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Pre-Exposure Prophylaxis for the Prevention of HIV Infection: A Systematic Review for the U.S. Preventive Services Task Force

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Structured Abstract

Background: Effective prevention strategies for HIV infection are an important public health priority. A 2019 review for the US Preventive Services Task Force (USPSTF) found oral pre-exposure prophylaxis (PrEP) associated with decreased risk of HIV infection compared with placebo or no PrEP in adults at increased risk of HIV infection, although effectiveness decreases with inadequate adherence. Newer PrEP regimens, including an extended release injectable formulation, are available.

Purpose: To synthesize evidence for the USPSTF on effects of PrEP on risk of HIV acquisition, mortality, harms, and other clinical outcomes; and accuracy of methods for identifying potential candidates for PrEP.

Data Sources: We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, and Embase from January 2019 to May 16, 2022, carried forward relevant included studies from the prior report, and manually reviewed reference lists; surveillance for new literature was conducted through March 24, 2023.

Study Selection: Randomized, controlled trials on the benefits and harms of PrEP versus placebo/no PrEP in adults and adolescents without HIV infection at high risk of becoming infected; trials on the benefits and harms of newer versus older PrEP regimens; and studies on the diagnostic accuracy of instruments for predicting incident HIV infection.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): In populations at higher risk of acquiring HIV infection, 11 trials (all in the prior USPSTF review) found oral PrEP was associated with decreased risk of HIV infection versus placebo or no PrEP (N=18,172; relative risk [RR], 0.46 [95% confidence interval (CI), 0.33 to 0.66; I^2=67%; absolute risk difference [ARD], -2.0% [95% CI, -2.8% to -1.2%] after 4 months to 4 years). Effects were consistent across HIV risk categories and for PrEP with tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) or TDF alone. There was a strong association between higher adherence and greater efficacy (adherence ≥70%: 6 trials; RR, 0.27 [95% CI, 0.19 to 0.39]; I^2=0%; adherence >40% to <70%: 3 trials; RR, 0.51 [95% CI, 0.38 to 0.70]; I^2=0%; and adherence ≤40%: 2 trials; RR, 0.93 [95% CI, 0.72 to 1.20]; I^2=0%; p<0.00001 for interaction). All trials of oral PrEP versus placebo evaluated daily PrEP, except for one trial of event-driven PrEP (n=400; RR, 0.14 [95% CI, 0.03 to 0.63]). There was no difference between PrEP versus placebo/no PrEP in risk of serious adverse events (12 trials, N=18,292; RR, 0.93 [95% CI, 0.77 to 1.12]; I^2=56%), sexually transmitted diseases, or adverse pregnancy-related outcomes; PrEP was associated with a non-statistically significant increased risk of fracture (7 trials, N=15,241; RR, 1.23 [95% CI, 0.97 to 1.56]; I^2=0%). PrEP was associated with increased risk of renal adverse events (12 trials, N=18,170; RR, 1.43 [95% CI, 1.18 to 1.75]; I^2=0%; ARD, 0.56% [95% CI, 0.09% to 1.04%]) and gastrointestinal adverse events (12 trials, N=18,300; RR, 1.63 [95% CI, 1.26 to 2.11]; I^2=43%; ARD, 1.95% [95% CI, 0.48% to 3.43%]); most adverse events were mild and reversible. Two trials not included in the

2019 USPSTF review found the dapivirine vaginal ring associated with decreased risk of HIV infection versus placebo ring in African women at higher risk of HIV infection (2 trials, N=4,564; RR, 0.71 [95% CI, 0.57 to 0.89]; I^2=0%; ARD, -2.23%, 95% CI, -3.75% to -0.74% at 1.4 to 1.6 years). One new trial found daily oral tenofovir alafenamide (TAF)-FTC to be non-inferior to TDF-FTC in men who have sex with men (MSM; n=5,387; RR, 0.53 [95% CI, 0.23 to 1.26]); TAF-FTC was associated with positive short-term effects on bone mineral density versus TDF-FTC and negative effects on lipid parameters and weight gain (mean difference 1.2 kg), without differences in clinical adverse events. Long-acting injectable cabotegravir was associated with decreased risk of HIV infection versus oral TDF-FTC in one new trial of cisgender MSM and transgender women (n=4,490, RR, 0.33 [95% CI, 0.18 to 0.62]) and one new trial of women at higher risk of HIV infection (n=3,178, RR, 0.11 [95% CI, 0.04 to 0.31]). Cabotegravir was associated with increased risk of injection site reactions and weight gain (mean differences <1 kg).

Instruments for predicting incident HIV infection had moderate discrimination in MSM (5 studies, N=25,488; area under the receiver operating characteristic [AUROC] curve ranged from 0.60 to 0.73) and moderate to high discrimination general populations of HIV-uninfected persons (2 studies, N=5,477,291; AUROC, 0.77 [95% CI, 0.74 to 0.79] and 0.84 [95% CI, 0.80 to 0.89]). Evidence on the accuracy of instruments for predicting incident HIV infection in specific populations other than MSM was very limited.

Limitations: Restricted to English language; some pooled analyses with statistical heterogeneity or imprecise estimates; most trials evaluating risk of sexually transmitted infections were blinded to receipt of PrEP; most randomized trials were conducted in low-income settings, potentially limiting applicability to U.S. primary care; and evidence lacking in adolescents and pregnant women.

Conclusions: In adults at increased risk of HIV infection, oral PrEP with TDF or TDF-FTC is associated with decreased risk of HIV infection compared with placebo or no PrEP, although effectiveness decreases with inadequate adherence. TAF-FTC was non-inferior to TDF-FTC in MSM and long-acting injectable cabotegravir was associated with decreased risk of HIV infection versus TDF-FTC in MSM or transgender women and women at higher risk for HIV infection. Instruments for predicting risk of incident HIV infection have moderate discrimination in MSM and moderate to high discrimination in general populations of persons without HIV infection.

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Chapter 1. Introduction and Background

Purpose

Effective strategies to prevent HIV infection are an important public health priority. Pre-exposure prophylaxis (PrEP) involves use of antiretroviral medications on an ongoing basis (e.g., daily or bimonthly) or before and after HIV exposure events ("on-demand" or "event-driven" PrEP) to decrease the risk of acquiring HIV infection. This report will be used by the U.S. Preventive Services Task Force (USPSTF) to update its 2019 recommendation on PrEP for the prevention of HIV infection; at the time, this was a new topic for the USPSTF. In 2019, the USPSTF recommended that clinicians offer PrEP with effective antiretroviral medications to persons at high risk of HIV acquisition (**Grade A Recommendation**).[1] The recommendation was based on convincing evidence that PrEP is of substantial benefit in reducing the risk of HIV infection in persons at high risk of HIV acquisition and adequate evidence of small harms, resulting in high certainty of substantial net benefit. The USPSTF also found convincing evidence that the effectiveness of PrEP is highly correlated with adherence.

In October 2019, following the release of the USPSTF recommendation, the U.S. Food and Drug Administration (FDA) approved tenofovir alafenamide fumarate (TAF)-emtricitabine (FTC) for PrEP. Subsequently, the USPSTF commissioned a brief, focused update on TAF-FTC for PrEP, which found it to be noninferior to the standard PrEP regimen of tenofovir disoproxil fumarate (TDF)-FTC in reducing risk of HIV infection. In December 2021, extended-release cabotegravir was FDA-approved for PrEP in December 2021.

This report will update the 2019 USPSTF review on PrEP.[2] Like the prior review, it will synthesize evidence on benefits and harms of PrEP (including newer regimens), effects of adherence, and accuracy of methods for identifying potential candidates for PrEP. In addition, it will address utilization of PrEP, including potential disparities, as well as methods for reducing disparities.

Note: Studies on PrEP vary in precision when describing the distribution of gender identity and sex assigned at birth of study populations. In the absence of specific and detailed information on gender and sex (e.g., cisgender man, transgender man), we will use gender terminology (e.g., man, woman) rather than terminology commonly used to describe biological sex at birth (e.g., male, female, intersex). We recognize that information on gender reported in studies is often inferred or assumed based on anatomy or personal presentation and may not reflect some patients' self-identified gender. We also recognize that binary construction of gender fails to account for individuals who do not identify as men or women. We aim to accurately describe the gender composition of the studies underlying the included evidence to the extent possible, and to use gender-inclusive language where reporting clarity can be retained without gender identifiers. In this document, the terms man and woman generally refers to cis man and cis woman, though it is not always certain that other genders are excluded.

Condition Background

Condition Definition

HIV is a ribonucleic acid retrovirus that infects immune cells in humans—in particular, CD4+ T helper cells (referred to as CD4 count in this report). Untreated, HIV infection results in progressive immunodeficiency and AIDS in more than 90 percent of patients. AIDS is a potentially life-threatening condition that occurs when HIV becomes severe, as defined by a CD4 count of 200 cells/mm^3 or less or one or more AIDS-defining neoplastic conditions or opportunistic infections.[3] HIV-1 infection is the most common variant in the United States. HIV-2 infection is rare in the United States, less clinically severe, and endemic in parts of West Africa.[4]

Prevalence and Burden of Disease/Illness

Since the first cases of AIDS (Stage 3 HIV) were reported in 1981, more than 766,380 persons diagnosed with AIDS in the United States have died, and 1,307,283 persons have been diagnosed.[5] The Centers for Disease Control and Prevention (CDC) estimates that approximately 1.2 million persons in the United States were living with HIV infection in 2019,[6] including 13 percent who were unaware of their infection. This represents a decrease since 2008, when approximately 20 percent of infected persons were estimated to be unaware of their HIV infection status.[7-9] In 2019, 36,585 persons were newly diagnosed with HIV, a rate of 11.1 per 100,000 people; whereas in 2016 there were 39,552 new infections.[10] There were 16,232 deaths among adults and adolescents with HIV in the United States in 2019 from any cause; there were 16,372 deaths in 2016.[10] Although the CDC reported that the number of HIV diagnoses declined to 30,403 in 2020, it noted that data might be less reliable due to COVID-19 related disruptions to HIV testing, care-related services, and surveillance.[10]

