosis of HIV and AIDS
Intent to Use: The applicant has a bona fide intention, and is entitled, to use the mark in commerce on or in connection with the identified goods/services. (15 U.S.C. Section 1051(b)).

For specific filing basis information for each item, you must view the display within the Input Table.
International Class 044: Providing medical information in the field of prevention, treatment, and diagnosis of HIV and AIDS
Intent to Use: The applicant has a bona fide intention, and is entitled, to use the mark in commerce on or in connection with the identified goods/services. (15 U.S.C. Section 1051(b)).

Disclaimer
No claim is made to the exclusive right to use PREP apart from the mark as shown.

The applicant's current Attorney Information:
Gretchen R. Stroud and Lori Mayall, Jack Wessel, Cynthia Smuzynska, Shelley Lai 333 Lakeside Drive
Foster City, California 94404
United States
trademarks@gilead.com (authorized)

The applicant's current Correspondence Information:
Gretchen R. Stroud
333 Lakeside Drive
Foster City, California 94404
trademarks@gilead.com;jack.wessel@gilead.com (authorized)
E-mail Authorization: I authorize the USPTO to send e-mail correspondence concerning the application to the applicant or the applicant's attorney, or the applicant's domestic representative at the e-mail address provided in this application. I understand that a valid e-mail address must be maintained and that the applicant or the applicant's attorney must file the relevant subsequent application-related submissions via the Trademark Electronic Application System (TEAS). Failure to do so will result in the loss of TEAS Plus status and a requirement to submit an additional processing fee of $125 per international class of goods/services.

A fee payment in the amount of $450 has been submitted with the application, representing payment for 2 class(es).

Declaration

☑ **Basis:**
If the applicant is filing the application based on use in commerce under 15 U.S.C. § 1051(a):

- The signatory believes that the applicant is the owner of the trademark/service mark sought to be registered;
- The mark is in use in commerce on or in connection with the goods/services in the application;
- The specimen(s) shows the mark as used on or in connection with the goods/services in the application; and
- To the best of the signatory's knowledge and belief, the facts recited in the application are accurate.

AND/OR
If the applicant is filing the application based on an intent to use the mark in commerce under 15 U.S.C. § 1051(b), § 1126(d), and/or § 1126(e):

- The signatory believes that the applicant is entitled to use the mark in commerce;
- The applicant has a bona fide intention to use the mark in commerce on or in connection with the goods/services in the application; and
- To the best of the signatory's knowledge and belief, the facts recited in the application are accurate.

☑ To the best of the signatory's knowledge and belief, no other persons, except, if applicable, concurrent users, have the right to use the mark in commerce, either in the identical form or in such near resemblance as to be likely, when used on or in connection with the goods/services of such other persons, to cause confusion or mistake, or to deceive.

☑ To the best of the signatory's knowledge, information, and belief, formed after an inquiry reasonable under the circumstances, the allegations and other factual contentions made above have evidentiary support.

☑ The signatory being warned that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements and the like may jeopardize the validity of the application or submission or any registration resulting therefrom, declares that all statements made of his/her own knowledge are true and all statements made on information and belief are believed to be true.

Declaration Signature

Signature: /Gretchen R. Stroud/ Date: 07/08/2019
Signatory's Name: Gretchen R. Stroud
Signatory's Position: Sr. Associate General Counsel, IP, California Bar Member
Payment Sale Number: 88504395
Payment Accounting Date: 07/09/2019

Serial Number: 88504395
Internet Transmission Date: Mon Jul 08 17:19:59 EDT 2019
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99-DA-5196-20190708122528297977

STEP UP. PREP UP.

EXHIBIT 87

PTO Form 1478 (Rev 09/2006)
OMB No. 0651-0009 (Exp 02/28/2021)

Trademark/Service Mark Application, Principal Register

Serial Number: 87794113
Filing Date: 02/12/2018

The table below presents the data as entered.

Input Field	Entered
SERIAL NUMBER	87794113
MARK INFORMATION	
***MARK**	\\TICRS\EXPORT17\IMAGEOUT 17\877\941\87794113\xml1\ RFA0002.JPG
SPECIAL FORM	YES
USPTO-GENERATED IMAGE	NO
COLOR MARK	YES
COLOR(S) CLAIMED (If applicable)	The color(s) blue is/are claimed as a feature of the mark.
***DESCRIPTION OF THE MARK (and Color Location, if applicable)**	The mark consists of a three-dimensional configuration of an oblong tablet, combined with the color blue as applied to the entire surface of the tablet.
PIXEL COUNT ACCEPTABLE	YES
PIXEL COUNT	828 x 446
REGISTER	Principal
APPLICANT INFORMATION	
***OWNER OF MARK**	Gilead Sciences, Inc.
***STREET**	333 Lakeside Drive
***CITY**	Foster City
***STATE (Required for U.S. applicants)**	California
***COUNTRY**	United States
***ZIP/POSTAL CODE (Required for U.S. and certain international addresses)**	94404
PHONE	650-522-2401
FAX	(650) 522-5575
EMAIL ADDRESS	trademarks@gilead.com
WEBSITE ADDRESS	www.gilead.com
LEGAL ENTITY INFORMATION	
TYPE	corporation
STATE/COUNTRY OF INCORPORATION	Delaware
GOODS AND/OR SERVICES AND BASIS INFORMATION	
INTERNATIONAL CLASS	005

*IDENTIFICATION	Pharmaceutical preparations for the treatment of HIV infection;
FILING BASIS	SECTION 1(a)
FIRST USE ANYWHERE DATE	At least as early as 08/05/2004
FIRST USE IN COMMERCE DATE	At least as early as 08/05/2004
SPECIMEN FILE NAME(S)	
ORIGINAL PDF FILE	SPE0-19918425319-20180209133913942595_._TRUVADA_Pill_Specimen.pdf
CONVERTED PDF FILE(S) (2 pages)	\\TICRS\EXPORT17\IMAGEOUT17\877\941\87794113\xml1\RFA0003.JPG
	\\TICRS\EXPORT17\IMAGEOUT17\877\941\87794113\xml1\RFA0004.JPG
SPECIMEN DESCRIPTION	image of the pill
INTERNATIONAL CLASS	005
*IDENTIFICATION	pharmaceutical preparations, namely, pre-exposure prophylaxis (PrEP) preparations for prevention and risk mitigation of contracting HIV
FILING BASIS	SECTION 1(a)
FIRST USE ANYWHERE DATE	At least as early as 07/16/2012
FIRST USE IN COMMERCE DATE	At least as early as 07/16/2012
SPECIMEN FILE NAME(S)	
ORIGINAL PDF FILE	SPE0-19918425319-20180209185233150574_._TRUVADA_Pill_Specimen.pdf
CONVERTED PDF FILE(S) (2 pages)	\\TICRS\EXPORT17\IMAGEOUT17\877\941\87794113\xml1\RFA0005.JPG
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ORIGINAL PDF FILE	SPE0-19918425319-20180209185233150574_._TRUVADA_for_PrEP_Specimen.pdf
CONVERTED PDF FILE(S) (2 pages)	\\TICRS\EXPORT17\IMAGEOUT17\877\941\87794113\xml1\RFA0007.JPG
	\\TICRS\EXPORT17\IMAGEOUT17\877\941\87794113\xml1\RFA0008.JPG
SPECIMEN DESCRIPTION	picture of a pill and point of sale brochure
ADDITIONAL STATEMENTS SECTION	
ACTIVE PRIOR REGISTRATION(S)	The applicant claims ownership of active prior U.S. Registration Number(s) 5030567 and 5154303.
SECTION 2(f) Claim of Acquired Distinctiveness, based on Five or More Years' Use	The mark has become distinctive of the goods/services through the applicant's substantially exclusive and continuous use of the mark in commerce that the U.S. Congress may lawfully regulate for at least the five years immediately before the date of this statement.
ATTORNEY INFORMATION	
NAME	Gretchen R. Stroud
FIRM NAME	Gilead Sciences, Inc.
STREET	333 Lakeside Drive
CITY	Foster City
STATE	California
COUNTRY	United States
ZIP/POSTAL CODE	94404

PHONE	650-522-2401
FAX	(650) 522-5575
EMAIL ADDRESS	trademarks@gilead.com
AUTHORIZED TO COMMUNICATE VIA EMAIL	Yes
OTHER APPOINTED ATTORNEY	Lori Mayall & Jack Wessel
CORRESPONDENCE INFORMATION	
NAME	Gretchen R. Stroud
FIRM NAME	Gilead Sciences, Inc.
STREET	333 Lakeside Drive
CITY	Foster City
STATE	California
COUNTRY	United States
ZIP/POSTAL CODE	94404
PHONE	650-522-2401
FAX	(650) 522-5575
***EMAIL ADDRESS**	trademarks@gilead.com; trademarks@gilead.com
***AUTHORIZED TO COMMUNICATE VIA EMAIL**	Yes
FEE INFORMATION	
APPLICATION FILING OPTION	TEAS RF
NUMBER OF CLASSES	1
APPLICATION FOR REGISTRATION PER CLASS	275
***TOTAL FEE DUE**	275
***TOTAL FEE PAID**	275
SIGNATURE INFORMATION	
SIGNATURE	/Gretchen R. Stroud/
SIGNATORY'S NAME	Gretchen R. Stroud
SIGNATORY'S POSITION	Associate General Counsel
SIGNATORY'S PHONE NUMBER	(650) 522-2401
DATE SIGNED	02/11/2018

PTO Form 1478 (Rev 09/2006)
OMB No. 0651-0009 (Exp 02/28/2021)

Trademark/Service Mark Application, Principal Register

Serial Number: 87794113
Filing Date: 02/12/2018

To the Commissioner for Trademarks:

MARK: (Stylized and/or Design, see mark)
The color(s) blue is/are claimed as a feature of the mark. The mark consists of a three-dimensional configuration of an oblong tablet, combined with the color blue as applied to the entire surface of the tablet.
The applicant, Gilead Sciences, Inc., a corporation of Delaware, having an address of

333 Lakeside Drive
Foster City, California 94404
United States
650-522-2401(phone)
(650) 522-5575(fax)
trademarks@gilead.com (not authorized)

requests registration of the trademark/service mark identified above in the United States Patent and Trademark Office on the Principal Register established by the Act of July 5, 1946 (15 U.S.C. Section 1051 et seq.), as amended, for the following:

International Class 005: Pharmaceutical preparations for the treatment of HIV infection;

In International Class 005, the mark was first used by the applicant or the applicant's related company or licensee or predecessor in interest at least as early as 08/05/2004, and first used in commerce at least as early as 08/05/2004, and is now in use in such commerce. The applicant is submitting one(or more) specimen(s) showing the mark as used in commerce on or in connection with any item in the class of listed goods/services, consisting of a(n) image of the pill.

Original PDF file:
SPE0-19918425319-20180209133913942595_._TRUVADA_Pill_Specimen.pdf
Converted PDF file(s) (2 pages)
Specimen File1
Specimen File2

International Class 005: pharmaceutical preparations, namely, pre-exposure prophylaxis (PrEP) preparations for prevention and risk mitigation of contracting HIV

In International Class 005, the mark was first used by the applicant or the applicant's related company or licensee or predecessor in interest at least as early as 07/16/2012, and first used in commerce at least as early as 07/16/2012, and is now in use in such commerce. The applicant is submitting one(or more) specimen(s) showing the mark as used in commerce on or in connection with any item in the class of listed goods/services, consisting of a(n) picture of a pill and point of sale brochure.

Original PDF file:
SPE0-19918425319-20180209185233150574_._TRUVADA_Pill_Specimen.pdf
Converted PDF file(s) (2 pages)
Specimen File1
Specimen File2
Original PDF file:
SPE0-19918425319-20180209185233150574_._TRUVADA_for_PrEP_Specimen.pdf
Converted PDF file(s) (2 pages)
Specimen File1
Specimen File2

Claim of Active Prior Registration(s)

The applicant claims ownership of active prior U.S. Registration Number(s) 5030567 and 5154303.

SECTION 2(f) Claim of Acquired Distinctiveness, based on Five or More Years' Use
The mark has become distinctive of the goods/services through the applicant's substantially exclusive and continuous use of the mark in commerce that the U.S. Congress may lawfully regulate for at least the five years immediately before the date of this statement.

For informational purposes only, applicant's website address is: www.gilead.com

The applicant's current Attorney Information:
Gretchen R. Stroud and Lori Mayall & Jack Wessel of Gilead Sciences, Inc. 333 Lakeside Drive
Foster City, California 94404
United States
650-522-2401(phone)
(650) 522-5575(fax)
trademarks@gilead.com (authorized)

The applicant's current Correspondence Information:
Gretchen R. Stroud
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, California 94404
650-522-2401(phone)
(650) 522-5575(fax)
trademarks@gilead.com;trademarks@gilead.com (authorized)
E-mail Authorization: I authorize the USPTO to send e-mail correspondence concerning the application to the applicant, the applicant's attorney, or the applicant's domestic representative at the e-mail address provided in this application. I understand that a valid e-mail address must be maintained and that the applicant or the applicant's attorney must file the relevant subsequent application-related submissions via the Trademark Electronic Application System (TEAS). Failure to do so will result in the loss of TEAS Reduced Fee status and a requirement to submit an additional processing fee of $125 per international class of goods/services.

A fee payment in the amount of $275 has been submitted with the application, representing payment for 1 class(es).

Declaration

☑ **Basis:**
If the applicant is filing the application based on use in commerce under 15 U.S.C. § 1051(a):

- The signatory believes that the applicant is the owner of the trademark/service mark sought to be registered;
- The mark is in use in commerce on or in connection with the goods/services in the application;
- The specimen(s) shows the mark as used on or in connection with the goods/services in the application; and
- To the best of the signatory's knowledge and belief, the facts recited in the application are accurate.

And/Or
If the applicant is filing the application based on an intent to use the mark in commerce under 15 U.S.C. § 1051(b), § 1126(d), and/or § 1126(e):

- The signatory believes that the applicant is entitled to use the mark in commerce;
- The applicant has a bona fide intention to use the mark in commerce on or in connection with the goods/services in the application; and
- To the best of the signatory's knowledge and belief, the facts recited in the application are accurate.

☑ To the best of the signatory's knowledge and belief, no other persons, except, if applicable, concurrent users, have the right to use the mark in commerce, either in the identical form or in such near resemblance as to be likely, when used on or in connection with the goods/services of such other persons, to cause confusion or mistake, or to deceive.

☑ To the best of the signatory's knowledge, information, and belief, formed after an inquiry reasonable under the circumstances, the allegations and other factual contentions made above have evidentiary support.

☑ The signatory being warned that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements and the like may jeopardize the validity of the application or submission or any registration

resulting therefrom, declares that all statements made of his/her own knowledge are true and all statements made on information and belief are believed to be true.