Groups more affected by HIV infection in the United States include men who have sex with men (MSM) and Black and Hispanic/Latinx persons. Between 2006 and 2009, there was a 21 percent increase in HIV incidence among persons ages 13 to 29 years, driven largely by a 34 percent increase among MSM, the only risk group to experience a significant increase in incidence during this period ($p<0.001$).[11] In 2019, of total HIV diagnoses, 29,589 (81%) were among adult and adolescent men (age 13 years or older), 6,939 (19%) were among adult and adolescent women, and 57 (0.1%) were among children younger than age 13 years.[10] Among adolescents, the incidence of HIV infection rose sharply from ages 13 to 14 years (0.2 cases per 100,000 persons) to ages 15 to 19 years (7.8 cases per 100,000 persons). In 2019, the highest rates (per 100,000 persons) by age group were 27.5 among persons 20 to 24 years of age, 31.4 among those 25 to 29 years of age, and 25.3 among those 30 to 34 years of age. By race/ethnicity, 42 percent of new diagnoses occurred among Black persons, 25 percent among White persons, and 27 percent among Hispanic/Latinx persons. Among men, having sex with men is the most common transmission method (81%), followed by heterosexual contact (9.1%), injection drug use (4.7%), and having sex with men and injection drug use together (5.1%). Among women, heterosexual contact is the most common transmission method (83%), followed by injection drug use (17%).[10] Among transgender women, the prevalence of HIV is 62 percent in Black

transgender women, 35 percent in Hispanic/Latinx transgender women, and 17 percent in White transgender women.[12]

Etiology and Natural History

HIV infection is acquired through mucosal or intravenous exposure to infected bodily fluids such as blood, semen, and genital tract secretions. The presence of sexually transmitted infections (STIs) increases risk, as do certain sexual behaviors (e.g., penile-anal or penile-vaginal intercourse without a condom, sex with multiple partners, sex with persons with HIV with a detectable viral load[13] or at high risk of HIV infection), and high viral load in the infected partner.[14,15] In persons who inject drugs (PWID), factors associated with HIV infection include increased frequency or duration of injection behaviors and certain drug use behaviors (e.g., sharing needles or backloading [injecting drugs from one syringe into the back of another opened syringe]).[16]

The primary HIV infection syndrome usually develops 2 to 4 weeks following initial exposure to HIV.[17] Acute infection is often associated with a clinical syndrome resembling infectious mononucleosis.[18,19] Very early after acute infection, there is rapid virus production that then declines to a set point (the set point varies between individuals) as the host immune system responds, although continuous rapid virus production and clearance occurs at all stages of infection.[20-25]

Although a small proportion of untreated persons with HIV remain asymptomatic and show little evidence of progressive immune suppression after 10 or more years of infection, more than 90 percent of untreated patients eventually develop AIDS.[3] In the era before highly active antiretroviral therapy (HAART) was available, the median time from seroconversion to the development of AIDS was 7.7 to 11.0 years, and median survival was 7.5 to 12 years.[26,27]

The primary mechanism through which chronic HIV infection causes immune deficiency is through a decrease in the level and functioning of CD4 cells. In untreated HIV infection, the CD4 count declines an average of 50 to 75 cells/mm^3 per year.[28] Most patients with CD4 counts over 200 cells/mm^3 are either asymptomatic or have mild disease,[29] although data indicate an increased risk of AIDS or death even in patients with CD4 counts over 500 cells/mm^3.[30] Patients with CD4 counts less than 200 cells/mm^3 have advanced immunodeficiency and are at markedly increased risk of AIDS-related opportunistic infections, other AIDS-related complications, and AIDS-associated mortality.[31-33]

A higher HIV viral load is a strong independent predictor of more rapid progression to AIDS.[31-36] Other predictors of more rapid progression include older age at the time of infection,[26,27,31,32,35,37,38] more severe symptoms at the time of primary HIV infection,[39] and other clinical and genetic factors. A factor associated with slower progression is the cysteine-cysteine chemokine receptor 5 delta32 genotype.[40-44]

Risk Factors

Persons at increased risk of HIV infection include MSM; men and women who have condomless

vaginal or anal intercourse with more than one partner; men and women who exchange sex for drugs or money; persons with a history of or current injection drug use; persons with or seeking treatment for other STIs; persons with a history of blood transfusion between 1978 and 1985; persons whose past or current sexual partners are infected with HIV with a detectable viral load,[13] bisexual, or PWID; transgender persons; and persons who do not report one of these risk factors but who request HIV testing.[45-47] Settings in which the prevalence of HIV infection is often more than 1 percent include STI clinics, correctional facilities, homeless shelters, tuberculosis clinics, clinics specialized in the care of sexual and gender minorities, and clinics caring for an adolescent community with a high prevalence of STIs.[48]

Rationale for Preventive Strategies

HIV infection remains incurable, requiring lifelong treatment, and can have important health consequences. Therefore, preventing HIV infection is an important public health and clinical priority. In the absence of an effective vaccine, HIV prevention strategies include screening, as recommended by the USPSTF[49] and others, to identify infected persons; treatment with antiretroviral therapy (ART) in persons with HIV to reduce risk of transmission[50]; and behavioral counseling to reduce high-risk sexual and drug use behaviors.

For persons at increased risk of HIV infection who are not infected, PrEP with antiretroviral medications[51-55] in combination with risk behavior counseling is another prevention strategy to reduce risk of acquiring HIV infection.[56] PrEP involves use of antiretroviral medications on an ongoing, regular (e.g., daily) basis or before and after HIV exposure events to lower the likelihood of acquiring HIV infection. PrEP differs from nonoccupational postexposure prophylaxis, which involves use of antiretroviral medications for 28 days *after* a single high-risk exposure.[57] Expanded use of PrEP has been highlighted as a critical component in the national initiative to end the HIV epidemic in the United States.[58]

Interventions/Treatment

The standard antiretroviral regimen for PrEP has been a daily oral fixed-dose combination of the nucleoside reverse transciptase inhibitors TDF (a prodrug of tenofovir) and FTC. This combination was selected because of its effectiveness as part of antiretroviral treatment for HIV infection, favorable safety profile, relatively high genetic barrier to resistance, and achievement of high concentrations in rectal tissue (TDF) and female genital tissue (FTC).[59] In 2012, the FDA approved daily oral TDF-FTC for PrEP in adults at risk of sexual acquisition of HIV-1 infection.[60] In 2018, the FDA expanded the indication for PrEP to include adolescents weighing at least 35 kg (77 lb).[61] Oral daily TDF without FTC has also been evaluated for PrEP, but is not FDA-approved for this indication. As described above, FDA approved TAF-FTC for PrEP in adolescents and adults weighing at least 35 kg in 2019 to reduce risk of sexually acquired HIV-1 infection, excluding those at risk of acquiring HIV through receptive vaginal sex, due to the lack of clinical data in this population.[62] Like TDF, TAF is a prodrug of tenofovir, a nucleoside reverse transcriptase inhibitor of HIV. However, TAF is transported into peripheral blood mononuclear cells (the target of HIV) more rapidly than TDF and achieves higher and more sustained intracellular drug levels at lower tenofovir serum levels.[63] Higher intracellular levels of tenofovir could result in increased effectiveness and lower serum levels could result in increased

safety, including reduction in known negative effects of tenofovir on kidney function and bone mineral density.

Because effectiveness of PrEP depends on adherence,[2,64] there has been interest in nondaily oral regimens that may enhance adherence while maintaining effectiveness of PrEP,[65] as well as other approaches to enhance adherence. Alternative regimens include event-driven[66] (taken before and after an anticipated HIV exposure event; also referred to as "on-demand" or "2-1-1" PrEP) or intermittent (scheduled, nondaily) dosing of oral PrEP.[67,68] Studies have also evaluated alternative, nonoral modes of PrEP that require infrequent dosing (e.g., long-acting injectables[69-71] or an intravaginal ring[72-74]). As mentioned earlier, on December 20, 2021, cabotegravir was FDA-approved in adults and adolescents >35 kg[75] for PrEP to reduce risk of sexually acquired HIV infection. In the trials conducted to obtain FDA approval, cabotegravir was initiated with a daily oral lead-in for up to five weeks, followed by monthly injections for two months, and then bimonthly injections. The oral lead-in was designed to assess tolerability; given the high tolerability observed in the trials, the FDA-approved label considers the oral lead-in to be optional.

Factors that may affect the balance of benefits and harms in persons prescribed PrEP include adverse drug-related events, the potential for antiretroviral resistance in persons who acquire HIV while taking PrEP, and the potential for behavioral risk compensation. Behavioral risk compensation refers to an increase in behaviors associated with HIV transmission (e.g., sex without a condom or multiple sexual partners). Because PrEP does not protect against STIs such as syphilis, chlamydia, and gonorrhea, behavioral risk compensation could increase the rate of STIs, a potential harm that could attenuate benefits from preventing HIV acquisition, or result in unintended pregnancy. Another potential harm is that PrEP could induce antiretroviral resistance in persons with HIV who inadvertently receive PrEP or in HIV-uninfected persons who acquire infection while on PrEP. With long-acting injectables such as cabotegravir, an extended pharmacokinetic tail (persistence of the drug at slowly declining levels) following administration poses a risk for selection of resistance in persons who are not adherent.[76] Adverse effects of TDF include negative effects on bone density and kidney function.[77-79] A potential advantage of TAF over TDF is that it achieves higher and more sustained intracellular drug levels at lower tenofovir serum levels, which could reduce negative impacts on kidney function and bone health.[63] The dapivirine vaginal ring is inserted monthly, may enhance autonomy in use of PrEP, and results in little systemic absorption, potentially increasing safety during pregnancy. However, data indicate lower efficacy than standard oral PrEP regimens.[80] Among transgender persons, potential issues related to use of PrEP include concerns that PrEP could negatively affect hormone therapy, or that hormones might decrease the efficacy of PrEP.[81]

Current Clinical Practice/Recommendations of Other Groups

In 2014, the United States Public Health Service issued a guideline[82] recommending PrEP with TDF-FTC in adults at high risk of infection, including MSM with a high number of sexual partners or inconsistent condom use, MSM and heterosexual persons in HIV-serodiscordant relationships, other high-risk heterosexual persons, and PWID who have an HIV positive partner or share injection equipment; the guideline was updated in 2017[83] and in 2021.[84] Required elements for PrEP include documentation of a negative HIV test prior to initiating PrEP, ongoing

adherence and behavioral risk reduction support, and periodic (every 6 months) screening for STIs. Criteria from the 2021 guideline for PrEP were revised and simplified in persons at risk due to sexual exposure to include those who have had anal or vaginal sex in the past 6 months and: 1) an HIV-positive sexual partner (particularly if the partner has an unknown or detectable viral load); 2) bacterial sexually transmitted infection in the last 6 months; or 3) inconsistent or no condom use with sexual partners(s) of unknown HIV status (**Table 1**). PrEP is also recommended in those who do not meet these criteria, but request it, due to potential undisclosed risk. Changes in the 2021 guideline[84] include recommendations for PrEP in adolescents weighing at least 35 kg; TAF-FTC as an option for men and transgender women at sexual risk; a recommendation and guidance for use of cabotegravir when FDA-approved (it was approved shortly after guideline publication[75]); and guidance on PrEP by telehealth, same-day PrEP initiation, and off-label use of TDF/FTC to MSM using an on-demand ("2-1-1") regimen. Unlike the prior guidelines, TDF alone is no longer a recommended option for PrEP. The guideline recommends that providers offer PrEP with TDF-FTC to women seeking to conceive and pregnant or breastfeeding persons whose sexual partner has HIV, especially when their current partner's viral load is unknown or detectable. FDA labeling information and perinatal antiretroviral treatment guidelines permit use of TDF-FTC (as well as TAF-FTC) during pregnancy, with data indicating no increased risk of adverse effects among fetuses exposed to these medications when used as PrEP or for HIV treatment. The guideline notes that evidence on safety of PrEP with TDF-FTC or TAF-FTC in breastfeeding infants is lacking, though data indicate limited exposure via breast milk. Data on safety of cabotegravir in pregnancy or while breastfeeding are lacking;[85] data suggest a possible association between fetal exposure to dolutegravir (a medication in the same integrase strand inhibitor class as cabotegravir) and small increase in risk of neural tube defects.[86]

The International Antiviral Society-USA also recommends PrEP in adults and adolescents at risk for HIV infection (**Table 1**).[87] Daily TDF-FTC is recommended for oral PrEP, with on-demand TDF-FTC an option for MSM and TAF-FTC for MSM at risk for kidney dysfunction, osteoporosis, or osteopenia. The society recommends injectable cabotegravir for cisgender men and transgender women who have sex with men contingent on FDA approval.[75] The guideline does not address cabotegravir for cisgender women, as the trial in which cabotegravir was evaluated in this population had not yet been published.[88]

The World Health Organization (WHO) recommends oral PrEP containing TDF for people at substantial risk of HIV infection.[89] "Substantial risk" was provisionally defined as HIV incidence around 3 per 100 person-years or higher in the absence of PrEP, including some groups of MSM, transgender women in many settings, and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection (**Table 1**). WHO now also recommends the dapivirine vaginal ring as an option for women at substantial risk of HIV infection.[80] However, the dapivirine ring is not approved by the Food and Drug Administration for any indication and has been withdrawn by its manufacturer from FDA review, due to the manufacturer's assessment of a low likelihood of obtaining approval.[90] The WHO has issued an implementation tool for PrEP.[91]

Recent data indicate that implementation of PrEP in the United States has increased,[92] but remains limited.[93] In 2019, the CDC estimated that approximately 285,000 of 1.2 million eligible

individuals for PrEP (or 23%) received it, an increase from about 20 percent in 2015.[94] A number of clinician and patient barriers to wider use of PrEP have been identified, including lack of knowledge/awareness of PrEP (particularly among primary care providers),[95-98] perception of HIV risk, stigma, distrust of healthcare providers and systems, access to PrEP and costs, and concerns about harms.[99,100] Even among academic primary care providers with high awareness of PrEP, one 2015 survey found that only a minority (approximately one-third) had adopted it.[101] An analysis of a large commercial insurance database found that primary care physicians prescribed 79 percent of PrEP while infectious disease physicians prescribed 7 percent; however, the majority of prescribing physicians provided HIV care (primary care or infectious disease).[92]

Under the Affordable Care Act, U.S. health plans are required to cover USPSTF "A" and "B" recommendations without cost sharing starting one year from the issue date of the recommendation (June 30, 2020),[102] potentially increasing utilization and uptake by removing a financial barrier. However, data on PrEP utilization following the 2019 USPSTF recommendation are not yet available.

Disparities

Significant disparities have been reported around use of PrEP. Although Black persons are estimated to account for approximately 40 percent of persons in the U.S. with indications for PrEP, data indicate that in 2019, the number of White persons prescribed PrEP was approximately five times higher than the number of Black persons.[103] In 2019, CDC estimated PrEP coverage (the proportion eligible that received PrEP) at 7.9 percent in Black persons and 13.8 percent in Hispanic/Latinx persons, compared with 60.5 percent among White persons. Other factors associated with decreased utilization of PrEP include younger age, being women, substance use disorder, and being uninsured.[103,104] Similar patterns were observed in 2020 and 2021; however, 2020 data were considered less reliable due to COVID-19 related disruptions and 2021 data were considered preliminary.[103] Although the incidence of HIV infection is particularly high among Black and Hispanic/Latino adolescent and young adult MSM, data indicate low awareness and uptake of PrEP in this population.[105] Utilization of PrEP also appears low in transgender persons; one study based on a national probability sample found that 3 percent of transgender persons at risk for HIV infection reported currently taking PrEP, despite most (72%) reporting favorable attitudes towards PrEP.[106] In populations with less utilization of PrEP, some evidence indicates that disparities may be related to both decreased likelihood of PrEP initiation as well as increased likelihood of discontinuation among those who initiate.[107]

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[108] the USPSTF and the Agency for Healthcare Research and Quality determined the scope and Key Questions for this review. Investigators created an analytic framework with the Key Questions and the patient populations, interventions, and outcomes reviewed (**Figure 1**). Key informants were engaged for input, the draft research plan was posted for public comment, and comments were addressed before finalization.

Key Questions

1. What are the benefits of PrEP in persons without pre-existing HIV infection vs. placebo or no PrEP (including deferred PrEP) on the prevention of HIV infection and quality of life?
    a. How do the benefits of PrEP differ by populations of interest (e.g., defined by age, sex, gender identity, race and ethnicity, and HIV risk category)?
    b. How do the benefits of PrEP differ by dosing strategy or regimen?
2. What are the benefits of newer PrEP regimens (oral TAF-FTC, injectable cabotegravir, or the dapivirine vaginal ring) vs. TDF-FTC?
3. What is the diagnostic accuracy of provider or patient risk assessment tools in identifying persons at increased risk of HIV acquisition who are candidates for PrEP?
4. What are the harms of PrEP vs. placebo or no PrEP when used for the prevention of HIV infection?
5. What are the harms of newer PrEP regimens (oral TAF-FTC, injectable cabotegravir, or the dapivirine vaginal ring) vs. TDF-FTC?

Contextual Questions

Six Contextual Questions were also requested by the USPSTF to help inform the report. Contextual Questions are not reviewed using systematic review methodology.

1. What are rates of adherence to and persistence of PrEP and factors associated with increased or decreased adherence in U.S. primary care settings?
2. How does adherence to and persistence of PrEP vary according to mode of administration (e.g., oral, injectable, or vaginal ring)?
3. What is the risk of infection with antiretroviral drug–resistant HIV in persons using PrEP, and what is the effect of infection with PrEP-related, antiretroviral drug–resistant HIV on treatment outcomes?
4. What factors (e.g., race and ethnicity, age, sex, gender, sexual orientation, HIV risk category, socioeconomic status, cultural factors, educational attainment, or health literacy) are associated with disparities in utilization of PrEP?
5. What is the effectiveness of primary care interventions to increase utilization of PrEP and decrease disparities in utilization?
6. What is the effectiveness of PrEP delivered using telehealth vs. office-based PrEP?

Search Strategies

We searched MEDLINE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Embase starting in January 2018 (the prior report searches went through June 2018, with surveillance through January 2019) to May 16, 2022, and carried forward the relevant included studies from the prior report. We also reviewed reference lists of relevant articles. Search strategies are available in **Appendix A1**. Additional surveillance for new literature was conducted through March 24, 2023, and no new eligible trials were found.

Study Selection

All titles and abstracts identified through searches were independently reviewed by two members of the research team for eligibility against predefined inclusion and exclusion criteria, as specified using the PICOTS (population, intervention, comparator, outcome, timing, study design) framework (**Appendix A2**). Studies marked for possible inclusion by any reviewer underwent full-text review. All results were tracked in an EndNote® database (Thomson Reuters, New York, NY). We excluded non-English–language articles and studies published only as conference abstracts. In accordance with the USPSTF Procedure Manual,[108] studies assessed as poor quality were excluded.

Each full-text article was independently reviewed by two members of the research team for inclusion or exclusion on the basis of the eligibility criteria. If the reviewers disagreed, conflicts were resolved by discussion and consensus or by consulting another member of the review team. Results of the full-text review were also tracked in the EndNote database, including the reason for exclusion for full-text publications. The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists the included studies, and **Appendix A5** lists the excluded studies with reasons for exclusion.

Scope of Review

The population of interest for PrEP was HIV-uninfected persons at higher risk of HIV acquisition. The review addresses evidence on PrEP in adults, including pregnant persons without HIV and persons without HIV seeking to become pregnant with a partner with HIV, as well as adolescents (defined as persons 13 to <18 years of age). Patient populations of interest were based on demographic characteristics (age, sex, gender identity, race and ethnicity, and pregnancy status) and HIV risk category (MSM, PWID, or persons at risk due to heterosexual contact). For the Key Question on risk assessment, we included studies on the diagnostic accuracy of provider or patient assessment instruments to predict HIV acquisition, for identification of potential candidates for PrEP.