Declaration Signature

Signature: /Gretchen R. Stroud/ Date: 02/11/2018
Signatory's Name: Gretchen R. Stroud
Signatory's Position: Associate General Counsel
Payment Sale Number: 87794113
Payment Accounting Date: 02/13/2018

Serial Number: 87794113
Internet Transmission Date: Mon Feb 12 14:09:11 EST 2018
TEAS Stamp: USPTO/BAS-XXX.XXX.XXX.XX-201802121409116
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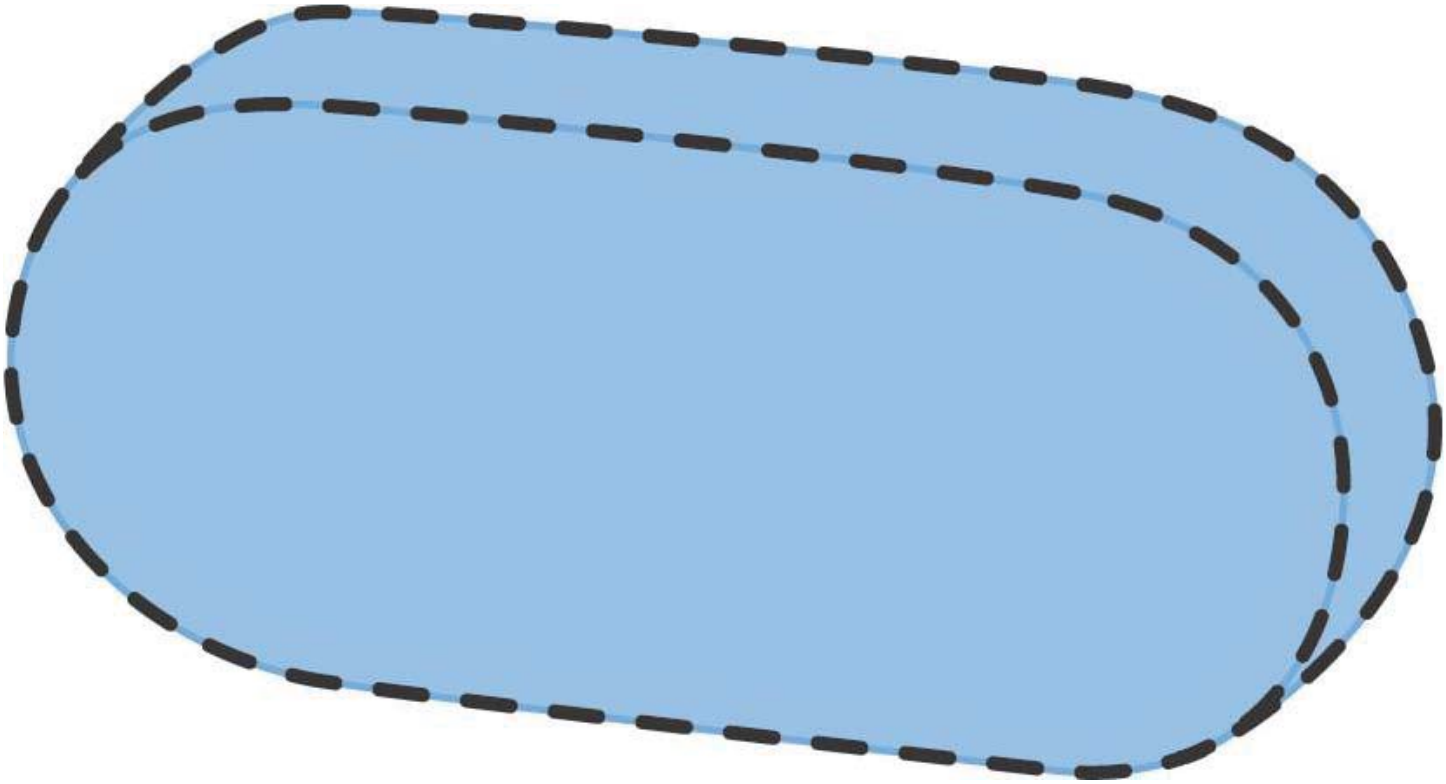


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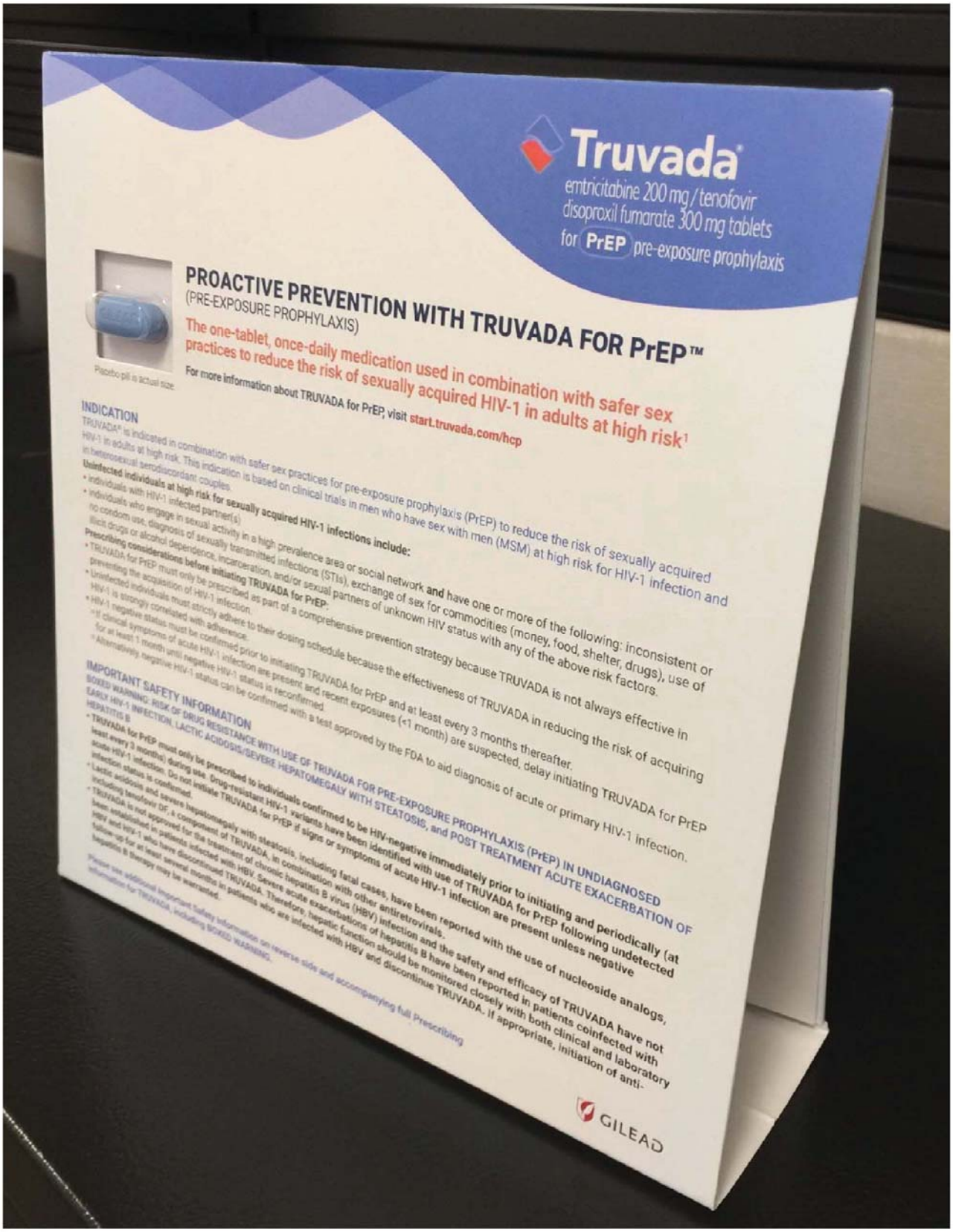
Truvada
emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg tablets
for PrEP pre-exposure prophylaxis
PROACTIVE PREVENTION WITH TRUVADA FOR PrEP™
(PRE-EXPOSURE PROPHYLAXIS)
The one-tablet, once-daily medication used in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 in adults at high risk[1]
Placebo pill is actual size.
For more information about TRUVADA for PrEP, visit start.truvada.com/hcp
INDICATION
TRUVADA® is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.
Uninfected individuals at high risk for sexually acquired HIV-1 infections include:
• individuals with HIV-1 infected partner(s)
• individuals who engage in sexual activity in a high prevalence area or social network and have one or more of the following: inconsistent or no condom use, diagnosis of sexually transmitted infections (STIs), exchange of sex for commodities (money, food, shelter, drugs), use of illicit drugs or alcohol dependence, incarceration, and/or sexual partners of unknown HIV status with any of the above risk factors.
Prescribing considerations before initiating TRUVADA for PrEP:
• TRUVADA for PrEP must only be prescribed as part of a comprehensive prevention strategy because TRUVADA is not always effective in preventing the acquisition of HIV-1 infection.
• Uninfected individuals must strictly adhere to their dosing schedule because the effectiveness of TRUVADA in reducing the risk of acquiring HIV-1 is strongly correlated with adherence.
• HIV-1 negative status must be confirmed prior to initiating TRUVADA for PrEP and at least every 3 months thereafter.
* If clinical symptoms of acute HIV-1 infection are present and recent exposures (<1 month) are suspected, delay initiating TRUVADA for PrEP for at least 1 month until negative HIV-1 status is reconfirmed.
* Alternatively, negative HIV-1 status can be confirmed with a test approved by the FDA to aid diagnosis of acute or primary HIV-1 infection.
IMPORTANT SAFETY INFORMATION
BOXED WARNING: RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION, LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS, AND POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B
• TRUVADA for PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and periodically (at least every 3 months) during use. Drug-resistant HIV-1 variants have been identified with use of TRUVADA for PrEP following undetected acute HIV-1 infection. Do not initiate TRUVADA for PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed.
• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir DF, a component of TRUVADA. In combination with other antiretrovirals.
• TRUVADA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of TRUVADA have not been established in patients infected with HBV. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HBV and HIV-1 who have discontinued TRUVADA. Therefore, hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.
Please see additional important safety information on reverse side and accompanying full Prescribing Information for TRUVADA, including BOXED WARNING.
GILEAD

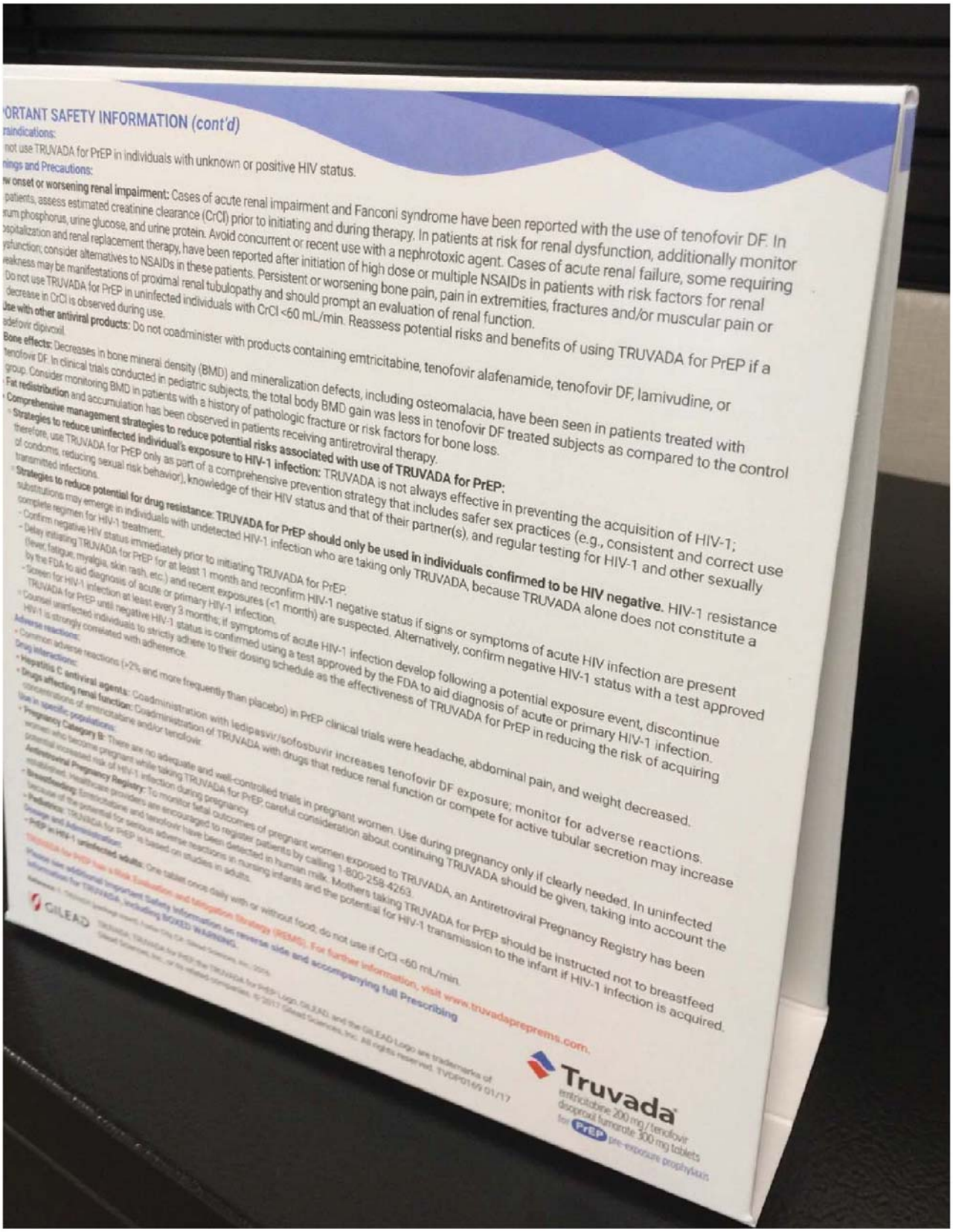
ORTANT SAFETY INFORMATION (cont'd)
raindications:
not use TRUVADA for PrEP in individuals with unknown or positive HIV status.
nings and Precautions:
w onset or worsening renal impairment: Cases of acute renal impairment and Fanconi syndrome have been reported with the use of tenofovir DF. In patients, assess estimated creatinine clearance (CrCl) prior to initiating and during therapy. In patients at risk for renal dysfunction, additionally monitor rum phosphorus, urine glucose, and urine protein. Avoid concurrent or recent use with a nephrotoxic agent. Cases of acute renal failure, some requiring spitalization and renal replacement therapy, have been reported after initiation of high dose or multiple NSAIDs in patients with risk factors for renal ysfunction; consider alternatives to NSAIDs in these patients. Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or eakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function.
Do not use TRUVADA for PrEP in uninfected individuals with CrCl <60 mL/min. Reassess potential risks and benefits of using TRUVADA for PrEP if a decrease in CrCl is observed during use.
Use with other antiviral products: Do not coadminister with products containing emtricitabine, tenofovir alafenamide, tenofovir DF, lamivudine, or adefovir dipivoxil.
Bone effects: Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with tenofovir DF. In clinical trials conducted in pediatric subjects, the total body BMD gain was less in tenofovir DF treated subjects as compared to the control group. Consider monitoring BMD in patients with a history of pathologic fracture or risk factors for bone loss.
Fat redistribution and accumulation has been observed in patients receiving antiretroviral therapy.
Comprehensive management strategies to reduce potential risks associated with use of TRUVADA for PrEP:
Strategies to reduce uninfected individual's exposure to HIV-1 infection: TRUVADA is not always effective in preventing the acquisition of HIV-1; therefore, use TRUVADA for PrEP only as part of a comprehensive prevention strategy that includes safer sex practices (e.g., consistent and correct use of condoms, reducing sexual risk behavior), knowledge of their HIV status and that of their partner(s), and regular testing for HIV-1 and other sexually transmitted infections.
Strategies to reduce potential for drug resistance: TRUVADA for PrEP should only be used in individuals confirmed to be HIV negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only TRUVADA, because TRUVADA alone does not constitute a complete regimen for HIV-1 treatment.
Confirm negative HIV status immediately prior to initiating TRUVADA for PrEP.
Delay initiating TRUVADA for PrEP for at least 1 month and reconfirm HIV-1 negative status if signs or symptoms of acute HIV infection are present (fever, fatigue, myalgia, skin rash, etc.) and recent exposures (<1 month) are suspected. Alternatively, confirm negative HIV-1 status with a test approved by the FDA to aid diagnosis of acute or primary HIV-1 infection.
Screen for HIV-1 infection at least every 3 months; if symptoms of acute HIV-1 infection develop following a potential exposure event, discontinue TRUVADA for PrEP until negative HIV-1 status is confirmed using a test approved by the FDA to aid diagnosis of acute or primary HIV-1 infection.
Counsel uninfected individuals to strictly adhere to their dosing schedule as the effectiveness of TRUVADA for PrEP in reducing the risk of acquiring HIV-1 is strongly correlated with adherence.
Adverse reactions:
Common adverse reactions (>2% and more frequently than placebo) in PrEP clinical trials were headache, abdominal pain, and weight decreased.
Drug interactions:
Hepatitis C antiviral agents: Coadministration with ledipasvir/sofosbuvir increases tenofovir DF exposure; monitor for adverse reactions.
Drugs affecting renal function: Coadministration of TRUVADA with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine and/or tenofovir.
Use in specific populations:
Pregnancy Category B: There are no adequate and well-controlled trials in pregnant women. Use during pregnancy only if clearly needed. In uninfected women who become pregnant while taking TRUVADA for PrEP, careful consideration about continuing TRUVADA should be given, taking into account the potential increased risk of HIV-1 infection during pregnancy.
Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to TRUVADA, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.
Breastfeeding: Because of the potential for serious adverse reactions in nursing infants and the potential for HIV-1 transmission to the infant if HIV-1 infection is acquired, healthcare providers instruct mothers taking TRUVADA for PrEP should be instructed not to breastfeed.
Pediatric: TRUVADA for PrEP is based on studies in adults.
Dosage and Administration:
PrEP in HIV-1 uninfected adults: One tablet once daily with or without food; do not use if CrCl <60 mL/min.
Please see additional important Safety Information on reverse side and accompanying full Prescribing Information for TRUVADA, including BOXED WARNING.
For further information, visit www.truvadapreprems.com.
GILEAD
Truvada
emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg tablets
for PrEP pre-exposure prophylaxis

EXHIBIT 88

Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection (DISCOVER)

ClinicalTrials.gov Identifier: NCT02842086

Recruitment Status : Active, not recruiting
First Posted : July 22, 2016
Last Update Posted : August 19, 2019

Sponsor:
Gilead Sciences

Information provided by (Responsible Party):
Gilead Sciences

Study Details | Tabular View | No Results Posted | Disclaimer
How to Read a Study Record

Study Description

Go to

Brief Summary:

The primary objective of this study is to assess the rates of HIV-1 infection in Men (MSM) and transgender women (TGW) who have sex with men and who are administered daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir DF (F/TDF) with a minimum follow-up of 48 weeks and at least 50% of participants have 96 weeks of follow-up after randomization.