The PrEP interventions addressed in this report were oral daily TDF-FTC, the first FDA-approved PrEP regimen and the more recently FDA-approved regimen of oral daily TAF-FTC. Oral TDF monotherapy was also included, even though it is not approved by the FDA for PrEP, since it has been evaluated in several randomized trials and a large trial found no clear difference

between TDF and TDF-FTC in effects on risk of HIV acquisition.[51] Although oral TDF monotherapy was noted as an option for PrEP in PWID and heterosexual men and women in the 2017 United States Public Health Service guideline[82] and the 2019 USPSTF recommendation,[1] it is no longer[84] a recommended option. Therefore, sensitivity analyses will be conducted without TDF monotherapy. We also included injectable cabotegravir for PrEP, given the publication of recent randomized trials and inclusion in recent guidelines;[84,87,109] on 12/20/21, injectable cabotegravir was approved by the FDA for PrEP.[75] We also evaluated alternative (non-daily) oral dosing schedules (e.g., event-driven [on-demand][66] or intermittent dosing[67,68]), which are not approved by the FDA but have been evaluated in randomized, controlled trials (RCTs) and adopted in some settings and recommended in the updated United States Public Health Service guideline as an option for MSM.[84] We stratified analyses according to the regimen used as well as the dosing regimen (daily or event-driven/intermittent). We also included the dapivirine vaginal ring, even though it is not currently FDA-approved for any indication (and has been withdrawn from FDA review), because it is recommended by the WHO as an option for PrEP in women at increased risk and is being studied in a randomized trial of PrEP during pregnancy.[73,74,80,110-112] We did not include other PrEP regimens (e.g., oral maraviroc,[113-115] tenofovir vaginal gel,[54,116,117] or injectable rilpivirine) because they are not approved by the FDA, have limited evidence of effectiveness or evidence of low effectiveness, and are not recommended in clinical practice guidelines. The main comparisons were PrEP versus placebo or delayed PrEP.[118] Because newer PrEP regimens have only been compared against TDF-FTC, we added new Key Questions assessing benefits and harms with this comparison. To address effects of dosing method on effectiveness, we also included randomized trials of daily versus nondaily (intermittent or event-driven) PrEP.

The primary outcome was the rate of HIV infection; other outcomes were mortality, quality of life, and harms, including rates of non-HIV STIs (gonorrhea, syphilis, chlamydia, herpes simplex virus [HSV] infection, or any STI), hepatitis B and C virus infection, renal insufficiency, fractures, gastrointestinal adverse events, and pregnancy-related outcomes. HSV infection was addressed as a potential harm because of possible effects of behavioral risk compensation, although tenofovir may have antiviral effects that decrease risk of HSV transmission.[119,120] Although the report focuses on effects of PrEP on health outcomes, for comparing newer versus older PrEP regimens effects on weight gain and lipid profiles were also addressed, given some data suggesting potential differences.[121]

We included randomized trials of PrEP versus placebo or no PrEP and randomized trials of newer PrEP regimens versus TDF-FTC. For evaluation of risk assessment instruments, we included studies assessing predictive utility.

Because the association between adherence and effectiveness of PrEP has been well established, we removed a Key Question from the 2019 review addressing this question. We included Contextual Questions on adherence to PrEP and factors associated with increased or decreased adherence in U.S. primary care practices in order to help assess current implementation of PrEP. Methods for measuring adherence include patient diaries and self-report, pill counts, adherence monitoring devices, drug levels (e.g., plasma, dried blood spots, or urine levels), and prescription fill data. In addition to adherence (taking PrEP as instructed) we also evaluated factors associated with PrEP persistence (continuation). We retained a Contextual Question on the association

between use of PrEP and presence of antiretroviral drug resistance, as well as effects of infection with antiretroviral drug–resistant HIV infection on clinical outcomes, given that this was identified as an evidence gap in the prior review. Like the prior review, this was not addressed as a Key Question because antiretroviral resistance due to PrEP appears to be uncommon, effects of antiretroviral resistance on clinical outcomes depend on a variety of factors (e.g., type of resistance mutation, availability of alternative antiviral regimens, and adherence to alternative regimens), and evidence on effects of PrEP-selected resistance on clinical outcomes appears to be very limited.[122] We added new Contextual Questions on disparities in utilization of PrEP and interventions to increase utilization (including same-day initiation) and reduce disparities. In the context of the COVID-19 era and to potentially facilitate implementation of PrEP, we also added a new Contextual Question on effectiveness of telehealth-delivered PrEP versus standard office-based PrEP.

Contextual Questions were addressed through targeted literature searches to identify key articles to inform the USPSTF. Contextual Questions on adherence and utilization focused on randomized trials of PrEP and large implementation studies, surveys, and other observational studies conducted in the United States. For antiretroviral resistance, we used randomized trials of PrEP and open-label extensions of the trials. For interventions to increase PrEP utilization and PrEP by telehealth, we used randomized trials and comparative observational studies relevant to U.S. primary care settings.

Data Abstraction and Quality Rating

For studies meeting inclusion criteria, we updated data abstraction forms from the prior USPSTF review to summarize characteristics of study populations, interventions, comparators, adherence, and methods for assessing adherence, outcomes, study designs, settings, and methods. One investigator conducted data abstraction, which was reviewed for completeness and accuracy by another team member.

Predefined criteria were used to assess the quality of individual controlled trials, systematic reviews, and observational studies by using criteria developed by the USPSTF; studies were rated as "good," "fair," or "poor" based on the seriousness of methodological shortcomings (**Appendix A6**). We evaluated the credibility of subgroup analyses based on whether the subgroups were predefined, whether subgroup characteristics were measured at baseline, whether the analyses were across or within studies, whether within-study comparisons were randomized, whether statistical tests for interaction were significant, the precision of estimates, the consistency of subgroup effects across studies, and whether results were biologically plausible.[123]

For each study, quality assessment was performed by two team members. Disagreements were resolved by consensus.

Data Synthesis and Analysis

Meta-analyses were updated and new meta-analyses were conducted for outcomes and comparisons for which there were multiple studies homogeneous enough to provide a meaningful combined estimate. The appropriateness of meta-analyses was based on the quality and number of studies and similarity between studies in design, patient population, interventions, and outcomes. Due to anticipated statistical heterogeneity, meta-analyses to calculate risk ratios for effects of PrEP on HIV infection, mortality, and harms were conducted using the DerSimonian and Laird random-effects model. Statistical heterogeneity was assessed using the I^2 statistic.[124] When the I^2 was greater than 30 percent, sensitivity analysis was performed with the profile likelihood method, as the DerSimonian and Laird model can result in overly narrow confidence intervals (CIs) in this situation.[125] We conducted sensitivity and stratified analyses based on study quality, PrEP drug regimen, HIV risk category (MSM, PWID, and men and women at increased risk via heterosexual contact), dosing schedule (daily or event-driven/intermittent), study duration (<1 year, ≥1 to <2 years, or ≥2 years), and country (United States and other high-income countries or low-/middle-income countries and international studies). We also conducted sensitivity analyses using data from the FDA medical review of PrEP on HIV incidence and fracture rates in place of data reported in journal articles for these outcomes.[126] For analyses with at least 10 trials, we constructed funnel plots and performed the Egger test to detect small sample effects (a marker for potential publication bias).[127]

Qualitative data was summarized in summary tables providing estimate ranges, descriptive analysis, and interpretation of results. Assessments of applicability were based on the countries in which studies were performed, the demographic characteristics of the patients enrolled, the PrEP interventions used, and rates of HIV acquisition, adherence, and use of postexposure prophylaxis.

For all Key Questions, the overall quality of evidence was determined using the approach described in the USPSTF Procedure Manual.[108] Evidence was rated "good," "fair," or "poor" based on the number, quality and size of studies, consistency of results between studies, and directness of evidence.[108]

USPSTF and AHRQ Involvement

The authors worked with USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and key questions and to resolve issues around scope for the final evidence synthesis.

AHRQ staff provided oversight for the project, coordinated the systematic review, reviewed the draft report, and assisted in an external review of the draft evidence synthesis.

Expert Review and Public Comment

The draft Research Plan was posted for public comment on the USPSTF website from November 4, 2021, to December 8, 2021. The Research Plan underwent minor revisions to improve clarity. In addition, hepatitis B was added as an outcome, "persistence" was added to Contextual Questions 1 and 2, and Contextual Question 5 was expanded to address primary care interventions to increase utilization of PrEP in general, in addition to addressing interventions to decrease disparities in utilization.

A draft version of this report was reviewed by content experts and Federal representatives (**Appendix A7**), and minor edits were made for clarity and language/terminology regarding gender. In addition, the draft was posted for public comment from 12/13/22 to 1/17/23. The comments were reviewed and minor edits were made to improve clarity, but no changes to the studies or conclusions were required.

Chapter 3. Results

A total of 2,576 new references from electronic database searches, manual searches of recently published studies, and prior report references were reviewed, and 208 full-text papers were evaluated for inclusion. Across all KQs, 32 studies (reported in 61 publications) were included (20 RCTs [N=36,575] and 12 diagnostic accuracy studies [N=5,544,500]).[51-55,66-68,70,73,74,88,118,120,121,128-173] Fourteen RCTs[51-55,66-68,118,120,128,130,133-139,141,146-150,152-154,156-161,168,170,172,173] and 7 diagnostic accuracy studies[131,140,142,145,155,166,167] (in 45 publications) were carried forward from the 2019 USPSTF review; six RCTs[70,73,74,88,121,144,162,163] (including 2 RCTs of dapivirine[73,74]) and 5 diagnostic accuracy studies[143,151,164,165,171] were new, and 3 new publications reported additional outcome or analyses for previously included trials[129,132,169] (in 16 publications). Included studies and quality ratings are described in **Appendix B**.

Key Question 1. What Are the Benefits of PrEP in Persons Without Pre-Existing HIV Infection vs. Placebo or No PrEP (Including Deferred PrEP) on the Prevention of HIV Infection and Quality of Life?

Summary

Oral PrEP vs. Placebo or No PrEP

- Oral PrEP with TDF-FTC or TDF was associated with decreased risk of HIV infection versus placebo or no PrEP in populations at higher risk of acquiring HIV (11 trials, N=18,172; relative risk [RR], 0.46 [95% CI, 0.33 to 0.66], I^2=67%; absolute risk reduction [ARR], -2.0% [95% CI, -2.8 to -1.2%] after 4 months to 4 years).[51-55,66,67,118,137,170,172]
- There was a strong association between degree of adherence and oral PrEP effectiveness (p<0.00001 for interaction)
  - Adherence ≥70%: 6 trials; RR, 0.27 [95% CI, 0.19 to 0.39]; I^2=0%[51,52,66,67,118,170]
  - Adherence >40% to <70%: 3 trials; RR, 0.51 [95% CI, 0.38 to 0.70]; I^2=0%[53,55,137]
  - Adherence ≤40%: 2 trials; RR, 0.93 [95% CI, 0.72 to 1.20]; I^2=0%[54,172]
- Oral PrEP with TDF-FTC or TDF alone was consistently associated with decreased risk of HIV infection versus placebo when trials were stratified according to HIV risk category, study duration, setting (high- or low-income), and study quality, and in subgroup analyses based on age[51,53,137,172] and gender.[51,53,170]
- Effects of oral PrEP versus placebo or no PrEP on risk of HIV infection were similar with TDF alone (RR, 0.49 [95% CI, 0.28 to 0.84]; I^2=58%) and TDF-FTC (RR, 0.44 [95% CI, 0.27 to 0.72]; I^2=74%); all trials evaluated daily PrEP, with the exception of one trial[66] of event-driven PrEP in MSM (RR, 0.14 [95% CI, 0.03 to 0.63]).
- Oral PrEP with TDF-FTC or FTC was associated with a statistically nonsignificant reduced risk of mortality versus no PrEP or placebo (9 trials; RR, 0.81 [95% CI, 0.59 to 1.11]; I^2=0%).[51-55,118,137,170,172]

- No trial reported the association between oral PrEP versus placebo or no PrEP and quality of life.

Dapivirine Vaginal Ring vs. Placebo Ring

- The dapivirine vaginal ring was associated with decreased risk of HIV infection versus placebo ring in African women at increased risk of HIV infection (2 trials, N=4,564; RR 0.71 [95% CI, 0.57 to 0.89], I^2=0%; ARR -2.23% [95% CI -3.75% to -0.74%] at 1.4 to 1.6 years).[73,74]

Evidence

Oral PrEP vs. Placebo or No PrEP

Twelve RCTs, all included in the prior USPSTF report, evaluated PrEP versus placebo or no PrEP (**Table 2; Appendix B Tables 1–3**). The trials were reported in 32 publications; 29[51-55,66-68,118,128,133,134,137,139,146,148-150,152,153,156-159,161,168,170,172,173] were included in the prior report, and three publications were added[129,132,169] for this update. The prior USPSTF review reported efficacy data for HIV infection from all trials; both publications added for this update were secondary publications reporting an additional outcome or analysis from IPERGAY,[66] a previously included trial.

Of the 12 trials of oral PrEP, two[67,68] enrolled 72 patients each; in the other 10 trials, the sample sizes ranged from 400 to 4,726 (total N=18,244). Duration of followup ranged from 4 months to 4 years. Eleven trials randomized patients to PrEP or placebo. The other open-label trial randomized patients to immediate versus delayed PrEP (no PrEP for 1 year, after which patients received PrEP).[118] Six trials[51,54,55,68,170,172] enrolled men and women at increased risk of HIV infection due to heterosexual contact, four trials[52,66,118,137] enrolled MSM or transgender women, one trial[67] enrolled both MSM and high-risk women, and one trial[53] enrolled PWID. The mean age in all trials was younger than age 40 years. No trial enrolled pregnant women or persons younger than age 18 years.

Three trials[52,53,55] evaluated TDF 300 mg, six trials[66-68,137,170,172] evaluated TDF 300 mg-FTC 200 mg, one trial[118] evaluated TDF 245 mg-FTC 200 mg, and two trials[51,54] evaluated both TDF 300 mg alone and TDF 300 mg-FTC 200 mg. PrEP was prescribed daily in 11 trials[51-55,67,68,118,137,170,172] and dosing was intermittent or event-driven in three trials (two of which also included daily dosing arms).[66-68] In one trial (the Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs [IPERGAY] trial), event-driven PrEP consisted of two tablets of TDF-FTC 2 to 24 hours before intercourse, followed by one tablet 24 hours and 48 hours after the first dose; additional dosing parameters were provided for multiple consecutive sexual encounters and situations in which event-driven PrEP had been taken within 1 week.[66] Two other trials evaluated intermittent/event-driven PrEP (consisting of PrEP twice weekly and within 2 hours of intercourse) but either reported no HIV infections or combined results with patients randomized to daily PrEP.[67,68] In all trials, HIV risk reduction and adherence counseling was

provided to all patients. Free condoms were provided in all trials except for one, in which condom provision was not specified.[118]

Seven trials were conducted in Africa,[51,54,55,67,68,170,172] one in Thailand,[53] two in Europe or Canada,[66,118] one in the United States,[52] and one trial was international (~10% of patients from U.S. sites).[137] The trial conducted in the United States (n=400) evaluated daily TDF versus placebo in MSM;[52] the two trials conducted in Europe and Canada[66,118] and the international trial[137] also focused on MSM. All trials of persons at higher risk of HIV infection via heterosexual contact were conducted in Africa, and the only trial of PWID was conducted in Thailand.[53] In that trial, most patients received PrEP through directly observed therapy and patients were provided bleach with instructions on how to clean needles. Patients were not provided sterile syringes, although these were available at low cost without a prescription at pharmacies. The adherence level in each trial and method for measuring adherence are shown in **Table 2**. All trials reported funding from government agencies or nonprofit organizations. One trial also reported industry funding,[118] three trials reported that study medications were donated by industry,[67,68,172] and one trial noted that two investigators received royalties or funding from industry.[170] One trial[118] was rated fair quality because of unclear allocation concealment methods and open-label design (**Appendix B Table 4**). The remaining trials were rated good quality.

Results for incident HIV infection are summarized in **Table 3**. Among 12 trials of PrEP versus placebo or no PrEP[51-55,66-68,118,137,170,172] one small (n=72) trial[68] reported no cases of HIV infection with either PrEP or placebo. In the other 11 trials (N=18,172), the proportion of patients with new HIV infection ranged from 0 to 5.6 percent among those randomized to PrEP and from 1.4 to 7.0 percent among those randomized to placebo or no PrEP (**Appendix B Table 1**). PrEP was associated with reduced risk of HIV infection versus placebo or no PrEP (RR, 0.46 [95% CI, 0.33 to 0.66]) (**Figure 2**), but statistical heterogeneity was present (I^2=67%). The ARR was -2.0 percent (95% CI, -2.8% to -1.2%; I^2=58%) after 4 months to 4 years. Funnel plot asymmetry was present and the test for small sample effects was statistically significant (Egger test p-value=0.03) (**Appendix C Figure 1**). Excluding the single fair-quality study[118] from the analysis had little effect on the pooled estimate (RR, 0.50 [95% CI, 0.36 to 0.70]) and did not reduce statistical heterogeneity (I^2=65%). Results were similar using the profile likelihood method (pooled RR, 0.45 [95% CI, 0.26 to 0.65]) and when FDA data on HIV incidence was used instead of the data reported in the journal publication for the Pre-Exposure Prophylaxis Initiative (iPrEx) trial.[126,137]

Two African trials (the Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women [FEM PrEP] trial and the Vaginal and Oral Interventions to Control the Epidemic [VOICE] trial)[54,172] of women at risk of HIV infection via heterosexual contact found PrEP to be substantially less effective (RR, 0.89 [95% CI, 0.55 to 1.44] and RR, 0.95 [95% CI, 0.70 to 1.28]) than the other 10 trials (RR estimates ranged from 0.07 to 0.53). In FEM PrEP and VOICE, adherence to PrEP was low, with 30 to 40 percent of patients randomized to PrEP having detectable plasma levels of tenofovir. A stratified analysis found a strong interaction (p<0.00001) between level of adherence and effectiveness of PrEP (adherence ≥70%: 6 trials; RR, 0.27 [95% CI, 0.19 to 0.39]; I^2=0%;[51,52,66,67,118,170] adherence >40% to <70%: 3 trials; RR, 0.51 [95% CI, 0.38 to 0.70]; I^2=0%;[53,55,137] and adherence ≤40%: 2 trials; RR, 0.93 [95% CI, 0.72

to 1.20]; I^2=0%[54,172]) and stratification eliminated statistical heterogeneity (**Table 3; Figure 3**).[51-55,66,67,118,137,170,172]

There was also a strong association between adherence and effectiveness when adherence was analyzed as a continuous variable in a meta-regression (p<0.0005) (**Figure 4**). In the meta-regression, the level of adherence accounted for all of the between-study heterogeneity. For every 10 percent increase in adherence, there was a 21 percent relative reduction in the relative risk. Meta-regression findings were similar when analyses were restricted to trials that evaluated adherence based on plasma levels or when trials were stratified according to whether they used TDF or TDF-FTC. Adherence is further addressed in Contextual Questions 1 and 2.

There was no clear difference in estimates of effectiveness of PrEP for preventing HIV infection when trials were stratified according to duration of followup (**Figure 5**) (p=0.35 for interaction) by less than 1 year (3 trials; RR, 0.21 [95% CI, 0.07 to 0.58]; I^2=0%; ARR, -3.0% [95% CI, -6.0% to -1.0%]; I^2=69%),[55,66,67] 1 to less than 2 years (4 trials; RR, 0.48 [95% CI, 0.28 to 0.84]; I^2=70%; ARR, -3.0% [95% CI, -5.0% to -1.0%]; I^2=76%),[118,137,170,172] or 2 or more years (4 trials; RR, 0.47 [95% CI, 0.22 to 1.00]; I^2=86%; ARR, -2.0% [95% CI, -3.0% to -1.0%; I^2=54%),[51-54] or whether trials reported receipt of industry support (3 trials; RR, 0.58 [95% CI, 0.27 to 1.22]; I^2=54%)[67,170,172] versus only reporting governmental or nonprofit funding (8 trials; RR, 0.39 [95% CI, 0.23 to 0.64]; I^2=77%)[51-55,66,118,137] (**Table 3**). PrEP was more effective at preventing HIV infection in trials conducted in the United States, Europe, or Canada (3 trials; RR, 0.13 [95% CI, 0.05 to 0.32]; I^2=0%)[52,66,118] than in trials conducted in Africa, Asia, or internationally (8 trials; RR, 0.54 [95% CI, 0.37 to 0.79]; I^2=72%; p=0.004 for interaction) (**Figure 6**).[51,53-55,67,68,137,170,172] All three trials conducted in the United States, Europe, or Canada reported high adherence and enrolled MSM.