Condition or disease	Intervention/treatment	Phase
Pre-Exposure Prophylaxis of HIV-1 Infection	Drug: F/TAF Drug: F/TDF Drug: F/TAF Placebo Drug: F/TDF Placebo	Phase 3

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	5400 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Investigator)
Primary Purpose:	Treatment
Official Title:	A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection
Actual Study Start Date :	September 2, 2016
Actual Primary Completion Date :	January 31, 2019
Estimated Study Completion Date :	September 2021

Resource links provided by the National Library of Medicine

MedlinePlus related topics:

Gay, Lesbian, Bisexual, and Transgender Health HIV/AIDS

Drug Information available for: Emtricitabine Tenofovir

U.S. FDA Resources

Arms and Interventions

Go to

Arm	Intervention/treatment
Experimental: F/TAF F/TAF+ F/TDF placebo for at least 96 weeks	Drug: F/TAF 200/25 mg tablet administered orally once daily Other Name: Descovy® Drug: F/TDF Placebo Tablet administered orally once daily
Experimental: F/TDF F/TDF+ F/TAF placebo for at least 96 weeks	Drug: F/TDF 200/300 mg tablet administered orally once daily Other Name: Truvada® Drug: F/TAF Placebo Tablet administered orally once daily
Experimental: Open-label Extension Once all participants have been on blinded treatment for at least 96 weeks, the study will be unblinded and participants will be offered the option to continue on open-label F/TAF treatment in the open-label extension for 48 weeks.	Drug: F/TAF 200/25 mg tablet administered orally once daily Other Name: Descovy®

Outcome Measures

Go to

Primary Outcome Measures :

1. Incidence of HIV-1 infection per 100 Person Years (PY) [Time Frame: When all participants have a minimum follow-up of 48 weeks and at least 50% of the participants have 96 weeks of follow-up after randomization]

   HIV-1 infection is defined by one or more of the following criteria of contributing HIV tests performed via central lab or local lab:

   - Serologic evidence of seroconversion (reactive screening HIV Antigen/Antibody or Antibody test, confirmed by reactive HIV-1/HIV-2 differentiation assay), excluding HIV vaccinated participants, or
   - Virologic evidence of HIV-1 infection (positive qualitative HIV-1 RNA test or any detectable quantitative HIV-1 RNA test), or
   - Evidence of acute HIV-1 infection (reactive p24 Antigen or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Antibody results)

Secondary Outcome Measures :

1. Percent Change From Baseline in Hip Bone Mineral Density (BMD) at Week 48 in the Blinded Phase in a Subset of Participants [Time Frame: Baseline; Week 48]
2. Percent Change From Baseline in Spine BMD at Week 48 in the Blinded Phase in a Subset of Participants [Time Frame: Baseline; Week 48]
3. Assessment of Renal Biomarkers at Week 48 in the Blinded Phase: Percent Change from Baseline in Urine Beta-2-Microglobulin to Creatinine Ratio [Time Frame: Baseline; Week 48]
4. Assessment of Renal Biomarkers at Week 48 in the Blinded phase: Percent Change from Baseline in Urine RBP to Creatinine Ratio [Time Frame: Baseline; Week 48]
5. Assessment of Renal Biomarkers at Week 48 in the Blinded Phase: Distribution of UP and Urine Protein to Creatinine Ratio (UPCR) Categories [Time Frame: Baseline; Week 48]
6. Change From Baseline in Serum Creatinine at Week 48 in the Blinded Phase [Time Frame: Baseline; Week 48]

7. Percent Change from Baseline in Hip BMD at Week 96 in the Blinded Phase in a Subset of Participants [Time Frame: Baseline; Week 96]
8. Percent Change from Baseline in Spine BMD at Week 96 in the Blinded Phase in a Subset of Participants [Time Frame: Baseline; Week 96]
9. Assessment of Renal Biomarkers at Week 96 in the Blinded Phase: Percent Change From Baseline in Urine Beta-2-Microglobulin to Creatinine Ratio [Time Frame: Baseline; Week 96]
10. Assessment of Renal Biomarkers at Week 96 in the Blinded Phase: Percent Change From Baseline in Urine RBP to Creatinine Ratio [Time Frame: Week 96]
11. Assessment of Renal Biomarkers at Week 96 in the Blinded Phase: Distribution of UP and UPCR categories [Time Frame: Week 96]
12. Change From Baseline in Serum Creatinine at Week 96 in the Blinded Phase [Time Frame: Week 96]
13. Incidence of Treatment-Emergent Adverse Events [Time Frame: At least 144 weeks plus 30 days]
14. Incidence of Treatment-Emergent Laboratory Toxicities [Time Frame: At least 144 weeks plus 30 days]
15. Incidence of HIV-1 Infection per 100 PY [Time Frame: When all participants have 96 weeks of follow-up after randomization]

    HIV-1 infection is defined by one or more of the following criteria of contributing HIV tests performed via central lab or local lab:

    - Serologic evidence of seroconversion (reactive screening HIV Antigen/Antibody or Antibody test, confirmed by reactive HIV-1/HIV-2 differentiation assay), excluding HIV vaccinated participants, or
    - Virologic evidence of HIV-1 infection (positive qualitative HIV-1 RNA test or any detectable quantitative HIV-1 RNA test), or
    - Evidence of acute HIV-1 infection (reactive p24 Antigen or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Antibody results)

Eligibility Criteria Go to

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Gender Based Eligibility:	Yes
Gender Eligibility Description:	Men and Transgender Women
Accepts Healthy Volunteers:	Yes

Criteria

Key Inclusion Criteria:

- Must be at high risk of sexual acquisition of HIV
- HIV-1 negative status
- MSM and TGW (male at birth) who have at least one of the following:
  - condomless anal intercourse with at least two unique male partners in the past 12 weeks (partners must be either HIV-infected or of unknown HIV status)
  - documented history of syphilis in the past 24 weeks
  - documented history of rectal gonorrhea or chlamydia in the past 24 weeks
- Adequate renal function: estimated glomerular filtration rate ≥ 60 mL/min according to the Cockcroft-Gault formula
- Adequate liver and hematologic function:
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN) and total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin
  - Absolute neutrophil count ≥ 1000/mm^3; platelets ≥ 75,000/mm^3; hemoglobin ≥ 10 g/dL

Key Exclusion Criteria

- Grade 3 or Grade 4 proteinuria or glycosuria that is unexplained or not clinically manageable.

NOTE: Other protocol defined Inclusion/ Exclusion criteria may apply.

Contacts and Locations

Go to

Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT02842086***

Hide Study Locations

Locations

United States, California

Beverly Hills, California, United States, 90211

Los Angeles, California, United States, 90036

Los Angeles, California, United States, 90069

Newport Beach, California, United States, 92663

Oakland, California, United States, 94609

Sacramento, California, United States, 95817

Sacramento, California, United States, 95825

San Diego, California, United States, 92103

San Francisco, California, United States, 94102

San Francisco, California, United States, 94103

San Francisco, California, United States, 94118

Torrance, California, United States, 90502

United States, Colorado

Aurora, Colorado, United States, 80045

Denver, Colorado, United States, 80209

United States, Connecticut

New Haven, Connecticut, United States, 06510

United States, District of Columbia

Washington, District of Columbia, United States, 20009

Washington, District of Columbia, United States, 20036

United States, Florida

Fort Lauderdale, Florida, United States, 33308

Fort Lauderdale, Florida, United States, 33316

Fort Pierce, Florida, United States, 34982

Miami, Florida, United States, 33136

Orlando, Florida, United States, 32803

Pensacola, Florida, United States, 32504

West Palm Beach, Florida, United States, 33401

United States, Georgia

Atlanta, Georgia, United States, 30308

Atlanta, Georgia, United States, 30309

Atlanta, Georgia, United States, 30312

Macon, Georgia, United States, 31201

United States, Illinois

Chicago, Illinois, United States, 60612

Chicago, Illinois, United States, 60613

United States, Louisiana

New Orleans, Louisiana, United States, 70119

United States, Massachusetts

Boston, Massachusetts, United States, 02215

Springfield, Massachusetts, United States, 01105

United States, Michigan

Berkley, Michigan, United States, 48072

Detroit, Michigan, United States, 48202

United States, Minnesota

Minneapolis, Minnesota, United States, 55415

United States, Nevada

Las Vegas, Nevada, United States, 89104

United States, New Jersey

Somers Point, New Jersey, United States, 08244

United States, New Mexico

Santa Fe, New Mexico, United States, 87505

United States, New York

Bronx, New York, United States, 10467

New York, New York, United States, 10029

New York, New York, United States, 10032

New York, New York, United States, 10037

United States, North Carolina

Chapel Hill, North Carolina, United States, 27599-7215

Huntersville, North Carolina, United States, 28078

United States, Ohio

Cleveland, Ohio, United States, 44109

United States, Pennsylvania

Philadelphia, Pennsylvania, United States, 19107

United States, Texas

Austin, Texas, United States, 78705

Dallas, Texas, United States, 75208

Dallas, Texas, United States, 75246

Houston, Texas, United States, 77098

United States, Washington

Seattle, Washington, United States, 98101

Seattle, Washington, United States, 98104

United States, Wisconsin

Milwaukee, Wisconsin, United States, 53226

Austria

Graz, Austria, 8051

Vienna, Austria, 1090

Canada, British Columbia

Vancouver, British Columbia, Canada, V6Z 2T1

Canada, Ontario

Toronto, Ontario, Canada, M5G 1K2

Canada, Quebec

Montreal, Quebec, Canada, H2l 4P9

Montreal, Quebec, Canada, H2L5B1

Montréal, Quebec, Canada, H2W 1T8

Denmark

Hvidovre, Region Hovedstaden, Denmark, 2650

Aarhus N, Region Midtjylland, Denmark, 8200

Copenhagen, RegionH, Denmark, 2100

Odense, Denmark, 5000

France

Nice, Alpe Maritimes, France, 6202

Marseille, Provence, France, 13006

Paris, Provence, France, 75020

Paris cedex 10, France, 75475

Germany

Munich, Bavaria, Germany, 81675

Berlin, Germany, 10439

Berlin, Germany, 10777

Frankfurt, Germany, 60596

Ireland

Dublin 7, Dublin, Ireland, D07 A8NN

Dublin, Ireland, 8

Italy

Milan, Italy, 20127

Roma, Italy, 00149

Netherlands

Amsterdam, Netherlands

Spain

Badalona, Barcelona, Spain, 08907

Barcelona, Spain, 08015

Madrid, Spain, 28010

Vigo, Spain, 36312

United Kingdom

Soho, London, United Kingdom, W1D 6AQ

Whitechapel, London, United Kingdom, E1 1BB

Edinburgh, Scotland, United Kingdom, EH3 9HA

Brighton, Sussex, United Kingdom, BN2 1ES

Birmingham, United Kingdom, B9 5SS

London, United Kingdom, E9 6SR

London, United Kingdom, SE18 4QH

London, United Kingdom, SE5 9RJ

London, United Kingdom, W2 1NY

London, United Kingdom, WC1E 6JB

Manchester, United Kingdom, M13 0FH

Sponsors and Collaborators

Gilead Sciences

Investigators

Study Director: Gilead Study Director Gilead Sciences

More Information

Go to

Responsible Party:	Gilead Sciences
ClinicalTrials.gov Identifier:	NCT02842086 History of Changes
Other Study ID Numbers:	GS-US-412-2055
	2016-001399-31 (EudraCT Number)
First Posted:	July 22, 2016 Key Record Dates
Last Update Posted:	August 19, 2019
Last Verified:	August 2019

Studies a U.S. FDA-regulated Drug Product:	Yes
Studies a U.S. FDA-regulated Device Product:	No

Additional relevant MeSH terms:

Infection	Tenofovir
Communicable Diseases	Emtricitabine
HIV Infections	Antiviral Agents
Lentivirus Infections	Anti-Infective Agents
Retroviridae Infections	Reverse Transcriptase Inhibitors
RNA Virus Infections	Nucleic Acid Synthesis Inhibitors
Virus Diseases	Enzyme Inhibitors
Sexually Transmitted Diseases, Viral	Molecular Mechanisms of Pharmacological Action
Sexually Transmitted Diseases	Anti-Retroviral Agents
Immunologic Deficiency Syndromes	Anti-HIV Agents
Immune System Diseases	

EXHIBIT 89

Company Statements

Statement on DISCOVER Study of F/TAF for PrEP

Foster City, Calif. - November 11, 2016 - Gilead Sciences is sponsoring a clinical trial, known as the DISCOVER study, to test whether a combination of emtricitabine and tenofovir alafenamide (F/TAF) is as safe and effective as Truvada® (emtricitabine and tenofovir disoproxil fumarate, F/TDF) at reducing the risk of HIV infection when used as pre-exposure prophylaxis (PrEP). F/TAF was recently approved for HIV treatment, but it is not yet known whether it is effective as PrEP.

Enrollment in the DISCOVER study is ongoing. If proven safe and effective for HIV prevention, F/TAF could be an important new PrEP option. TAF has demonstrated improvement in markers of renal and bone safety compared to TDF, and its lower dose could reduce generic manufacturing costs, leading to lower prices in developing countries.

As always, the health and safety of trial participants is Gilead's top priority. It is important for anyone considering the DISCOVER study to understand that we do not yet know if F/TAF is effective for PrEP. As with any study Gilead conducts, all potential participants are carefully informed, in their preferred language, of the potential risks and benefits of participation in the study. Trial documents that explain the background and rationale for conducting this study have been carefully written by scientific experts at Gilead, in consultation with external academic experts. Importantly, local and centralized ethics review boards, all investigators and their institutions, health and regulatory authorities in multiple countries, and Gilead legal, regulatory compliance, and business conduct specialists have reviewed and approved these documents prior to implementation at any DISCOVER study site. Because the DISCOVER trial is conducted in a double-blind fashion, participants will not know whether they are receiving Truvada or F/TAF. Participants will receive regular medical check-ups, including testing for HIV and other sexually transmitted infections, as well as HIV counseling and access to condoms.

With helpful feedback from both clinical investigators and community advocates, Gilead has made changes to the trial protocol. These changes include elimination of a 30-day "washout" period in which potential participants were to stop using Truvada for PrEP before entering the trial. In addition, the study language has been made simpler and more patient friendly to reduce any chance for confusion or misinformation.

Input from community advocates also led Gilead to strengthen its guidance to trial sites to ensure that all recruitment materials accurately convey the investigational nature of F/TAF for PrEP. All

locally produced materials are reviewed by Gilead for accuracy and completeness, and are also reviewed by local or central ethics boards at academic institutions. In the small number of cases in which trial sites used materials that did not meet these standards, Gilead has worked with investigators to ensure that all potential education and recruitment materials are scientifically accurate and meet strict standards of quality and appropriateness.

Additional community feedback addressed the discussion of risk in consent materials for the DISCOVER trial. Following this feedback, Gilead initiated a review of all consent materials with the study Institutional Review Boards. The review concluded that the current trial consent materials convey risk sufficiently and appropriately.

Consistent with all HIV studies conducted by Gilead, an Independent Data Monitoring Committee (IDMC) has been formed which will review unblinded data from the study to ensure the safety of all participants; for the DISCOVER study this panel includes a community representative.

To strengthen HIV community engagement in the DISCOVER trial, Gilead is establishing community advisory groups in North America and Europe for the study. We are using a community-provided document to help draft terms of reference and membership eligibility, aligned with good participatory practices. Gilead is also forming a permanent, ongoing Community Advisory Council to provide input on many areas of our work, including the design and conduct of HIV prevention, treatment and cure research.

We welcome additional feedback on Gilead's work in HIV prevention and treatment, and we are committed to ongoing dialogue with community advocates. Anyone with questions or recommendations about the DISCOVER trial can contact advocacy@gilead.com.

About Gilead Sciences

Gilead Sciences is a biopharmaceutical company that discovers, develops and commercializes innovative therapeutics in areas of unmet medical need. We strive to transform and simplify care for people with life-threatening illnesses around the world, always keeping the patients and the communities we serve at the forefront.

EXHIBIT 90

Press Releases

March 06, 2019

Gilead Announces Data Demonstrating Non-Inferiority of Once-Daily Descovy® vs. Once-Daily Truvada® for Prevention of HIV Infection

– DISCOVER Trial Meets Primary and Secondary Endpoints and Will Support Supplemental Regulatory Filing for Descovy for Pre-Exposure Prophylaxis (PrEP) –

FOSTER CITY, Calif.--(BUSINESS WIRE)--Mar. 6, 2019-- Gilead Sciences, Inc. (NASDAQ: GILD) today announced results from the DISCOVER trial, a two-year Phase 3 randomized, controlled, double-blind study evaluating the safety and efficacy of the investigational use of once-daily Descovy® (emtricitabine 200 mg and tenofovir alafenamide 25mg) for HIV pre-exposure prophylaxis (PrEP), compared with Truvada® (emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg), in men who have sex with men and transgender women at risk for sexually acquired HIV infection.

In a late-breaker oral abstract presented today at the Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, 5,387 study participants were randomized in a 1:1 ratio and received either Descovy or Truvada. Among the 2,694 participants (4,370 patient-years) who were at risk of HIV-1 infection and received once-daily Descovy, seven HIV infections (HIV incidence 0.16/100 person-years (PY)) were reported. Among the 2,693 participants (4,386 patient-years) who were at risk of HIV-1 infection and received Truvada, 15 HIV infections (0.34/100 PY) were reported. Descovy met the pre-established criteria for non-inferiority to Truvada using a stringent rate ratio statistical comparison, as demonstrated by the upper bound of the 95 percent confidence interval for HIV-1 infection rate ratio being less than the predefined non-inferiority margin of 1.62/100 PY. Additionally, statistically significant advantages with respect to bone and renal laboratory parameters were observed for participants receiving Descovy as compared with those receiving Truvada, which were pre-specified secondary endpoints.

“As the largest HIV prevention trial conducted to date, the DISCOVER trial results clearly demonstrate Descovy for PrEP™ achieved a clinical profile similar to the high efficacy of Truvada and a more favorable bone and renal safety profile,” said John McHutchison, AO, MD, Chief Scientific Officer and Head of Research and Development, Gilead Sciences. “We look forward to filing regulatory applications for Descovy for the PrEP indication as a potential important new option to prevent individuals from becoming infected and contribute to the achievement of national and global HIV prevention goals.”

In the U.S., Descovy is approved in combination with other antiretroviral agents for the treatment of HIV infection in patients weighing ≥ 35 kg and is not indicated for PrEP. Truvada is indicated in combination with safer sex practices for HIV PrEP to reduce the risk of sexually acquired HIV in at-risk adults and adolescents weighing ≥ 35 kg. Descovy and Truvada each have a Boxed Warning in their respective product labels regarding the risk of post-treatment acute exacerbation of hepatitis B; the Truvada label also carries a Boxed Warning for the risk of drug resistance with PrEP in undiagnosed early HIV infection. See below for Important Safety Information and complete Indications.

“The DISCOVER trial enrolled more than 5,000 men who have sex with men and transgender women who were at risk of acquiring HIV in order to gain insights about the efficacy and safety of Descovy and Truvada for PrEP in populations with some of the highest rates of HIV infection,” said Brad Hare, MD, Chief of Infectious Diseases at Kaiser-Permanente, San Francisco. “The very low incidence of HIV in both treatment arms, combined with Descovy’s improved renal and bone safety as compared with Truvada, demonstrate that Descovy for PrEP may help build on the progress made by Truvada, a proven public health tool in the fight against HIV.”

All DISCOVER study participants were adult cis-men who have sex with men or transgender women who had risk of HIV infection through documented high-risk sexual behavior at study entry. Sexually transmitted infection (STI) screening results also demonstrated that participants maintained their sexual risk behavior during the study. Per study protocol, all participants were tested for STIs every three months at three anatomic sites (oropharynx, urethra, rectum), and all received medical treatment and contact tracing as appropriate. Overall, during the study, 57 percent were diagnosed with gonorrhea or chlamydia (from any anatomic site), 42 percent were diagnosed with rectal gonorrhea or rectal chlamydia, and 10 percent were diagnosed with syphilis.

Among the 22 HIV infections reported in the DISCOVER study, five were likely acquired before study entry, 15 occurred in the setting of low or undetectable intracellular drug levels, and two occurred with intermediate or expected intracellular drug levels detected.

Descovy and Truvada were well tolerated and had low discontinuation rates due to adverse events of 1.3 percent and 1.8 percent, respectively. The most common (>15 percent in either group) adverse events were similar in each group and included anal chlamydia, oropharyngeal gonorrhea and rectal gonorrhea.

Study participants randomized to receive Descovy had improved bone and renal safety outcomes relative to those who received Truvada. Bone mineral density (BMD) was tested in a subset of 383 participants. The percent change in spine BMD was reduced by 1.1 percent for those on Truvada while it increased by 0.5 percent in those on Descovy ($p<0.001$) at Week 48. The percent change in hip BMD was reduced by 1.0 percent in those on Truvada while it was increased by 0.2 percent for those on Descovy ($p<0.001$) at Week 48.

All DISCOVER study participants had renal laboratory testing at every visit. The creatinine clearance (estimated glomerular filtration rate) increased by 1.8 mL/min for those randomized to Descovy while it was reduced by 2.3 mL/min in those who received Truvada ($p<0.001$) at Week 48. There were no cases of Fanconi Syndrome in the Descovy arm while one case was reported in the Truvada arm, which led to premature discontinuation of study drug.

The use of Descovy for the prevention of HIV is investigational and has not been determined to be safe or efficacious and is not approved anywhere globally.

IMPORTANT U.S. SAFETY INFORMATION AND INDICATION FOR DESCOVY

BOXED WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- **Descovy is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of Descovy have not been established in patients coinfected with HIV-1 and HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of Descovy. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue Descovy. If appropriate, initiation of anti-hepatitis B therapy may be warranted.**

Warnings and precautions

- Immune reconstitution syndrome, including the occurrence of autoimmune disorders with variable time to onset, has been reported.
- New onset or worsening renal impairment: Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. In clinical trials of FTC and tenofovir alafenamide with elvitegravir and cobicistat, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Do not initiate Descovy in patients with estimated creatinine clearance (CrCl) <30 mL/min. Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue Descovy in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.
  Renal monitoring: In all patients, monitor CrCl, urine glucose, and urine protein prior to initiating and during therapy. In patients with chronic kidney disease, additionally monitor serum phosphorus.
- Lactic acidosis and severe hepatomegaly with steatosis: Fatal cases have been reported with the use of nucleoside analogs, including FTC and TDF. Discontinue Descovy if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity develop, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

Adverse reactions

- Most common adverse reaction (incidence ≥10%; all grades) in clinical studies was nausea (10%).

Drug interactions

- Prescribing information: Consult the full prescribing information for Descovy for more information on potentially significant drug interactions, including clinical comments.
- Metabolism: Drugs that inhibit P-gp can increase the concentrations of components of Descovy. Drugs that induce P-gp can decrease the concentrations of components of Descovy, which may lead to loss of efficacy and development of resistance.
- Drugs affecting renal function: Coadministration of Descovy with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine and tenofovir and the risk of adverse reactions.

Dosage and administration

- Dosage: Patients who weigh ≥25 kg: 1 tablet taken orally once daily with or without food.
- Renal impairment: Not recommended in patients with CrCl <30 mL/min.
- Testing prior to initiation: Test patients for HBV infection and assess CrCl, urine glucose and urine protein.
- Pediatrics: The safety and effectiveness of Descovy coadminstered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

Pregnancy and lactation

- Pregnancy: There is insufficient human data on the use of Descovy during pregnancy. An Antiretroviral Pregnancy Registry (APR) has been established; available data from the APR for FTC shows no difference in the rates of birth defects compared with a U.S. reference population.
- Lactation: Women infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV-1 transmission.

INDICATION

Descovy is indicated in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in patients weighing at least 35 kg.

Descovy is also indicated, in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor, for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg.

Limitations of Use:

Descovy is not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of acquiring HIV-1 infection.

IMPORTANT U.S. SAFETY INFORMATION AND INDICATION FOR TRUVADA FOR PREP

BOXED WARNING: RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR PrEP IN UNDIAGNOSED EARLY HIV-1 INFECTION and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- **Truvada for PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiation and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of Truvada for PrEP following undetected acute HIV-1 infection. Do not initiate if signs or symptoms of acute HIV-1 infection are present unless HIV-negative status is confirmed**
- **Severe acute exacerbations of hepatitis B have been reported in HBV-infected patients who discontinued Truvada. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients with HBV after discontinuing Truvada. If appropriate, initiation of anti-hepatitis B therapy may be warranted**

Contraindications

- Do not use Truvada for PrEP in individuals with unknown or positive HIV status

Warnings and precautions: Comprehensive risk reduction strategies

- **Reduce HIV-1 risk:** Truvada for PrEP is not always effective in preventing HIV-1. Use only as part of a comprehensive prevention strategy that includes safer sex practices, regular testing for HIV-1 and other STIs, and counseling on reducing sexual risk behaviors
- **Reduce potential for drug resistance:** Truvada for PrEP should only be used in individuals confirmed to be HIV-negative immediately prior to initiation, at least every 3 months while taking Truvada, and upon an STI diagnosis. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only Truvada. Truvada alone is not a complete regimen for treating HIV-1
  - HIV antibody tests may not detect acute HIV infection. If recent exposures are suspected or symptoms of acute HIV infection are present (e.g., fever, fatigue, myalgia, skin rash), delay initiating (≥1 month) or discontinue use and confirm HIV-negative status with a test approved by U.S. Food and Drug Administration (FDA) for the diagnosis of acute HIV infection
  - If a screening test indicates possible HIV-1 infection, convert the HIV-1 PrEP regimen to an HIV treatment regimen until HIV-negative status is confirmed.
- **Counsel on adherence:** Counsel individuals to strictly adhere to their dosing schedule, as efficacy is strongly correlated with adherence. Some individuals, such as adolescents, may benefit from more frequent visits and counseling.

Warnings and precautions

- **New onset or worsening renal impairment:** Cases of acute renal impairment and Fanconi syndrome have been reported with the use of tenofovir disoproxil fumarate (TDF). Truvada is not recommended in individuals with estimated creatinine clearance (CrCl) <60 mL/min. Avoid concurrent or recent use with a nephrotoxic agent. Acute renal failure has been reported after initiation of high dose or multiple NSAIDs in patients at risk for renal dysfunction; consider alternatives to NSAIDs in these patients. Monitor renal function in all patients – See Dosage and Administration
- **Bone effects:** Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia associated with proximal renal tubulopathy, have been reported with the use of TDF Consider monitoring BMD in patients with a history of pathologic fracture or risk factors for bone loss

- **Lactic acidosis and severe hepatomegaly with steatosis:** Fatal cases have been reported with the use of nucleoside analogs, including Truvada. Discontinue use if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity develop, including hepatomegaly and steatosis in the absence of marked transaminase elevations
- **Drug interactions:** See Drug Interactions section. Consider the potential for drug interactions prior to and during use of Truvada and monitor for adverse reactions

Adverse reactions

- **Common adverse reactions** (>2% and more frequently than placebo) of Truvada for PrEP in clinical trials were headache, abdominal pain, and weight loss

Drug interactions

- **Prescribing information:** Consult the full Prescribing Information for Truvada for more information, warnings, and potentially significant drug interactions, including clinical comments
- **Hepatitis C antivirals:** Coadministration with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, or sofosbuvir/velpatasvir/voxilaprevir increases TDF exposure; monitor for adverse reactions
- **Drugs affecting renal function:** Coadministration of Truvada with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine and/or tenofovir

Pregnancy and lactation

- **Pregnancy:** An Antiretroviral Pregnancy Registry (APR) has been established. Available data from observational studies and the APR show no increase in the rate of major birth defects for Truvada compared with a US reference population. Consider HIV prevention methods, including Truvada for PrEP in at-risk women due to the potential increased risk of HIV-1 infection during pregnancy and mother to child transmission during acute HIV-1 infection
- **Lactation:** Emtricitabine and tenofovir have been detected in human milk. Evaluate the benefits and risks of Truvada for PrEP in breastfeeding women, including the risk of HIV-1 acquisition due to nonadherence, and subsequent mother to child transmission. Health benefits of breastfeeding should be considered along with potential adverse effects of Truvada on the child, which are unknown

Dosage and administration

- **Dosage:** One tablet once daily with or without food
- **HIV screening:** Test for HIV-1 infection prior to initiating and at least every 3 months during treatment
- **HBV screening:** Test for HBV infection prior to or when initiating treatment
- **Renal impairment and monitoring:** Not recommended in individuals with CrCl <60 mL/min. In all patients, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein on a clinically appropriate schedule. In patients with chronic kidney disease, also assess serum phosphorus

INDICATION

Truvada for PrEP (pre-exposure prophylaxis) is indicated to reduce the risk of sexually acquired HIV-1 in adults and adolescents (≥35 kg) who are at risk for HIV, when used in

combination with safer sex practices. HIV-negative status must be confirmed immediately prior to initiation

- If clinical symptoms of acute HIV-1 infection are present and recent exposures (<1 month) are suspected, delay initiation for at least 1 month until HIV-negative status is reconfirmed. Alternatively, confirm HIV-negative status with a test cleared by FDA to aid in the diagnosis of acute HIV-1 infection

Individuals at risk for sexually acquired HIV-1 may include those:

- With HIV-1 infected partner(s), or
- Who engage in sexual activity in a high prevalence area or social network and have additional risk factors, such as: inconsistent or no condom use, diagnosis of sexually transmitted infections (STIs), exchange of sex for commodities, use of illicit drugs or alcohol dependence, incarceration, or sexual partners of unknown HIV status with any of these risk factors

About Gilead Sciences

Gilead Sciences, Inc. is a research-based biopharmaceutical company that discovers, develops and commercializes innovative medicines in areas of unmet medical need. The company strives to transform and simplify care for people with life-threatening illnesses around the world. Gilead has operations in more than 35 countries worldwide, with headquarters in Foster City, California.

For nearly 30 years, Gilead has been a leading innovator in the field of HIV, driving advances in treatment, prevention, testing and linkage to care, and cure research. Today, it's estimated that more than 11.5 million people living with HIV globally receive antiretroviral therapy provided by Gilead or one of the company's manufacturing partners.

For more information on Gilead Sciences, please visit the company's website at www.gilead.com.

Forward-Looking Statement

This press release includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 that are subject to risks, uncertainties and other factors, including the risk that regulatory authorities, including FDA, may not approve Descovy for PrEP in the currently anticipated timelines or at all, and any marketing approvals, if granted, may have significant limitations on their use. As a result, Descovy for PrEP may never be successfully commercialized. These risks, uncertainties and other factors could cause actual results to differ materially from those referred to in the forward-looking statements. The reader is cautioned not to rely on these forward-looking statements. These and other risks are described in detail in Gilead's Annual Report on Form 10-K for the year ended December 31, 2018, as filed with the U.S. Securities and Exchange Commission. All forward-looking statements are based on information currently available to Gilead, and Gilead assumes no obligation to update any such forward-looking statements.

*U.S. full prescribing information for Descovy and Truvada, including **BOXED WARNING**, is available at www.gilead.com.*

For more information on Gilead Sciences, please visit the company's website at www.gilead.com, follow Gilead on Twitter (@GileadSciences) or call Gilead Public Affairs at 1-800-GILEAD-5 or 1-650-574-3000.

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EXHIBIT 91

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DESCOVY safely and effectively. See full prescribing information for DESCOVY.

DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF DESCOVY FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION
See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of DESCOVY. Hepatic function should be monitored closely in these individuals. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

DESCOVY used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use.
Drug-resistant HIV-1 variants have been identified with use of FTC/TDF for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate DESCOVY for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed. (5.2)

----------RECENT MAJOR CHANGES----------

Boxed Warning	10/2019
Indications and Usage (1.2)	10/2019
Dosage and Administration (2.1, 2.2, 2.4, 2.5)	10/2019
Contraindications (4)	10/2019
Warnings and Precautions (5.2)	10/2019

----------INDICATIONS AND USAGE----------
HIV-1 Treatment (1.1):
DESCOVY is a two-drug combination of emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated:
- in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg.
- in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg.

HIV-1 PrEP (1.2):
DESCOVY is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating DESCOVY for HIV-1 PrEP.
Limitations of Use (1.2):
The indication does not include use of DESCOVY in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

----------DOSAGE AND ADMINISTRATION----------
- Testing: Prior to or when initiating DESCOVY, test for hepatitis B virus infection. Prior to or when initiating DESCOVY, and during use on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus. (2.1)
- HIV-1 Screening: Screen all individuals for HIV-1 infection immediately prior to initiating DESCOVY for HIV-1 PrEP and at least once every 3 months while taking DESCOVY, and upon diagnosis of any other sexually transmitted infections (STIs). (2.2)
- Recommended dosage:
  - Treatment of HIV-1 Infection: One tablet taken once daily with or without food in patients with body weight at least 25 kg. (2.3)
  - HIV-1 PrEP: One tablet taken once daily with or without food in individuals with body weight at least 35 kg. (2.4)
- Renal impairment: DESCOVY is not recommended in individuals with estimated creatinine clearance below 30 mL per minute. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 200 mg of FTC and 25 mg of TAF (3)

----------CONTRAINDICATIONS----------
DESCOVY for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status. (4)

----------WARNINGS AND PRECAUTIONS----------
- Comprehensive management to reduce the risk of sexually transmitted infections (STIs), including HIV-1, when DESCOVY is used for HIV-1 PrEP: Counsel on adherence to daily dosing and safer sex practices, including condoms, to reduce the risk of STIs. (5.2)
- Management to reduce the risk of acquiring HIV-1 drug resistance when DESCOVY is used for HIV-1 PrEP: refer to full prescribing information for additional detail. (5.2)
- Immune reconstitution syndrome during treatment of HIV-1 infection: May necessitate further evaluation and treatment. (5.3)
- New onset or worsening renal impairment: Assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein when initiating DESCOVY and during use on a clinically appropriate schedule in all individuals. Also assess serum phosphorus in individuals with chronic kidney disease. (5.4)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue DESCOVY in individuals who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)

----------ADVERSE REACTIONS----------
- In HIV-1 infected patients, the most common adverse reaction (incidence greater than or equal to 10%, all grades) was nausea. (6.1)
- In HIV-1 uninfected adults in a PrEP trial, the most common adverse reaction (incidence greater than or equal to 5%, all grades) was diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Consult the Full Prescribing Information prior to and during use for potential drug interactions. (7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Mothers infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV transmission. (8.2)
- Pediatrics:
  - Treatment of HIV-1 Infection: Not recommended for patients weighing less than 25 kg. (8.4)
  - HIV-1 PrEP: Not recommended for individuals weighing less than 35 kg. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF DESCOVY FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of DESCOVY.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in individuals who are infected with HBV and discontinue DESCOVY. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

DESCOVY used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of FTC/TDF for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate DESCOVY for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Treatment of HIV-1 Infection

DESCOVY is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg.

DESCOVY is indicated, in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor, for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg.

1.2 HIV-1 Pre-Exposure Prophylaxis (PrEP)

DESCOVY is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating DESCOVY for HIV-1 PrEP *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.

Limitations of Use:

The indication does not include use of DESCOVY in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated *[see Clinical Studies (14.3)].*

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Use of DESCOVY for Treatment of HIV-1 Infection or for HIV-1 PrEP

Prior to or when initiating DESCOVY, test individuals for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to or when initiating DESCOVY, and during use of DESCOVY on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.4)].*

2.2 HIV-1 Screening for Individuals Receiving DESCOVY for HIV-1 PrEP

Screen all individuals for HIV-1 infection immediately prior to initiating DESCOVY for HIV-1 PrEP and at least once every 3 months while taking DESCOVY, and upon diagnosis of any other sexually transmitted infections (STIs) *[see Indications and Usage (1.2), Contraindications (4), and Warnings and Precautions (5.2)].*

If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, use a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection *[see Warnings and Precautions (5.2), Use in Specific Populations (8.4), and Clinical Studies (14.3)].*

2.3 Recommended Dosage for Treatment of HIV-1 Infection in Adults and Pediatric Patients Weighing at Least 25 kg

DESCOVY is a two-drug fixed dose combination product containing 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of DESCOVY for treatment of HIV-1 is one tablet taken orally once daily with or without food in adults and pediatric patients with body weight at least 25 kg and creatinine clearance greater than or equal to 30 mL per minute *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

For specific dosing recommendations for coadministered third agents, refer to their respective prescribing information *[see Drug Interactions (7)]*. The safety and effectiveness of DESCOVY coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

2.4 Recommended Dosage for HIV-1 PrEP in Adults and Adolescents Weighing at Least 35 kg

The dosage of DESCOVY for HIV-1 PrEP is one tablet (containing 200 mg of FTC and 25 mg of TAF) once daily taken orally with or without food in HIV-1 uninfected adults and adolescents weighing at least 35 kg and with a creatinine clearance greater than or equal to 30 mL per minute, excluding individuals at risk from receptive vaginal sex *[see Clinical Pharmacology (12.3)].*

2.5 Not Recommended in Individuals with Severe Renal Impairment for Treatment of HIV-1 Infection or for HIV-1 PrEP

DESCOVY is not recommended in individuals with estimated creatinine clearance below 30 mL per minute *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

Each DESCOVY tablet contains 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). The tablets are blue, rectangular-shaped, film-coated, debossed with “GSI” on one side and “225” on the other side.

4 CONTRAINDICATIONS

DESCOVY for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status *[see Warnings and Precautions (5.2)].*

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Individuals with HBV Infection

All individuals should be tested for the presence of hepatitis B virus (HBV) before or when initiating DESCOVY *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in HBV-infected individuals who have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of DESCOVY. Individuals infected with HBV who discontinue DESCOVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in individuals with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. HBV-uninfected individuals should be offered vaccination.

5.2 Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When DESCOVY Is Used for HIV-1 PrEP

Use DESCOVY for HIV-1 PrEP to reduce the risk of HIV-1 infection as part of a comprehensive prevention strategy, including adherence to daily administration and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections (STIs). The time from initiation of DESCOVY for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

Risk for HIV-1 acquisition includes behavioral, biological, or epidemiologic factors including but not limited to condomless sex, past or current STIs, self-identified HIV risk, having sexual partners of unknown HIV-1 viremic status, or sexual activity in a high prevalence area or network.

Counsel individuals on the use of other prevention measures (e.g., consistent and correct condom use, knowledge of partner(s)' HIV-1 status, including viral suppression status, regular testing for STIs that can facilitate HIV-1 transmission). Inform uninfected individuals about and support their efforts in reducing sexual risk behavior.

Use DESCOVY to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-1 negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only DESCOVY, because DESCOVY alone does not constitute a complete regimen for HIV-1 treatment *[see Microbiology (12.4)];* therefore, care should be taken to minimize the risk of initiating or continuing DESCOVY before confirming the individual is HIV-1 negative.

- Some HIV-1 tests only detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating DESCOVY for HIV-1 PrEP, ask seronegative individuals about recent (in past month) potential exposure events (e.g., condomless sex or condom breaking during sex with a partner of unknown HIV-1 status or unknown viremic status, or a recent STI), and evaluate for current or recent signs or symptoms consistent with acute HIV-1 infection (e.g., fever, fatigue, myalgia, skin rash).
- If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, use a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection.

While using DESCOVY for HIV-1 PrEP, HIV-1 testing should be repeated at least every 3 months, and upon diagnosis of any other STIs.

- If an HIV-1 test indicates possible HIV-1 infection, or if symptoms consistent with acute HIV-1 infection develop following a potential exposure event, convert the HIV-1 PrEP regimen to an HIV treatment regimen until negative infection status is confirmed using a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection.

Counsel HIV-1 uninfected individuals to strictly adhere to the once daily DESCOVY dosing schedule. The effectiveness of DESCOVY in reducing the risk of acquiring HIV-1 is strongly correlated with adherence, as demonstrated by measurable drug levels in a clinical trial of DESCOVY for HIV-1 PrEP. Some individuals, such as adolescents, may benefit from more frequent visits and counseling to support adherence *[see Use in Specific Populations (8.4), Microbiology (12.4), and Clinical Studies (14.3)].*

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including FTC, a component of DESCOVY. During the initial phase of combination antiretroviral treatment, HIV-1 infected patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.4 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of FTC+TAF with cobicistat (COBI) plus elvitegravir (EVG) in HIV-1 infected patients there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT). In clinical trials of FTC+TAF with EVG+COBI in treatment-naïve subjects and in virally suppressed subjects switched to FTC+TAF with EVG+COBI with estimated creatinine clearance greater than 50 mL per minute, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with FTC+TAF with EVG+COBI. In a study of virally suppressed subjects with baseline estimated creatinine clearance between 30 and 69 mL per minute treated with FTC+TAF with EVG+COBI for a median duration of 43 weeks, FTC+TAF with EVG+COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects with a baseline estimated creatinine clearance between 30 and 50 mL per minute *[see Adverse Reactions (6.1)]*. DESCOVY is not recommended in individuals with estimated creatinine clearance below 30 mL per minute because data in this population are insufficient.

Individuals taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating DESCOVY, and during treatment with DESCOVY on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus. Discontinue DESCOVY in individuals who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.5 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of DESCOVY, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with DESCOVY should be suspended in any individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Severe Acute Exacerbations of Hepatitis B *[see Warnings and Precautions (5.1)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.3)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.4)]*.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.5)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug (or a drug given in various combinations with other concomitant therapy) cannot be directly compared to rates in the clinical trials of another drug (or drug given in the same or different combination therapy) and may not reflect the rates observed in practice.

Adverse Reactions in Clinical Trials of FTC+TAF with EVG+COBI in Treatment-Naïve Adults with HIV-1 Infection

In pooled 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, the most common adverse reaction in subjects treated with FTC+TAF with EVG+COBI (N=866) (incidence greater than or equal to 10%, all grades) was nausea (10%). In this treatment group, 0.9% of subjects discontinued FTC+TAF with EVG+COBI due to adverse events during the 48-week treatment period *[see Clinical Studies (14.2)]*. The safety profile was similar in virologically-suppressed

adults with HIV-1 infection who were switched to FTC+TAF with EVG+COBI (N=799). Antiretroviral treatment-naïve adult subjects treated with FTC+TAF with EVG+COBI experienced mean increases of 30 mg/dL of total cholesterol, 15 mg/dL of LDL cholesterol, 7 mg/dL of HDL cholesterol, and 29 mg/dL of triglycerides after 48 weeks of use.

Renal Laboratory Tests

In two 48-week trials in antiretroviral treatment-naïve HIV-1 infected adults treated with FTC+TAF with EVG+COBI (N=866) with a median baseline eGFR of 115 mL per minute, mean serum creatinine increased by 0.1 mg per dL from baseline to Week 48. Median urine protein-to-creatinine ratio (UPCR) was 44 mg per gram at baseline and at Week 48. In a 48-week trial in virologically-suppressed TDF-treated adults who switched to FTC+TAF with EVG+COBI (N=959) with a mean baseline eGFR of 112 mL per minute, mean serum creatinine was similar to baseline at Week 48; median UPCR was 61 mg per gram at baseline and 46 mg per gram at Week 48. In a 24-week trial in adults with renal impairment (baseline eGFR 30 to 69 mL per minute) who received FTC+TAF with EVG+COBI (N=248), mean serum creatinine was 1.5 mg per dL at both baseline and Week 24. Median UPCR was 161 mg per gram at baseline and 93 mg per gram at Week 24.

Bone Mineral Density Effects

In the pooled analysis of two 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, bone mineral density (BMD) from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA). Mean BMD decreased from baseline to Week 48 −1.30% with FTC+TAF with EVG+COBI at the lumbar spine and −0.66% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 10% of FTC+TAF with EVG+COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 7% of FTC+TAF with EVG+COBI subjects. The long-term clinical significance of these BMD changes is not known.

In 799 virologically-suppressed TDF-treated adult subjects that switched to FTC+TAF with EVG+COBI, at Week 48 mean BMD increased (1.86% lumbar spine, 1.95% total hip). BMD declines of 5% or greater at the lumbar spine were experienced by 1% of FTC+TAF with EVG+COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 1% of FTC+TAF with EVG+COBI subjects.

Adverse Reactions in Clinical Trials in Pediatric Subjects with HIV-1 Infection

In an open-label trial of antiretroviral treatment-naïve HIV-1 infected pediatric subjects between the ages of 12 to less than 18 years weighing at least 35 kg through 48 weeks (N=50; Cohort 1) and virologically-suppressed subjects between the ages of 6 to less than 12 years weighing at least 25 kg (N=23; Cohort 2) who received FTC+TAF with EVG+COBI through 24 weeks, with the exception of a decrease in the mean CD4+ cell count observed in cohort 2, the safety of this combination was similar to that of adults.

Bone Mineral Density Effects

Cohort 1: Treatment-naïve adolescents (12 to less than 18 years; at least 35 kg)

Among the subjects in cohort 1 receiving FTC+TAF with EVG+COBI, mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for the total body less head (TBLH). Mean changes from baseline BMD Z-scores were −0.07 for lumbar spine and −0.20 for TBLH at Week 48. One subject had significant (at least 4%) lumbar spine BMD loss at Week 48.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Among the subjects in cohort 2 receiving FTC+TAF with EVG+COBI, mean BMD increased from baseline to Week 24, +2.9% at the lumbar spine and +1.7% for TBLH. Mean changes from baseline BMD Z-scores were -0.06 for lumbar spine and -0.18 for TBLH at Week 24. Two subjects had significant (at least 4%) lumbar spine BMD loss at Week 24.

Change from Baseline in CD4+ cell counts

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Cohort 2 evaluated pediatric subjects (N=23) who were virologically-suppressed and who switched from their antiretroviral regimen to FTC+TAF with EVG+COBI. Although all subjects had HIV-1 RNA < 50 copies/mL, there was a decrease from baseline in CD4+ cell count at Week 24. The mean baseline and mean change from baseline in CD4+ cell count and in CD4% from Week 2 to Week 24 are presented in Table 1. All subjects maintained their CD4+ cell counts above 400 cells/mm^3 *[see Use in Specific Populations (8.4)].*

Table 1 Mean Change in CD4+ Count and Percentage from Baseline to Week 24 in Virologically-Suppressed Pediatric Patients from 6 to <12 Years Who Switched to FTC+TAF with EVG+COBI

		Mean Change from Baseline			
	Baseline	**Week 2**	**Week 4**	**Week 12**	**Week 24**
CD4+ Cell Count (cells/mm^3)	966 (201.7)[a]	-162	-125	-162	-150
CD4%	40 (5.3)[a]	+0.5%	-0.1%	-0.8%	-1.5%

a. Mean (SD)

Adverse Reactions from Clinical Trial Experience in HIV-1 Uninfected Individuals Taking DESCOVY for HIV-1 PrEP

The safety profile of DESCOVY for HIV-1 PrEP was comparable to that observed in clinical trials of HIV-infected subjects based on a double-blind, randomized, active-controlled trial (DISCOVER) in which a total of 5,387 HIV-1 uninfected adult men and transgender women who have sex with men received DESCOVY

(N=2,694) or TRUVADA (N=2,693) once daily for HIV-1 PrEP *[see Clinical Studies (14.3)]*. Median duration of exposure was 86 and 87 weeks, respectively. The most common adverse reaction in participants who received DESCOVY (incidence greater than or equal to 5%, all grades) was diarrhea (5%). Table 2 provides a list of the most common adverse reactions that occurred in 2% or more of participants in either treatment group. The proportion of participants who discontinued treatment with DESCOVY or TRUVADA due to adverse events, regardless of severity, was 1.3% and 1.8%, respectively.