Nine trials (N=17,744)[51-55,118,137,170,172] reported mortality; one other trial reported no deaths with or without PrEP,[66] and two small, short-term trials (n=72 each; followup 4 months) did not report mortality.[67,68] PrEP was associated with a modestly decreased risk of mortality that was not statistically significant (9 trials; RR, 0.81 [95% CI, 0.59 to 1.11]; I^2=0%); however, due to small numbers of mortality events, risk estimates from individual trials and the pooled estimate were imprecise (**Figure 7**). There was no funnel plot asymmetry (**Appendix C Figure 2**). Results for mortality were similar when trials were stratified according to geographic setting and when the profile likelihood method was used for pooling (RR, 0.82 [95% CI, 0.54 to 1.14]). No trial reported effects of PrEP versus placebo on quality of life.

Dapivirine Vaginal Ring vs. Placebo Ring

Two RCTs,[73,74] (reported in three publications[73,74,163]) both added for this update, evaluated the dapivirine vaginal ring (25 mg monthly) versus a placebo ring (**Table 3; Appendix B Tables 1-3**). Both trials (n=2,629 and 1,959; total N=4,588) enrolled sexually active (defined as vaginal intercourse at least once in the last 3 months[73] or an average or at least once per month in the last 3 months[74]), HIV-negative women 18 to 45 years of age (mean 27 and 32 years) living in high HIV prevalence areas in sub-Saharan Africa. Pregnant and breastfeeding persons were excluded and participants were required to use stable contraception. The duration of followup was 1.6 years (median) in 1 trial[73] and 1.4 years (mean) in the other trial.[74] One trial was funded by

government[73] and one by a combination of government, nonprofit, and industry.[74] In both trials, HIV risk reduction and adherence counseling and condoms were provided to all patients. The trials were rated good quality (**Appendix B Table 4**).

Both trials (N=4,564) found the dapivirine ring associated with a similarly decreased risk of HIV infection versus placebo (5.4% vs. 7.4%, RR 0.73 [95% CI 0.54 to 0.98][73] and 5.9% vs. 8.6%, RR 0.69 [95% CI 0.49 to 0.96]),[74] with a pooled RR of 0.71 (95% CI 0.57 to 0.89, I^2=0%; **Figure 8**). The ARD was -2.23% (95% CI -3.75% to -0.74%) at 1.4 to 1.6 years. Adherence to the dapivirine ring was 82 and 84 percent in the trials, based on dapivirine plasma levels >95 pg/mL.

The trials were not designed to assess effects of the dapivirine vaginal ring on mortality and reported very few events, with an imprecise estimate (N=4,587, 0.23% vs. 0.20%, RR 1.23, 95% CI 0.35 to 4.38, I^2=0%).[73,74]

Key Question 1a. How Do the Benefits of PrEP Differ by Population Subgroups?

Oral PrEP vs. Placebo or No PrEP

PrEP was effective across population subgroups defined by HIV risk category (**Table 4**). There were no clear differences in estimates of effectiveness for PrEP versus placebo or no PrEP in risk of HIV infection when trials were stratified according to whether they enrolled men and women at increased risk of HIV infection via heterosexual contact (5 trials; RR, 0.54 [95% CI, 0.31 to 0.97]; I^2=82%),[51,54,55,68,170,172] MSM or transgender women (4 trials; RR, 0.23 [95% CI, 0.08 to 0.62]; I^2=64%),[52,66,118,137] or PWID (1 trial; RR, 0.52 [95% CI, 0.29 to 0.92]; p=0.43 for interaction) (**Figure 9**),[53] although evidence of effectiveness in PWID was limited to one trial conducted in Asia. As noted above, the two trials (FEM-PrEP and VOICE) which found PrEP to be ineffective were conducted in African women at high risk of HIV infection in whom adherence was low.[54,172]

Five trials performed within-study stratified analyses of PrEP effectiveness (**Table 4**).[51,53,137,170,172] Four trials[51,53,137,172] found no clear differences in PrEP effectiveness in populations defined according to age, and three trials[51,53,170] found no clear differences between men and women. A post-hoc analysis of the iPrEx trial[137] found that PrEP was effective in MSM (hazard ratio [HR], 0.50 [95% CI, 0.34 to 0.75]) but not in transgender women (HR, 1.1 [95% CI, 0.5 to 2.7]), although the interaction was not statistically significant (p=0.09).[134] No other trial compared how results for transgender women differed from other risk groups. Evidence on how effects of PrEP vary by race/ethnicity was limited to iPrEx, which found similar effectiveness in Hispanic and non-Hispanic persons.[137] Among three trials conducted in the United States, Europe, or Canada, the proportion of participants who were White ranged from 73 to 91 percent.[52,66,118]

Data were limited regarding effects of risk behaviors on effectiveness of PrEP. One trial (iPrEx) found PrEP was effective in transgender women and MSM who reported receptive anal

intercourse (HR, 0.42 [95% CI, 0.26 to 0.68]) but not in those who did not report receptive anal intercourse (HR, 1.59 [95% CI, 0.66 to 3.84]; p=0.01 for interaction).[137] One trial (Partners PrEP) found PrEP to be effective in men and women at risk of HIV infection through heterosexual contact regardless of whether they did or did not report sex without condoms.[51] This trial also found both TDF and TDF-FTC associated with similar effectiveness when analyzed according to sexual risk behaviors and partner's viral load (**Appendix B Table 1**).[161] A trial of PWID (the Bangkok Tenofovir Study) found no association between drug injection or needle sharing in the 12 weeks before enrollment and effectiveness of PrEP.[53] A new post-hoc analysis of data from IPERGAY evaluated effects of event-driven PrEP among MSM stratified according to frequency of sexual intercourse and adherence in order to assess effects of more sporadic use of PrEP in persons engaging in less frequent sexual intercourse (compared to persons engaging in frequent sexual intercourse, in whom the frequency of event-driven PrEP more closely resembles daily PrEP).[129] It found event-driven PrEP associated with decreased HIV incidence versus placebo among those who took ≤15 pills per month with high adherence (0 vs. 9.2 per 100 person-years, p=0.013) and those who took >15 pills per month (0 vs. 8.1 per 100 person-years, p=0.004), but not among those who took ≤15 pills per month with low or no adherence (10.2 vs. 0 per 100 person-years, p=0.19).

When stratified according to patient population, pooled estimates for effects of PrEP versus placebo or no PrEP on mortality were similar (p=0.90 for interaction) in trials of women and men at increased risk of HIV infection via heterosexual contact (4 trials; RR, 0.71 [95% CI, 0.36 to 1.42]; I^2=0%),[51,54,170,172] MSM or transgender women (4 trials; RR, 0.87 [95% CI, 0.22 to 3.41]; I^2=0%),[52,55,118,137] and PWID (1 trial; RR, 0.85 [95% CI, 0.58 to 1.23]) (**Figure 10**).[53]

Dapivirine Vaginal Ring vs. Placebo Ring

Both trials of the dapivirine vaginal ring conducted analyses stratified by age. Although the dapivirine ring was associated with reduced effectiveness in younger patients in both trials (likely related to lower adherence), the trials differed in the age thresholds evaluated and there was either no statistically significant subgroup difference or a statistical test for a subgroup difference was not reported. In one trial, the dapivirine ring was associated with significant reduction in risk of HIV acquisition among patients older than 21 years (HR 0.63, 95% CI 0.41 to 0.97) but not in those 21 years of age and younger (HR 0.85, 95% CI 0.45 to 1.60; p for interaction=0.43).[74] The other trial reported a more pronounced difference in effects of the dapivirine ring on reduced risk of incident HIV infection among persons 25 years or older (HR 0.39. 95% CI 0.23 to 0.68) than those younger than 25 years (HR 0.90, 95% CI 0.57 to 1.41; p for interaction not reported).[73]

One of the trials (Microbicide Trials Network 020-A Study To Prevent Infection with a Ring for Extended Use, or ASPIRE)[73] conducted additional stratified analyses based on STI status, number of sexual partners, and sexual behaviors. The dapivirine ring was associated with smaller reduction in risk of HIV acquisition among persons with an STI at baseline (HR 0.78, 95% CI 0.45 to 1.34) than those without an STI at baseline (HR 0.53, 95% CI 0.34 to 0.83, p for interaction not reported).[73] The dapivirine ring was associated with smaller reduction in risk of HIV acquisition among persons who engaged in anal intercourse compared with those who did not engage in anal intercourse (risk reduction 18%, 95% CI -57% to 57% and risk reduction

27%, 95% CI -5% to 49%, respectively), but the difference was not statistically significant (p for interaction=0.77).[163] The reduction in HIV acquisition risk was very similar among persons with two or more sexual partners (HR 0.62, 95% CI 0.31 to 1.23) and those with zero or one sexual partner (HR 0.63, 95% CI 0.42 to 0.93.[73]

Key Question 1b. How Do the Benefits of PrEP Differ by Dosing Strategy or Regimen?