Table 2 Adverse Reactions (All Grades) Reported in ≥2% in Either Arm in the DISCOVER Trial of HIV-1 Uninfected Participants

	DESCOVY (N=2,694)	TRUVADA (N=2,693)
Diarrhea	5%	6%
Nausea	4%	5%
Headache	2%	2%
Fatigue	2%	3%
Abdominal pain[a]	2%	3%

a. Includes the following terms: abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, and abdominal discomfort

Renal Laboratory Tests

Changes from baseline to Week 48 in renal laboratory data are presented in Table 3. The long-term clinical significance of these renal laboratory changes on adverse reaction frequencies between DESCOVY and TRUVADA is not known.

Table 3 Laboratory Assessments of Renal Function Reported in HIV-1 Uninfected Participants Receiving DESCOVY or TRUVADA in the DISCOVER Trial

	DESCOVY (N=2,694)	TRUVADA (N=2,693)
Serum Creatinine (mg/dL)[a] Change at Week 48	−0.01 (0.107)	0.01 (0.111)
$eGFR_{CG}$ (mL/min)[b] Change at Week 48	1.8 (−7.2, 11.1)	−2.3 (−10.8, 7.2)
Percentage of Participants who Developed UPCR >200 mg/g[c] At Week 48	0.7%	1.5%

$eGFR_{CG}$=estimated Glomerular Filtration Rate by Cockcroft-Gault; UPCR=urine protein/creatinine ratio
a. Mean (SD).
b. Median (Q1, Q3).
c. Based on N who had normal UPCR (≤ 200 mg/g) at baseline.

Bone Mineral Density Effects

In the DISCOVER trial, mean increases from baseline to Week 48 of 0.5% at the lumbar spine (N=159) and 0.2% at the total hip (N=158) were observed in participants receiving DESCOVY, compared to mean decreases of 1.1% at the lumbar spine (N=160) and 1.0% at the total hip (N=158) in participants receiving

TRUVADA. BMD declines of 5% or greater at the lumbar spine and 7% or greater at the total hip were experienced by 4% and 1% of participants, respectively, in both treatment groups at Week 48. The long-term clinical significance of these BMD changes is not known.

Serum Lipids

Changes from baseline to Week 48 in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio are presented in Table 4.

Table 4 Fasting Lipid Values, Mean Change from Baseline, Reported in HIV-1 Uninfected Participants Receiving DESCOVY or TRUVADA in the DISCOVER Trial[a]

	DESCOVY (N=2,694)		TRUVADA (N=2,693)	
	Baseline	Week 48	Baseline	Week 48
	mg/dL	Change[b]	mg/dL	Change[b]
Total Cholesterol (fasted)	176 [c]	0 [c]	176 [d]	-12 [d]
HDL-Cholesterol (fasted)	51 [c]	-2 [c]	51 [d]	-5 [d]
LDL-Cholesterol (fasted)	103 [e]	0 [e]	103 [f]	-7 [f]
Triglycerides (fasted)	109 [c]	+9 [c]	111 [d]	-1 [d]
Total Cholesterol to HDL ratio	3.7 [c]	0.2 [c]	3.7 [d]	0.1 [d]

a. Excludes subjects who received lipid lowering agents during the treatment period.
b. The baseline and change from baseline are for subjects with both baseline and Week 48 values.
c. N=1,098
d. N=1,124
e. N=1,079
f. N=1,107

6.2 Postmarketing Experience

The following reactions have been identified during postapproval use of products containing TAF. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders
Angioedema, urticaria, and rash

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect One or More Components of DESCOVY

TAF, a component of DESCOVY, is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp and BCRP activity may lead to changes

in TAF absorption (see Table 5). Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of DESCOVY and development of resistance. Coadministration of DESCOVY with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A *in vitro*. TAF is not an inhibitor or inducer of CYP3A *in vivo*.

7.2 Drugs Affecting Renal Function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of DESCOVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.4)]*.

7.3 Established and Other Potentially Significant Interactions

Table 5 provides a listing of established or potentially clinically significant drug interactions with recommended steps to prevent or manage the drug interaction (the table is not all inclusive). The drug interactions described are based on studies conducted with either DESCOVY, the components of DESCOVY (emtricitabine and tenofovir alafenamide) as individual agents, or are predicted drug interactions that may occur with DESCOVY. For magnitude of interaction, *see Clinical Pharmacology (12.3)*.

Table 5 Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents: Protease Inhibitors (PI)		
tipranavir/ritonavir	↓ TAF	Coadministration with DESCOVY is not recommended.
Other Agents		
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓ TAF	Consider alternative anticonvulsant.
Antimycobacterials: rifabutin rifampin rifapentine	↓ TAF	Coadministration of DESCOVY with rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ TAF	Coadministration of DESCOVY with St. John's wort is not recommended.

a. This table is not all inclusive.
b. ↓=Decrease

7.4 Drugs without Clinically Significant Interactions with DESCOVY

Based on drug interaction studies conducted with the components of DESCOVY, no clinically significant drug interactions have been either observed or are expected when DESCOVY is combined with the following antiretroviral agents: atazanavir with ritonavir or cobicistat, darunavir with ritonavir or cobicistat, dolutegravir, efavirenz, ledipasvir, lopinavir/ritonavir, maraviroc, nevirapine, raltegravir, rilpivirine, and sofosbuvir. No clinically significant drug interactions have been either observed or are expected when DESCOVY is combined with the following drugs: buprenorphine, itraconazole, ketoconazole, lorazepam, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to DESCOVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Available data from the APR show no increase in the risk of overall major birth defects for emtricitabine (FTC) compared with the background rate for major birth

defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). There are insufficient tenofovir alafenamide (TAF) data from the APR to adequately assess the risk of major birth defects. The rate of miscarriage for individual drugs is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15–20%.

In animal studies, no adverse developmental effects were observed when the components of DESCOVY were administered separately during the period of organogenesis at exposures 60 and 108 times (mice and rabbits, respectively) the FTC exposure and at exposure equal to or 53 times (rats and rabbits, respectively) the TAF exposure at the recommended daily dose of DESCOVY *(see Data).* Likewise, no adverse developmental effects were seen when FTC was administered to mice through lactation at exposures up to approximately 60 times the exposure at the recommended daily dose of DESCOVY. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 14 times the exposure at the recommended daily dosage of DESCOVY.

Data

Human Data

Emtricitabine: Based on prospective reports to the APR through January 2019 of over 4,450 exposures to FTC-containing regimens during pregnancy (including over 3,150 exposed in the first trimester and over 1,300 exposed in the second/third trimester), there was no difference between FTC and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.4% (95% CI: 1.9% to 3.0%) with first trimester exposure to FTC-containing regimens and 2.3% (95% CI: 1.5% to 3.2%) with the second/third trimester exposure to FTC-containing regimens.

Tenofovir Alafenamide: Based on prospective reports to the APR of over 220 exposures to TAF-containing regimens during pregnancy (including over 160 exposed in the first trimester and over 60 exposed in the second/third trimester), there have been 6 birth defects with first trimester exposure to TAF-containing regimens.

Methodologic limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

Additionally, published observational studies on emtricitabine and tenofovir exposure in pregnancy have not shown an increased risk for major malformations.

Animal Data

Emtricitabine: FTC was administered orally to pregnant mice (250, 500, or 1000 mg/kg/day) and rabbits (100, 300, or 1000 mg/kg/day) through organogenesis (on

gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with FTC in mice at exposures (area under the curve [AUC]) approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the recommended daily dose. In a pre/postnatal development study with FTC, mice were administered doses up to 1000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended daily dose.

Tenofovir Alafenamide: TAF was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures approximately similar to (rats) and 53 (rabbits) times higher than the exposure in humans at the recommended daily dose of DESCOVY. TAF is rapidly converted to tenofovir; the observed tenofovir exposures in rats and rabbits were 59 (rats) and 93 (rabbits) times higher than human tenofovir exposures at the recommended daily dose. Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to tenofovir disoproxil fumarate (TDF, another prodrug for tenofovir) administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 (and lactation day 20) at tenofovir exposures of approximately 14 (21) times higher than the exposures in humans at the recommended daily dose of DESCOVY.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants, to avoid risking postnatal transmission of HIV-1.

Based on limited data, FTC has been shown to be present in human breast milk; it is not known if TAF is present in human breast milk. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *(see Data)*. It is not known if TAF is present in animal milk.

It is not known if DESCOVY affects milk production or has effects on the breastfed child.

Because of the potential for: 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are taking DESCOVY for the treatment of HIV-1 *(see Data)*.

Data

Animal Data

Tenofovir Alafenamide: Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11. Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.4 Pediatric Use

Treatment of HIV-1 Infection

The safety and effectiveness of DESCOVY, in combination with other antiretroviral agents, for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg *[see Indication and Usage (1.1) and Dosage and Administration (2.3)]*.

Use of DESCOVY in pediatric patients between the ages of 12 to less than 18 years weighing at least 35 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in antiretroviral treatment-naïve HIV-1 infected pediatric subjects ages 12 to less than 18 years and weighing at least 35 kg (N=50; cohort 1). The safety and efficacy of FTC+TAF with EVG+COBI in these pediatric subjects was similar to that of HIV-1 infected adults on this regimen *[see Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

Use of DESCOVY in pediatric patients weighing at least 25 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in virologically-suppressed pediatric subjects between the ages of 6 to less than 12 years weighing at least 25 kg, in which subjects were switched from their antiretroviral regimen to FTC+TAF with EVG+COBI (N=23; cohort 2). The safety in these subjects through 24 weeks of FTC+TAF with EVG+COBI was similar to that of HIV-1 infected adults on this regimen, with the exception of a decrease in mean change from baseline in CD4+ cell count *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

Safety and effectiveness of DESCOVY coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg *[see Dosage and Administration (2.3)]*.

Safety and effectiveness of DESCOVY for treatment of HIV-1 infection in pediatric patients less than 25 kg have not been established.

HIV-1 PrEP

Safety and effectiveness of DESCOVY for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg, excluding individuals at risk from receptive vaginal sex, is supported by data from an adequate and well-controlled trial of DESCOVY for HIV-1 PrEP in adults with additional data from safety and pharmacokinetic studies in previously conducted trials with the individual drug products, FTC and TAF, with EVG+COBI, in HIV-1 infected adults and pediatric subjects *[see Dosage and Administration (2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3 and 12.4), and Clinical Studies (14)].*

While using DESCOVY for HIV-1 PrEP, HIV-1 testing should be repeated at least every 3 months, and upon diagnosis of any other STIs. Previous studies in at-risk adolescents indicated waning adherence to a daily oral PrEP regimen once visits were switched from monthly to quarterly visits. Adolescents may therefore benefit from more frequent visits and counseling *[see Warnings and Precautions (5.2)].*

Safety and effectiveness of DESCOVY for HIV-1 PrEP in pediatric patients less than 35 kg have not been established.

8.5 Geriatric Use

In clinical trials of an FTC+TAF-containing regimen for treatment of HIV-1, 80 of the 97 subjects enrolled aged 65 years and over received FTC+TAF and EVG+COBI. No differences in safety or efficacy have been observed between elderly subjects and adults between 18 and less than 65 years of age.

8.6 Renal Impairment

DESCOVY is not recommended in individuals with severe renal impairment (estimated creatinine clearance below 30 mL per minute). No dosage adjustment of DESCOVY is recommended in individuals with estimated creatinine clearance greater than or equal to 30 mL per minute *[see Dosage and Administration (2.5) and Clinical Studies (14.2)].*

8.7 Hepatic Impairment

No dosage adjustment of DESCOVY is recommended in individuals with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DESCOVY has not been studied in individuals with severe hepatic impairment (Child-Pugh Class C) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No data are available on overdose of DESCOVY in patients. If overdose occurs, monitor the individual for evidence of toxicity. Treatment of overdose with DESCOVY consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the individual.

Emtricitabine (FTC): Limited clinical experience is available at doses higher than the recommended dose of FTC in DESCOVY. In one clinical pharmacology study,

single doses of FTC 1200 mg (6 times the FTC dose in DESCOVY) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

Hemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL per minute and a dialysate flow rate of 600 mL per minute). It is not known whether FTC can be removed by peritoneal dialysis.

Tenofovir Alafenamide (TAF): Limited clinical experience is available at doses higher than the recommended dose of TAF. A single dose of 125 mg TAF (5 times the TAF dose in 200/25 mg DESCOVY) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

11 DESCRIPTION

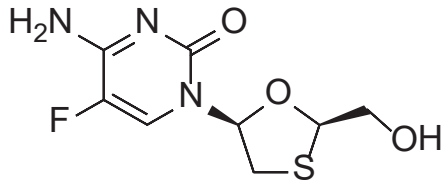
DESCOVY (emtricitabine and tenofovir alafenamide) is a fixed dose combination tablet containing emtricitabine (FTC) and tenofovir alafenamide (TAF) for oral administration.

- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

Each 200/25 mg tablet contains 200 mg of FTC and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate) and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Emtricitabine: The chemical name of FTC is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one. FTC is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position.

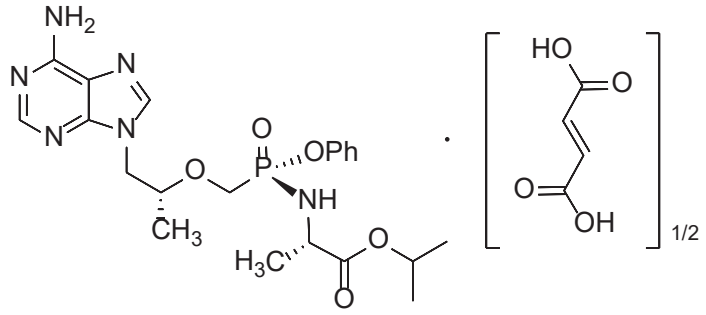
FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24 and has the following structural formula:



FTC is a white to off-white powder with a solubility of approximately 112 mg per mL in water at 25 °C.

Tenofovir Alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

Tenofovir alafenamide fumarate has an empirical formula of $C_{21}H_{29}O_5N_6P \bullet ½(C_4H_4O_4)$ and a formula weight of 534.50 and has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DESCOVY is a fixed dose combination of antiretroviral drugs emtricitabine (FTC) and tenofovir alafenamide (TAF) *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT/QTc study in 48 healthy subjects, TAF at the recommended dose or at a dose approximately 5 times the recommended dose, did not affect the QT/QTc interval and did not prolong the PR interval. The effect of the other component of DESCOVY, FTC, or the combination of FTC and TAF on the QT interval is not known.

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic (PK) properties of the components of DESCOVY are provided in Table 6. The multiple dose PK parameters of FTC and TAF and its metabolite tenofovir are provided in Table 7. HIV status has no effect on the pharmacokinetics of FTC and TAF in adults.

Table 6 Pharmacokinetic Properties of the Components of DESCOVY

	Emtricitabine	Tenofovir Alafenamide
Absorption		
T_{max} (h)	3	1
Effect of high fat meal (relative to fasting)[a]	AUC Ratio = 0.91 (0.89, 0.93) C_{max} Ratio = 0.74 (0.69, 0.78)	AUC Ratio = 1.75 (1.64, 1.88) C_{max} Ratio= 0.85 (0.75, 0.95)
Distribution		
% Bound to human plasma proteins	<4	~80
Source of protein binding data	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.6	1.0
Metabolism		
Metabolism	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination		
Major route of elimination	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
$t_{1/2}$ (h)[c]	10	0.51
% Of dose excreted in urine[d]	70	<1
% Of dose excreted in feces[d]	13.7	31.7

PBMCs=peripheral blood mononuclear cells; CES1=carboxylesterase 1

a. Values refer to geometric mean ratio [High-fat meal/ fasting] in PK parameters and (90% confidence interval). High-calorie/high-fat meal = ~800 kcal, 50% fat.

b. *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

c. $t_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

d. Dosing in mass balance studies: FTC (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for 10 days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

Table 7 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration with Food in HIV-Infected Adults

Parameter Mean (CV%)	Emtricitabine[a]	Tenofovir Alafenamide[b]	Tenofovir[c]
C_{max} (microgram per mL)	2.1 (20.2)	0.16 (51.1)	0.02 (26.1)
AUC_{tau} (microgram•hour per mL)	11.7 (16.6)	0.21 (71.8)	0.29 (27.4)
C_{trough} (microgram per mL)	0.10 (46.7)	NA	0.01 (28.5)

CV=Coefficient of Variation; NA=Not Applicable

a. From Intensive PK analysis in a phase 2 trial in HIV-infected adults treated with FTC+TAF and EVG+COBI.

b. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC+TAF with EVG+COBI (N=539).

c. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC+TAF with EVG+COBI (N=841).

Specific Populations

Geriatric Patients

Pharmacokinetics of FTC and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of FTC+TAF and EVG+COBI showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

Treatment of HIV-1 Infection: Mean exposures of TAF in 24 pediatric subjects aged 12 to less than 18 years who received FTC+TAF with EVG+COBI were decreased (23% for AUC) and FTC exposures were similar compared to exposures achieved in treatment-naïve adults following administration of this dosage regimen. The TAF exposure differences are not thought to be clinically significant based on exposure-response relationships (Table 8).

Table 8 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide, and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (microgram•hour per mL)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.10[b] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection (N=24).
b. N=23

Exposures of FTC and TAF achieved in 23 pediatric subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (55 lbs) who received FTC+TAF with EVG+COBI were higher (20% to 80% for AUC) than exposures achieved in adults following the administration of this dosage regimen; however, the increase was not considered clinically significant (Table 9) *[see Use in Specific Populations (8.4)]*.

Table 9 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in virologically-suppressed pediatric subjects with HIV-1 infection (N=23).

b. N=22

HIV-1 PrEP: The pharmacokinetic data for FTC and TAF following administration of DESCOVY in HIV-1 uninfected adolescents weighing 35 kg and above are not available. The dosage recommendations of DESCOVY for HIV-1 PrEP in this population are based on known pharmacokinetic information in HIV-infected adolescents taking FTC and TAF for treatment *[see Use in Specific Populations (8.4)].*

Race and Gender

Based on population pharmacokinetic analyses, there are no clinically meaningful differences based on race or gender.

Patients with Renal Impairment

The pharmacokinetics of FTC+TAF combined with EVG+COBI in HIV-infected subjects with renal impairment (eGFR 30 to 69 mL per minute by Cockcroft-Gault method) were evaluated in a subset of virologically-suppressed subjects in an open-label trial (Table 10).

Table 10 Pharmacokinetics of the Components of DESCOVY and a Metabolite of TAF (Tenofovir) in HIV-Infected Adults with Renal Impairment Compared to Subjects with Normal Renal Function[a]

	AUC_{tau} (microgram·hour per mL) Mean (CV%)		
Creatinine Clearance	**≥90 mL per minute (N=18)[b]**	**60–89 mL per minute (N=11)[c]**	**30–59 mL per minute (N=18)**
Emtricitabine	11.4 (11.9)	17.6 (18.2)	23.0 (23.6)
Tenofovir Alafenamide*	0.23 (47.2)	0.24 (45.6)	0.26 (58.8)
Tenofovir	0.32 (14.9)	0.46 (31.5)	0.61 (28.4)

*AUC_{last}
a. Trial in HIV-infected adults with renal impairment treated with FTC+TAF with EVG+COBI.
b. From a phase 2 trial in HIV-infected adults with normal renal function treated with FTC+TAF with EVG+COBI.
c. These subjects had an eGFR ranging from 60 to 69 mL per minute.

Patients with Hepatic Impairment

Emtricitabine: The pharmacokinetics of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited.

Tenofovir Alafenamide: Clinically relevant changes in tenofovir pharmacokinetics in subjects with hepatic impairment were not observed in subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment *[see Use in Specific Populations (8.7)]*.

Hepatitis B and/or Hepatitis C Virus Infection

The pharmacokinetics of FTC and TAF have not been fully evaluated in subjects infected with hepatitis B and/or C virus.

Drug Interaction Studies

The effects of coadministered drugs on the exposure of TAF are shown in Table 11 and the effects of DESCOVY or its components on the exposure of coadministered drugs are shown in Table 12 [these studies were conducted with DESCOVY or the components of DESCOVY (FTC or TAF) administered alone]. For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 11 Drug Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Coadministered Drug(s)[a]

Coadministered Drug	Coadministered Drug(s) Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of TAF PK Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 (+100 ritonavir)	10	10	1.77 (1.28, 2.44)	1.91 (1.55, 2.35)	NC
Cobicistat	150	8	12	2.83 (2.20, 3.65)	2.65 (2.29, 3.07)	NC
Darunavir	800 (+150 cobicistat)	25[b]	11	0.93 (0.72, 1.21)	0.98 (0.80, 1.19)	NC
Darunavir	800 (+100 ritonavir)	10	10	1.42 (0.96, 2.09)	1.06 (0.84, 1.35)	NC
Dolutegravir	50	10	10	1.24 (0.88, 1.74)	1.19 (0.96, 1.48)	NC
Efavirenz	600	40[b]	11	0.78 (0.58, 1.05)	0.86 (0.72, 1.02)	NC
Lopinavir	800 (+200 ritonavir)	10	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	NC
Rilpivirine	25	25	17	1.01 (0.84, 1.22)	1.01 (0.94, 1.09)	NC
Sertraline	50 (dosed as a single dose)	10[c]	19	1.00 (0.86, 1.16)	0.96 (0.89, 1.03)	NC

NC=Not Calculated

a. All interaction studies conducted in healthy volunteers.
b. Study conducted with DESCOVY (FTC/TAF).
c. Study conducted with FTC+TAF with EVG+COBI.

Table 12 Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of DESCOVY or the Individual Components[a]

Coadministered Drug	Coadministered Drug Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of Coadministered Drug PK Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 +100 ritonavir	10	10	0.98 (0.89, 1.07)	0.99 (0.96, 1.01)	1.00 (0.96, 1.04)
Darunavir	800 +150 cobicistat	25[b]	11	1.02 (0.96, 1.09)	0.99 (0.92, 1.07)	0.97 (0.82, 1.15)
Darunavir	800 +100 ritonavir	10	10	0.99 (0.91, 1.08)	1.01 (0.96, 1.06)	1.13 (0.95, 1.34)
Dolutegravir	50 mg	10	10	1.15 (1.04, 1.27)	1.02 (0.97, 1.08)	1.05 (0.97, 1.13)
Lopinavir	800 +200 ritonavir	10	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam[c]	2.5 (single dose, orally)	25	18	1.02 (0.92, 1.13)	1.13 (1.04, 1.23)	NC
	1 (single dose, intravenous)			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Rilpivirine	25	25	16	0.93 (0.87, 0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)
Sertraline	50 (single dose)	10[d]	19	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NC

NC=Not Calculated
a. All interaction studies conducted in healthy volunteers.
b. Study conducted with DESCOVY (FTC/TAF).
c. A sensitive CYP3A4 substrate.
d. Study conducted with FTC+TAF with EVG+COBI.

12.4 Microbiology

Mechanism of Action

Emtricitabine: FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, Ɛ, and mitochondrial DNA polymerase γ.

Tenofovir Alafenamide: TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity against HIV-1. Cell culture studies have shown that both tenofovir and FTC can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Antiviral Activity in Cell Culture

Emtricitabine: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary peripheral blood mononuclear cells. The EC_{50} values for FTC were in the range of 0.0013–0.64 micromolar. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 micromolar) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 micromolar).

In a study of FTC with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, non-nucleoside reverse transcriptase inhibitors [NNRTIs], integrase strand transfer inhibitors [INSTIs], and PIs) no antagonism was observed for these combinations.

Tenofovir Alafenamide: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs) no antagonism was observed for these combinations.

Prophylactic Activity in a Nonhuman Primate Model of HIV-1 Transmission

Emtricitabine and Tenofovir Alafenamide: The prophylactic activity of the combination of oral FTC and TAF was evaluated in a controlled study of macaques administered once weekly intra-rectal inoculations of chimeric simian/human immunodeficiency type 1 virus (SHIV) for up to 19 weeks (n=6). All 6 macaques that received FTC and TAF at doses resulting in PBMC exposures consistent with

those achieved in humans administered a dose of FTC/TAF 200/25 mg remained SHIV uninfected.

Resistance

In Cell Culture

Emtricitabine: HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir Alafenamide: HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

In Clinical Trials

Treatment of HIV-1

The resistance profile of DESCOVY in combination with other antiretroviral agents for the treatment of HIV-1 infection is based on studies of FTC+TAF with EVG+COBI in the treatment of HIV-1 infection. In a pooled analysis of antiretroviral-naïve subjects, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 48, or at time of early study drug discontinuation. Genotypic resistance developed in 7 of 14 evaluable subjects. The resistance-associated substitutions that emerged were M184V/I (N=7) and K65R (N=1). Three subjects had virus with emergent R, H, or E at the polymorphic Q207 residue in reverse transcriptase.

One subject was identified with emergent resistance to FTC (M184M/I) out of 4 virologic failure subjects in a clinical study of virologically-suppressed subjects who switched from a regimen containing FTC+TDF to FTC+TAF with EVG+COBI (N=799).

HIV-1 PrEP

In the DISCOVER trial of HIV-1 uninfected men and transgender women who have sex with men and who are at risk of HIV-1 infection receiving DESCOVY or TRUVADA for HIV-1 PrEP, genotyping was performed on participants found to be infected during the trial who had HIV-1 RNA ≥400 copies/mL (6 of 7 participants receiving DESCOVY and 13 of 15 participants receiving TRUVADA). The development of FTC resistance-associated substitutions, M184I and/or M184V, was observed in 4 HIV-1 infected participants in the TRUVADA group who had suspected baseline infections.

Cross-Resistance

Emtricitabine: FTC-resistant viruses with the M184V or I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine-thymidine analog substitutions (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution or other substitutions associated with resistance to NNRTIs was susceptible to FTC.

Tenofovir Alafenamide: Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir.

HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine

In long-term carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (23 times the human systemic exposure at the recommended dose of 200 mg per day in DESCOVY) or in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the recommended dose in DESCOVY).

FTC was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

FTC did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times higher exposures (AUC) than in humans given the recommended 200 mg daily dosage in DESCOVY. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended 200 mg daily dosage in DESCOVY.

Tenofovir Alafenamide

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the recommended dose of TDF (300 mg) for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 55 times (rat) those observed in humans after administration of the daily recommended dose of DESCOVY. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300 mg TDF) and 167 times

(DESCOVY) the exposure observed in humans. In rats, the study was negative for carcinogenic findings.

TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

There were no effects on fertility, mating performance, or early embryonic development when TAF was administered to male rats at a dose equivalent to 62 times (25 mg TAF) the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three- and nine-month administration of TAF; reversibility was seen after a three-month recovery period. No eye toxicity was observed in the dog at systemic exposures of 5 (TAF) and 15 (tenofovir) times the exposure seen in humans with the recommended daily TAF dose in DESCOVY.

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

The efficacy and safety of DESCOVY have been evaluated in the trials summarized in Table 13.

Table 13 Trials Conducted with FTC+TAF-Containing Products for HIV-1 Treatment and DESCOVY for HIV-1 PrEP

Trial	Population	Study Arms (N)	Timepoint
Study 104 [a] (NCT01780506) Study 111 [a] (NCT01797445)	HIV-1 infected treatment-naïve adults	FTC+TAF with EVG+COBI [b] (866) FTC+TDF with EVG+COBI [c] (867)	48 Weeks
Study 109 [d] (NCT01815736)	HIV-1 infected virologically suppressed [f] adults	FTC+TAF with EVG+COBI [b] (799) ATRIPLA® or TRUVADA®+atazanavir+cobicistat or ritonavir or FTC+TDF with EVG+COBI [c] (397)	48 Weeks
Study 112 [e] (NCT01818596)	HIV-1 infected virologically suppressed [f] adults with renal impairment [g]	FTC+TAF with EVG+COBI [b] (242)	24 Weeks
Study 106 [e] (Cohort 1) NCT01854775)	HIV-1 infected treatment-naïve adolescents between the ages of 12 to less than 18 years (at least 35 kg)	FTC+TAF with EVG+COBI [b] (50)	48 Weeks
Study 106 [e] (Cohort 2) NCT01854775)	HIV-1 infected, virologically suppressed children between the ages of 6 to less than 12 years (at least 25 kg)	FTC+TAF with EVG+COBI [b] (23)	24 Weeks
DISCOVER [a] (NCT02842086)	HIV-1 uninfected men or transgender women who have sex with men	DESCOVY (2,670) TRUVADA® (2,665)	4,370 person-years[h]

a. Randomized, double-blind, active-controlled study.
b. Administered as GENVOYA®.
c. Administered as STRIBILD®.
d. Randomized, open-label, active controlled trial.
e. Open label trial
f. HIV-1 RNA less than 50 copies per mL.
g. Estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method.
h. Exposure in the DESCOVY group.

14.2 Clinical Trial Results for Treatment of HIV-1

In trials of FTC+TAF with EVG+COBI in HIV-1 infected adults as initial therapy in those with no antiretroviral treatment history (N=866) and to replace a stable antiretroviral regimen in those who were virologically-suppressed for at least 6 months with no known resistance substitutions (N=799), 92% and 96% of patients in the two populations, respectively, had HIV-1 RNA less than 50 copies per mL at Week 48.

An open-label, single arm trial of FTC+TAF with EVG+COBI enrolled 50 treatment-naïve HIV-1 infected adolescents aged 12 to less than 18 years weighing at least 35 kg (cohort 1) and 23 virologically suppressed children aged 6 to less than 12 years weighing at least 25 kg (cohort 2). In cohort 1, the virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) was 92% (46/50) and the mean increase from baseline in CD4+ cell count was 224 cells per mm^3 at Week 48. In cohort 2, 100% of subjects remained virologically suppressed at Week

24. From a mean (SD) baseline CD4+ cell count of 966 (201.7), the mean change from baseline in CD4+ cell count was -150 cells/mm^3 and the mean (SD) change in CD4% was -1.5% (3.7%) at Week 24. All subjects maintained CD4+ cell counts above 400 cells/mm^3 *[see Adverse Reactions (6.1) and Use in Specific Populations (8.4)].*

In a trial in 248 HIV-1 infected adult patients with estimated creatinine clearance greater than 30 mL per minute but less than 70 mL per minute, 95% (235/248) of the combined population of treatment-naïve subjects (N=6) began on FTC+TAF with EVG+COBI and those previously virologically-suppressed on other regimens (N=242) and switched to FTC+TAF with EVG+COBI had HIV-1 RNA less than 50 copies per mL at Week 24.

14.3 Clinical Trial Results for HIV-1 PrEP

The efficacy and safety of DESCOVY to reduce the risk of acquiring HIV-1 infection were evaluated in a randomized, double-blind multinational trial (DISCOVER) in HIV-seronegative men (N=5,262) or transgender women (N=73) who have sex with men and are at risk of HIV-1 infection, comparing once daily DESCOVY (N=2,670) to TRUVADA (FTC/TDF 200 mg/300 mg; N=2,665). Evidence of risk behavior at entry into the trial included at least one of the following: two or more unique condomless anal sex partners in the past 12 weeks or a diagnosis of rectal gonorrhea/chlamydia or syphilis in the past 24 weeks. The median age of participants was 34 years (range, 18-76); 84% were White, 9% Black/Mixed Black, 4% Asian, and 24% Hispanic/Latino. At baseline, 897 participants (17%) reported receiving TRUVADA for PrEP.

At weeks 4, 12, and every 12 weeks thereafter, all participants received local standard of care HIV-1 prevention services, including HIV-1 testing, evaluation of adherence, safety evaluations, risk-reduction counseling, condoms, management of sexually transmitted infections, and assessment of sexual behavior.

Trial participants maintained a high risk of sexual HIV-1 acquisition, with high rates of rectal gonorrhea (DESCOVY, 24%; TRUVADA, 25%), rectal chlamydia (DESCOVY, 30%; TRUVADA, 31%), and syphilis (14% in both treatment groups) during the trial.

The primary outcome was the incidence of documented HIV-1 infection per 100 person-years in participants randomized to DESCOVY and TRUVADA (with a minimum follow-up of 48 weeks and at least 50% of participants having 96 weeks of follow-up). DESCOVY was non-inferior to TRUVADA in reducing the risk of acquiring HIV-1 infection (Table 14). The results were similar across the subgroups of age, race, gender identity, and baseline TRUVADA for PrEP use.