Estimates of effectiveness of oral PrEP versus placebo or no PrEP on risk of HIV infection were very similar when analyses were stratified according to use of TDF (5 trials; RR, 0.49 [95% CI, 0.28 to 0.84]; I^2=58%)[51-55] or TDF-FTC (8 trials; RR, 0.44 [95% CI, 0.27 to 0.72]; I^2=74%; p=0.79 for interaction) (**Table 3**; **Figure 2**).[51,54,66,67,118,137,170,172] Among the trials that used intermittent or event-driven dosing, one trial[68] reported no HIV events and one trial[67] combined results for intermittent/event-driven and daily dosing of PrEP arms. The third trial (IPERGAY)[66] found event-driven PrEP associated with a lower risk of HIV infection than placebo in MSM (RR, 0.14 [95% CI, 0.03 to 0.63]). Although the estimate was stronger than that among trials that used daily dosing (9 trials; RR, 0.47 [95% CI, 0.32 to 0.71]; I^2=75%) (**Table 3**; **Figure 11**),[51-55,118,137,170,172] the interaction was not statistically significant (p=0.13). The estimate from IPERGAY was similar to the pooled estimate for trials of daily dosing that reported high adherence (5 trials; RR, 0.28 [95% CI, 0.20 to 0.41]).[51,52,67,118,170] In IPERGAY, men randomized to PrEP took an average of about four doses of PrEP per week (15 doses per month) and had an average of 10 episodes of sexual intercourse per month.

The open-label HIV Prevention Trials Network 067/Alternative Dosing to Augment PrEP pill Taking (HPTN 067/ADAPT) trial, included in the prior USPSTF report, compared daily versus intermittent (twice a week, plus a dose after sex) or event-driven PrEP with TDF-FTC in MSM or transgender women[136] (n=357) and heterosexual African women[130] (n=178) (**Tables 5 and 6; Appendix B Tables 1-3**), but was not powered to evaluate effects on incident HIV infection (five total cases). One new, small (n=119), fair-quality crossover trial conducted in Hong Kong compared event-driven versus daily oral TDF-FTC among high-risk HIV-negative MSM, but also was not designed to assess effects on incident HIV infection and only reported one case (**Tables 5 and 6; Appendix B Tables 1-3**).[144]

Data on the effects of use of postexposure prophylaxis on efficacy of PrEP was limited. In the open-label Pre-Exposure Option for Reducing HIV in the United Kingdom: Immediate or Deferred (PROUD) trial, PrEP was more effective than no PrEP at reducing risk of HIV infection in MSM (RR, 0.14, 95% CI, 0.03 to 0.63), despite much less frequent use of postexposure prophylaxis (4.4% vs. 32%) and an increased rate of receptive anal sex without a condom with 10 or more partners (21% vs. 12%) among persons randomized to PrEP.[118] No other trial reported the proportion of patients who used postexposure prophylaxis, although three trials described postexposure prophylaxis as an HIV prevention intervention offered to all patients;[51,66,137] PrEP was effective in all three trials (RR, 0.14 to 0.53).

For mortality, estimates for PrEP versus placebo or no PrEP were similar when trials were stratified according to whether they used TDF or TDF-FTC (p=0.65 for interaction) (**Figure 7**).

Key Question 2. What Are the Benefits of Newer PrEP Regimens (TAF-FTC, Injectable Cabotegravir, or the Dapivirine Vaginal Ring) vs. TDF-FTC?

Summary

Oral TAF-FTC vs. TDF-FTC

- Oral TAF-FTC was non-inferior to TDF-FTC in cisgender MSM (98.6%) and transgender women (1.4%) who have sex with men for risk of incident HIV infection and associated with a non-statistically significant decreased risk (1 new trial, n=5,387; 0.3% vs. 0.6%, RR 0.53 [95% CI, 0.23 to 1.26][162]).

Long-Acting Injectable Cabotegravir vs. Daily Oral TDF-FTC

- Long-acting injectable cabotegravir was associated with decreased risk of HIV infection versus oral TDF-FTC in 1 new trial of cisgender MSM (87%) and transgender women (12%) who have sex with men (n=4,490, 0.6% vs. 1.7%; RR 0.33 [95% CI, 0.18 to 0.62][70]) and in 1 new trial of African women at high risk of HIV infection (n=3,178, 0.3% vs. 2.3%; RR 0.11 [95% CI, 0.04 to 0.31][88]).

No trials compared the dapivirine vaginal ring to TDF-FTC.

Evidence

Oral TAF-FTC vs. TDF-FTC

One trial, published subsequent to the prior USPSTF report, compared PrEP with oral TAF-FTC versus TDF-FTC[121,162] (**Tables 5 and 6, Appendix B Tables 1–3**) The DISCOVER trial (n=5,387) was conducted in Europe and North America in HIV-negative cisgender adult men (98.6%) and transgender women (1.4%) who have sex with men and are at high risk of HIV acquisition, based on having condomless anal intercourse with at least two partners in the previous 12 weeks or a STI (syphilis, rectal gonorrhea, or rectal chlamydia) in the previous 24 weeks (**Tables 1–3**).[121] Patients were randomized to once-daily oral TAF-FTC (25-200 mg) or TDF-FTC (300-200 mg) and followed for 96 weeks. Mean age was 34 years. Nine percent of participants were Black and 4 percent were Asian; 24 percent were Hispanic/Latinx ethnicity. Sixteen percent of participants were receiving TDF-FTC PrEP at the time of enrollment. The trial was blinded and rated good quality (**Appendix B Table 4**).

At 96 weeks, TAF-FTC was associated with a non-statistically significant decreased risk of HIV infection versus TDF-FTC (0.3% vs. 0.6%, RR 0.53, 95% CI 0.23 to 1.26[162]); results were within the pre-specified non-inferiority margin. Adherence was high (98% based on median pill count) and 84 to 96 percent based on dried blood spot samples consistent with ≥4 doses/week (**Tables 5 and 6**).[121,162] Findings were similar when five patients suspected of acquiring HIV infection

before baseline (diagnosed at week 4) were excluded, or when patients suspected of acquiring HIV infection before baseline or with poor adherence were excluded. There were no statistically significant interactions between effects on HIV infection risk and age (<25 vs. ≥25 years), race (Black vs. other, ethnicity (Hispanic/Latinx vs. other), region (United States vs. other), recreational drug use (yes vs. no), binge alcohol use (yes vs. no), or number of unprotected receptive anal intercourse partners (≤3 vs. >3).[121] However, stratified estimates were imprecise. No infections occurred in transgender women in either arm. DISCOVER was not designed to evaluate mortality; at 96 weeks, there were a total of five deaths (3 in the TAF-FTC arm and 2 in the TDF-FTC arm).[162]

Long-Acting Injectable Cabotegravir vs. Daily Oral PrEP

Two concurrently conducted trials (HPTN trials 083 and 084) compared long-acting injectable cabotegravir (600 mg intramuscular every 8 weeks, following a 5 week oral lead-in phase of 30 mg daily) versus daily oral TDF-FTC (300 mg TDF and 200 mg emtricitabine) (**Tables 5 and 6, Evidence B Tables 1–3**).[70,88] HPTN 083 enrolled cisgender MSM or transgender women who have sex with men and HPTN 084 (also referred to as the Long-acting Injectable For the Epidemic [LIFE] trial) enrolled women at high risk for sexual acquisition of HIV infection. Both trials were discontinued early, based on cabotegravir meeting pre-defined thresholds for superiority over oral TDF-FTC in pre-planned interim analyses. The trials were rated good quality (**Appendix B Table 4**).

In HPTN 083 (n=4,566), 87 percent of participants were MSM and 12 percent were transgender women who have sex with men. The trial was conducted in the United States (37%), Latin America (43%), Asia (16%), and Africa (3.3%).[70] Among U.S. participants, 50 percent were Black and 50 percent non-Black. High risk for HIV acquisition (required for enrollment) was defined as any of the following within the last six months: condomless receptive anal intercourse (except within a monogamous HIV seronegative concordant relationship), >5 sexual partners, stimulant drug use, or STI (rectal or urethral gonorrhea or chlamydia or incident syphilis).

HPTN 083 was designed as a three-year trial but stopped after the first interim analysis. At median follow-up of 1.4 years, injectable cabotegravir was associated with decreased risk of HIV acquisition versus oral TDF-FTC (0.6% vs. 1.7%; RR 0.33, 95% CI 0.18 to 0.62). Adherence was 91.5% for cabotegravir (based on injections received with a delay of less than 2 weeks) and 74% with TDF-FTC (based on a tenofovir plasma concentration >40 ng/ml, consistent with receipt of daily TDF-FTC in the prior week). In stratified analysis, results were similar in MSM (HR 0.35, 95% CI 0.18 to 0.68) and transgender women (HR 0.34, 95% CI 0.08 to 1.56); however, the estimate for transgender women was imprecise. Among U.S. patients, cabotegravir was associated with decreased risk of HIV acquisition among Black (HR 0.28, 95% CI 0.10 to 0.84) and non-Black persons (HR 0.09, 95% CI 0.00 to 2.05); however, no cases occurred in non-Black persons, resulting in an imprecise estimate. Findings were also similar when results were stratified by age (≤30 vs. >30 years) and geographic region.

HPTN 084 (n=3,178) was conducted in seven countries in sub-Saharan Africa.[88] Participants were aged 18 to 45 years (median 25 years), female sex assigned at birth, reported at least two episodes of vaginal intercourse in the prior 30 days and were assessed as being at high risk for

HIV acquisition using a risk prediction instrument. The risk prediction instrument was developed and validated in African women and has items on: age, married/living with partner, partner providing financial or material support, partner having other partner, alcohol use, sexually transmitted infections, and herpes simplex virus 2 serostatus (score range 0 to 11, high risk defined as score ≥5).[174] Pregnant and breastfeeding persons were not eligible for enrollment; persons who became pregnant during the trial were switched to open-label TDF-FTC through the end of pregnancy and breastfeeding.

HPTN 084 was designed as a 3.5-year trial but stopped after the second interim analysis. At median follow-up of 1.2 years, injectable cabotegravir was associated with decreased risk of HIV acquisition versus oral TDF-FTC (0.3% vs. 2.3%, RR 0.11, 95% CI 0.04 to 0.31). Adherence with cabotegravir was 93.0 percent (based on injection received with a delay of less than 2 weeks) and for TDF-FTC it was 41.9 percent (based on a plasma concentration ≥40 ng/ml) or 18 percent (based on TFV-DP level consistent with taking ≥4 doses/week). Results were similar in stratified analyses based on age (<25 vs. ≥25 years; for interaction=0.53), contraception method (p for interaction=0.87), and body mass index (≤30 vs. >30 kg/m^2; p for interaction=0.47).