Table 14 HIV-1 Infection Results in DISCOVER Trial – Full Analysis Set

	DESCOVY (N=2,670)	TRUVADA (N=2,665)	Rate Ratio (95% CI)
	4,370 person-years	4,386 person-years	
HIV-1 infections, n	7	15	
Rate of HIV-1 infections per 100 person-years	0.16	0.34	0.468 (0.19, 1.15)

CI = Confidence interval.

Of the 22 participants diagnosed with HIV-1 infection in the trial, five had suspected baseline infection prior to study entry (DESCOVY, 1; TRUVADA, 4). In a case-control substudy of intracellular drug levels and estimated number of daily doses as measured by dried blood spot testing, median intracellular tenofovir diphosphate concentrations were substantially lower in participants infected with HIV-1 at the time of diagnosis compared with uninfected matched control participants. For both DESCOVY and TRUVADA, efficacy was therefore strongly correlated to adherence to daily dosing.

16 HOW SUPPLIED/STORAGE AND HANDLING

DESCOVY 200 mg/25 mg tablets are blue, rectangular-shaped, and film-coated with “GSI” debossed on one side and “225” on the other side. Each bottle contains 30 tablets (NDC 61958-2002-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

- Keep container tightly closed.
- Dispense only in original container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Important Information for Uninfected Individuals Taking DESCOVY for HIV-1 PrEP

Advise HIV-1 uninfected individuals about the following *[see Warnings and Precautions (5.2)]:*

- The need to confirm that they are HIV-negative before starting to take DESCOVY to reduce the risk of acquiring HIV-1.
- That HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking DESCOVY, because DESCOVY alone does not constitute a complete regimen for HIV-1 treatment.
- The importance of taking DESCOVY on a regular dosing schedule and strict adherence to the recommended dosing schedule to reduce the risk of acquiring HIV-1. Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses.

- That DESCOVY does not prevent other sexually acquired infections and should be used as part of a complete prevention strategy including other prevention measures.
- To use condoms consistently and correctly to lower the chances of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- The importance of knowing their HIV-1 status and the HIV-1 status of their partner(s).
- The importance of virologic suppression in their partner(s) with HIV-1.
- The need to get tested regularly for HIV-1 (at least every 3 months, or more frequently for some individuals such as adolescents) and to ask their partner(s) to get tested as well.
- To report any symptoms of acute HIV-1 infection (flu-like symptoms) to their healthcare provider immediately.
- That the signs and symptoms of acute infection include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- To get tested for other sexually transmitted infections, such as syphilis, chlamydia, and gonorrhea, that may facilitate HIV-1 transmission.
- To assess their sexual risk behavior and get support to help reduce sexual risk behavior.

Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Infection

Inform individuals that severe acute exacerbations of hepatitis B have been reported in patients who are infected with HBV and have discontinued products containing FTC and/or TDF and may likewise occur with discontinuation of DESCOVY *[see Warnings and Precautions (5.1)]*. Advise HBV-infected individuals to not discontinue DESCOVY without first informing their healthcare provider.

Immune Reconstitution Syndrome

Advise HIV-1 infected patients to inform their healthcare provider immediately of any symptoms of infection. In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.3)]*.

New Onset or Worsening Renal Impairment

Advise HIV-1 infected patients and uninfected individuals to avoid taking DESCOVY with concurrent or recent use of nephrotoxic agents. Renal impairment, including cases of acute renal failure, has been reported in association with the use of tenofovir prodrugs *[see Warnings and Precautions (5.4)].*

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to DESCOVY. Advise HIV-1 infected patients and uninfected individuals that they should stop DESCOVY if they

develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.5)]*.

Dosage Recommendations for Treatment of HIV-1 Infection

Inform HIV-1 infected patients that it is important to take DESCOVY with other antiretroviral drugs for the treatment of HIV-1 on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance *[see Dosage and Administration (2.3)]*.

Pregnancy Registry

Inform individuals using DESCOVY that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to DESCOVY *[see Use in Specific Populations (8.1)].*

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because of the risk of passing the HIV-1 virus to the baby *[see Use in Specific Populations (8.2)]*.

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Medication Guide
DESCOVY® (des-KOH-vee)
(emtricitabine and tenofovir alafenamide)
tablets

Read this Medication Guide before you start taking DESCOVY and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

This Medication Guide provides information about two different ways that DESCOVY may be used. See the section **"What is DESCOVY?"** for detailed information about how DESCOVY may be used.

What is the most important information I should know about DESCOVY?

DESCOVY can cause serious side effects, including:

- **Worsening of hepatitis B virus infection (HBV). Your healthcare provider will test you for HBV infection before or when you start treatment with DESCOVY. If you have HBV infection and take DESCOVY, your HBV may get worse (flare-up) if you stop taking DESCOVY. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - Do not run out of DESCOVY. Refill your prescription or talk to your healthcare provider before your DESCOVY is all gone.
  - Do not stop taking DESCOVY without first talking to your healthcare provider.
  - If you stop taking DESCOVY, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection, or give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking DESCOVY.

For more information about side effects, see the section "What are the possible side effects of DESCOVY?"

Other important information for people who take DESCOVY to help reduce their risk of getting human immunodeficiency virus-1 (HIV-1) infection, also called pre-exposure prophylaxis or "PrEP":

Before taking DESCOVY to reduce your risk of getting HIV-1:

- **You must be HIV-1 negative to start DESCOVY. You must get tested to make sure that you do not already have HIV-1 infection.**
- **Do not take DESCOVY for HIV-1 PrEP unless you are confirmed to be HIV-1 negative.**
- Some HIV-1 tests can miss HIV-1 infection in a person who has recently become infected. If you have flu-like symptoms, you could have recently become infected with HIV-1. Tell your healthcare provider if you had a flu-like illness within the last month before starting DESCOVY or at any time while taking DESCOVY. Symptoms of new HIV-1 infection include:
  - tiredness
  - fever
  - joint or muscle aches
  - headache
  - sore throat
  - vomiting or diarrhea
  - rash
  - night sweats
  - enlarged lymph nodes in the neck or groin

While you are taking DESCOVY for HIV-1 PrEP:

- **DESCOVY does not prevent other sexually transmitted infections (STIs). Practice safer sex by using a latex or polyurethane condom to reduce the risk of getting STIs.**
- **You must stay HIV-1 negative to keep taking DESCOVY for HIV-1 PrEP.**
  - Know your HIV-1 status and the HIV-1 status of your partners.
  - Ask your partners with HIV-1 if they are taking HIV-1 medicines and have an undetectable viral load. An undetectable viral load is when the amount of virus in the blood is too low to be measured in a lab test. To maintain an undetectable viral load, your partners must keep taking HIV-1 medicines every day. Your risk of getting HIV-1 is lower if your partners with HIV-1 are taking effective treatment.
  - Get tested for HIV-1 at least every 3 months or when your healthcare provider tells you.
  - Get tested for other STIs such as syphilis, chlamydia, and gonorrhea. These infections make it easier for HIV-1 to infect you.

- If you think you were exposed to HIV-1, tell your healthcare provider right away. They may want to do more tests to be sure you are still HIV-1 negative.
- Get information and support to help reduce sexual risk behaviors.
- Do not miss any doses of DESCOVY. Missing doses increases your risk of getting HIV-1 infection.

- If you do become HIV-1 positive, you need more medicine than DESCOVY alone to treat HIV-1. DESCOVY by itself is not a complete treatment for HIV-1.

If you have HIV-1 and take only DESCOVY, over time your HIV-1 may become harder to treat.

What is DESCOVY?

DESCOVY is a prescription medicine that may be used in two different ways. DESCOVY is used:

- to treat HIV-1 infection
  - in adults and children who weigh at least 77 pounds (35 kg) together with other HIV-1 medicines
  - in children who weigh at least 55 pounds (25 kg) and less than 77 pounds (35 kg) together with certain other HIV-1 medicines. Your healthcare provider will determine which other HIV-1 medicines may be used with DESCOVY.
- for HIV-1 PrEP to reduce the risk of getting HIV-1 infection in adults and adolescents who weigh at least 77 pounds (35 kg). It is not known if DESCOVY is effective in reducing the risk of getting HIV-1 from certain types of sex.
  - DESCOVY for PrEP is not for use in people born female (assigned female at birth) who are at risk of getting HIV-1 infection from vaginal sex, because its effectiveness has not been studied.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

DESCOVY contains the prescription medicines emtricitabine and tenofovir alafenamide.

It is not known if DESCOVY for treatment of HIV-1 infection is safe and effective in children who weigh less than 55 pounds (25 kg).

It is not known if DESCOVY is safe and effective in reducing the risk of HIV-1 infection in people who weigh less than 77 pounds (35 kg).

For people taking DESCOVY for HIV-1 PrEP:
Do not take DESCOVY for HIV-1 PrEP if:

- **you already have HIV-1 infection.** If you are HIV-1 positive, you need to take other medicines with DESCOVY to treat HIV-1. DESCOVY by itself is not a complete treatment for HIV-1.
- **you do not know your HIV-1 infection status.** You may already be HIV-1 positive. You need to take other HIV-1 medicines with DESCOVY to treat HIV-1 infection.

DESCOVY can only help reduce your risk of getting HIV-1 infection **before** you are infected.

What should I tell my healthcare provider before taking DESCOVY?

Before taking DESCOVY, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, including HBV infection
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if DESCOVY can harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with DESCOVY.

  Pregnancy Registry: There is a pregnancy registry for people who take DESCOVY during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed.
  - Do not breastfeed if you take DESCOVY for treatment of HIV-1 because of the risk of passing HIV-1 to your baby.
  - One of the ingredients in DESCOVY (emtricitabine) passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines may interact with DESCOVY. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with DESCOVY.
- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take DESCOVY with other medicines.

How should I take DESCOVY?

- Take DESCOVY exactly as your healthcare provider tells you to take it. If you take DESCOVY to treat HIV-1 infection, you need to take DESCOVY with other HIV-1 medicines. Your healthcare provider will tell you what medicines to take and how to take them.
- Take DESCOVY 1 time each day with or without food.
- Do not change your dose or stop taking DESCOVY without first talking with your healthcare provider. Stay under a healthcare provider's care when taking DESCOVY. Do not miss a dose of DESCOVY.
- If you take too much DESCOVY, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your DESCOVY supply starts to run low, get more from your healthcare provider or pharmacy.
  - If you are taking DESCOVY for treatment of HIV-1, the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to DESCOVY and become harder to treat.
  - If you are taking DESCOVY for HIV-1 PrEP, missing doses increases your risk of getting HIV-1 infection.

What are the possible side effects of DESCOVY?

DESCOVY may cause serious side effects, including:

- **See "What is the most important information I should know about DESCOVY?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking medicines to treat HIV-1 infection. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting your HIV-1 medicine.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and while taking DESCOVY. Your healthcare provider may tell you to stop taking DESCOVY if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effect of DESCOVY for treatment of HIV-1 is nausea.

The most common side effect of DESCOVY for HIV-1 PrEP is diarrhea.

These are not all the possible side effects of DESCOVY.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DESCOVY?

- Store DESCOVY between 68°F to 77°F (20°C to 25°C).
- Keep DESCOVY in its original container.
- Keep the container tightly closed.

Keep DESCOVY and all medicines out of reach of children.

General information about the safe and effective use of DESCOVY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DESCOVY for a condition for which it was not prescribed. Do not give DESCOVY to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about DESCOVY that is written for health professionals.

What are the ingredients in DESCOVY?

Active ingredients: emtricitabine and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

The tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

208215-GS-3

For more information, call 1-800-445-3235 or go to www.DESCOVY.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 10/2019

EXHIBIT 92

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Actor portrayal.

Co-pay Support

Clinical Trial

Safety Profile

INDICATION

DESCOVY® for HIV-1 pre-exposure prophylaxis (PrEP) is indicated in at-risk adults and adolescents (≥35 kg) to reduce the risk of sexually acquired HIV-1 infection, excluding individuals at risk from receptive vaginal sex. HIV-1–negative status must be confirmed immediately prior to initiation.

Limitation of Use: DESCOVY FOR PrEP™ is not indicated in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: RISK OF DRUG RESISTANCE WITH USE OF DESCOVY FOR PrEP IN UNDIAGNOSED EARLY HIV-1 INFECTION and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- DESCOVY FOR PrEP must be prescribed only to patients confirmed to be HIV negative immediately prior to initiation and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate if signs or symptoms of acute HIV-1 infection are present unless HIV-negative status is confirmed
- Severe acute exacerbations of hepatitis B have been reported in patients infected with hepatitis B virus (HBV) who discontinued products containing FTC and/or TDF and may occur with discontinuation of DESCOVY. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients with HBV who discontinue DESCOVY. If appropriate, anti-hepatitis B therapy may be warranted

Contraindication

- DESCOVY FOR PrEP is contraindicated in patients with unknown or positive HIV status

Warnings and precautions

- **Comprehensive management to reduce risks:**
  - Use DESCOVY FOR PrEP to reduce the risk of HIV-1 infection as part of a comprehensive strategy that includes adherence to daily dosing and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections (STIs)
  - **HIV-1 risk factors:** Behavioral, biological, or epidemiologic HIV-1 risk factors may include, but are not limited to: condomless sex, past or current STIs, self-identified HIV risk, having sexual partners of unknown HIV-1 viremic status, or sexual activity in a high-prevalence area or network
  - **Reduce STI risk:** Counsel on the use of STI prevention measures (e.g., consistent and correct condom use, knowledge of partner's HIV-1 viremic status, regular testing for STIs)
  - **Reduce potential for drug resistance:** Only prescribe DESCOVY FOR PrEP to patients confirmed to be HIV negative immediately prior to initiation, at least every 3 months while taking DESCOVY, and upon an STI diagnosis. HIV-1 resistance substitutions may emerge in patients with undetected HIV-1 infection who are taking only DESCOVY because DESCOVY alone is not a complete regimen for treating HIV-1
  - Some HIV tests may not detect acute HIV infection. Prior to initiating DESCOVY FOR PrEP, ask patients about potential recent exposure events. If recent (<1 month) exposures are reported or suspected, or symptoms of acute HIV infection (e.g., fever, fatigue, myalgia, skin rash) are present, confirm HIV-negative status with a test approved by the FDA for use in the diagnosis of acute HIV infection
  - If HIV-1 infection is suspected or if symptoms of acute infection are present while taking DESCOVY FOR PrEP, convert the DESCOVY FOR PrEP regimen to a complete HIV treatment regimen until HIV-negative status is confirmed by a test approved by the FDA for use in the diagnosis of acute HIV infection
  - **Counsel on adherence:** Counsel patients to strictly adhere to daily dosing, as efficacy is strongly correlated with adherence. Some patients, such as adolescents, may benefit from more frequent visits and counseling
- **New onset or worsening renal impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. Do not initiate DESCOVY in patients with estimated creatinine clearance (CrCl) <30 mL/min. Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue DESCOVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Monitor renal function in all patients (see Dosage and Administration section)
- **Lactic acidosis and severe hepatomegaly with steatosis:** Fatal cases have been reported with the use of nucleoside analogs, including FTC and TDF. Discontinue use if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity develop, including hepatomegaly and steatosis in the absence of marked transaminase elevations

Adverse reactions

- **Most common adverse reactions** (≥2%) in the DESCOVY FOR PrEP clinical trial were diarrhea, nausea, headache, fatigue, and abdominal pain

Drug interactions

- **Prescribing information:** Consult the full Prescribing Information for DESCOVY for more information, warnings, and potentially significant drug interactions, including clinical comments
- **Metabolism:** Drugs that inhibit P-gp can increase the concentrations of tenofovir alafenamide (TAF), a component of DESCOVY. Drugs that induce P-gp can decrease the concentrations of TAF, which may lead to loss of efficacy
- **Drugs affecting renal function:** Coadministration of DESCOVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC and tenofovir and the risk of adverse reactions

Dosage and administration

- **Dosage:** One tablet taken once daily with or without food
- **HIV screening:** Test for HIV-1 infection immediately prior to initiating, at least every 3 months during use, and upon diagnosis of an STI (see Warnings and Precautions section)
- **HBV screening:** Test for HBV infection prior to or when initiating DESCOVY
- **Renal impairment and monitoring:** Not recommended in patients with creatinine clearance (CrCl) <30 mL/min. Prior to or when initiating DESCOVY, and during use on a clinically appropriate schedule, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, assess serum phosphorus

Please see full Prescribing Information for **DESCOVY FOR PrEP**, including **BOXED WARNING**.

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Tap for Important Safety Information, including **BOXED WARNING**.