Key Question 3. What Is the Diagnostic Accuracy of Provider or Patient Risk Assessment Tools in Identifying Persons at Increased Risk of HIV Acquisition Who Are Candidates for PrEP?

Summary

- In MSM, five studies (three included in the prior USPSTF report and two new; N=25,488 in validation cohorts) of five different instruments (number of items ranged from 4 to 12) reported moderate discrimination for predicting incident HIV infection in validation cohorts (area under the receiver operating characteristic curve [AUROC], 0.60 to 0.73).[140,155,165,166,171] Evidence on how discrimination varied by race/ethnicity was inconsistent, with some studies showing lower discrimination and others showing similar discrimination.
- In PWID, one study (n=1,904) included in the prior USPSTF found a 10-item instrument associated with AUROC of 0.72 for incident HIV infection, but had methodological limitations.[167]
- In women evaluated in the emergency department, one new study found a 6-item risk prediction instrument on electronic medical record data associated with sensitivity of 95% for incident HIV infection (21 cases); specificity was not reported.[164]
- In general populations of HIV-uninfected persons, two new studies (n=33,404 and 606,701 in validation cohorts) found two different instruments (number of items 23 and 44) based on automated computerized algorithms on electronic medical record data associated with moderate to high discrimination for incident HIV infection (AUROC 0.77, 95% CI 0.74 to 0.79 and 0.84, 95% CI 0.80 to 0.89).[143,151]

Evidence

Twelve studies evaluated instruments developed and validated in U.S. cohorts for predicting incident HIV infection (**Appendix B Tables 5 and 6**).[131,140,142,143,145,151,155,164-167,171] Seven studies[131,140,142,145,155,166,167] were included in the prior USPSTF review and five studies[143,151,164,165,171] were added for this update. Eight studies (two new)[165,171] evaluated risk prediction instruments in MSM,[131,140,142,145,155,165,166,171] one study (included in the prior USPSTF report) in PWID,[167] one study (new) in cisgender women,[164] and two studies (both new) in general populations of HIV-uninfected persons.[143,151] No study evaluated instruments for predicting incident HIV infection risk in pregnant or postpartum U.S. persons. Sample sizes (including development and validation cohorts) ranged from 21 to 3,750,664 patients (total N=5,544,500). The duration of assessment for incident HIV infection ranged from 0.77 to 7.85 years in studies that reported this information.

In the studies of general populations[143,151] and the study of cisgender women,[164] HIV risk assessment was based solely on data extracted from electronic health records; in the studies of MSM and persons who inject drugs, risk assessment was based on information obtained from patient interviews, questionnaires, and health records. One study evaluated patients attending a clinic for lesbian, gay, bisexual, and transgender persons,[131] two studies evaluated patients attending STI clinics,[155,171] one study evaluated patients in the emergency department,[164] and two studies[143,151] evaluated patients in large health systems (in one of these studies,[143] the external validation cohort was a health center focusing on sexual health care); the other studies evaluated persons enrolled in research studies.

All studies had methodological shortcomings (**Appendix B Table 7**). In all studies, risk assessment instruments were developed and validated using previously collected data, except for two studies[143,151] that performed prospective validation. In some cases, the criteria had to be slightly modified to match the data available. In eight studies, new HIV infections were identified in the study sample by repeat testing using a longitudinal (cohort) design. One study of MSM identified new HIV infections based on a single test for markers for acute or early HIV infection.[140] Two studies[143,151] of general populations excluded patients with HIV infection at baseline but did not perform HIV testing in all patients at baseline; the study of cisgender women[164] focused on patients with a new positive HIV test in the emergency department and did not describe methods for ruling out prior HIV infection. Four studies used cohorts that included persons who had HIV testing before the year 2000.[155,165-167] In nine studies, the predictive utility of risk assessment instruments was tested (validated) in cohorts independent from the one used to develop the instrument.[140,142,143,145,151,155,165,166,171] In two studies, accuracy was only reported for the cohort used to develop the instrument[131,167] and the study of cisgender women[164] only reported sensitivity (only cases included in analysis). Cutoffs to define a positive test were predefined in four studies.[142,145,164,171]

MSM

Eight studies (N=65,284) including development and validation cohorts) evaluated risk prediction instruments in MSM.[131,140,142,145,155,165,166,171] The studies evaluated six different risk assessment instruments or criteria; four of these (Beymer, the San Diego Early Test [SDET], the

Assessing the Risk of Contracting HIV in Men Who Have Sex With Men [ARCH-MSM], and Menza) were in the prior USPSTF report and two instruments (Seattle PrEP Score and SexPro) were added for this update (**Table 7**). The number of criteria in the risk assessment instruments ranged from 4 to 12). Items assessed in all of the risk instruments were presence of STIs, sex without a condom (particularly receptive anal sex), and number of sexual partners (**Appendix B Tables 5 and 6**). Age, race/ethnicity, and illicit drug use were included in some instruments but not others. None of the instruments include an item on plasma HIV viral load or use of antiretroviral therapy (ART) in a sexual partner with HIV. Two of the studies compared the performance of risk prediction instruments against the 2014 CDC indications for PrEP in MSM.[131,171]

In the cohorts used to develop the risk assessment instruments, four studies reported that the proportion of Black participants ranged from 6 to 15.2 percent of the population;[131,140,165,171] two studies reported that 5.0 and 7.4 percent of the population was Hispanic/Latinx,[165,171] one study reported that 5.6 percent of the populations was Asian and 1.2 percent was Native American or Alaskan Native.[171] One study reported that 23 percent of the population was non-White, Asian, or Pacific Islander;[155] and two studies reported a non-White proportion of 14 and 35 percent.[166,171] Two studies evaluated the performance of previously developed risk assessment instruments in MSM cohorts in which 46 percent[142] or all participants[145] were Black. In one other study,[165] all participants were Black in one of four cohorts used to develop and validate a new risk assessment instrument; in the other three cohorts the proportion of Black participants ranged from 3.4 to 18.3 percent.[165] One study evaluated patients attending a clinic for lesbian, gay, bisexual, and transgender persons,[131] two studies evaluated patients attending STI clinics,[155,171] one study evaluated patients in the emergency department,[164]The incidence of HIV infection in the validation cohorts ranged from 1.1 to 11 percent.

For five instruments, discrimination was similar, with AUROCs in the original validation cohorts (N=25,488) ranging from 0.60 to 0.73.[140,155,165,166,171] A sixth study (n=9,841)[131] found that a 10-item instrument developed using data from the Los Angeles Lesbian Gay Bisexual and Transgender (LGBT) Center was associated with better goodness of fit based on the Akaike Information Criterion score than instruments developed in two other studies[155,166] or criteria from the 2014 CDC guidelines for offering PrEP in MSM.[82] However, the instrument was not validated using a separate (nondevelopment) sample. In addition, some of the items used in the other risk prediction instruments were not identical to variables available in the Los Angeles LGBT Center database, necessitating use of alternative variables for goodness of fit testing. Other studies reported similar discrimination of different risk assessment instruments in MSM.[140,155,165,171]

The six-item ARCH-MSM instrument is included in the CDC PrEP guideline[175] as a potential tool to identify PrEP-eligible candidates.[166] ARCH-MSM was developed using a cohort of patients enrolled in an (ineffective) HIV vaccine trial and validated in a cohort of patients enrolled in an (ineffective) behavioral intervention trial.[166] Based on a suggested post-hoc cutoff of 10 or greater (range, 0 to 48), 62.4 percent of men in the validation cohort (n=3,368) met the threshold, with a sensitivity for future HIV infection of 81.2 percent and specificity of 37.7 percent, and an AUROC of 0.72. The data in the cohorts used to validate and develop the ARCH-MSM instrument were older (collected in 1998–1999 and 1999–2001, respectively) and

had a high prevalence of inhaled nitrite and amphetamine use, both of which are included as items in the instrument.

A four-item instrument by Menza et al (score range, 0 to 19) was validated using data from the same validation cohort (n=2,081) as ARCH-MSM.[155] A cutoff score of 3 or greater with this instrument provided comparable sensitivity (76%) and specificity (43%) to ARCH-MSM for incident HIV infection at a cutoff of 10 or greater, with 64 percent of the sample meeting this threshold. Discrimination was slightly lower with this instrument (0.66 [95% CI, 0.61 to 0.71]) than with ARCH-MSM (0.72 [CI not reported]). Methamphetamine and inhaled nitrite use were included as a single item in the Menza instrument.

The four-item SDET (score range, 0 to 10 points) was developed using a more contemporary (2008–2014) cohort.[140] As noted earlier, HIV incidence was estimated based on markers for acute or early HIV infection on a single test. In the validation cohort (n=2,758) A cutoff score of 1 or greater resulted in a sensitivity (73%) and specificity (48%) for incident HIV infection most comparable to ARCH-MSM at a cutoff of 10 or greater. The proportion of the sample meeting this threshold was not reported. Discrimination of the SDET score was very similar to ARCH-MSM (0.70 [95% CI, 0.62 to 0.78] vs. 0.72 [CI not reported]). The SDET does not include items on drug use.

A 10-item instrument by Beymer et al was also developed using a more contemporary cohort (Los Angeles LGBT Center 2009–2014; n=9,481).[131] The instrument includes items on race/ethnicity, partner age and race/ethnicity, and intimate partner violence, as well as illicit drug use. As noted above, a methodological limitation is that this instrument has only been evaluated in the cohort used to develop the instrument. In addition, methods for scoring the instrument (e.g., points assigned for individual items) were unclear. Using a cutoff score of 5 or greater, 51 percent of the cohort met this threshold, with a sensitivity of 74.6 percent and specificity of 50.2 percent for incident HIV infection. The AUROC was not reported. Goodness of fit testing based on the Akaike Information Criterion and Schwarz Bayesian Criteria was slightly better with this instrument than with the ARCH-MSM and similar to the Menza instrument, but this finding is difficult to interpret because goodness of fit was evaluated using data from the same cohort used to develop this instrument, and the other instruments included items that were not an exact match with data available in this database.

The 2014 CDC guideline includes recommended indications for PrEP in MSM (any anal sex without condoms in past 6 months, any STI diagnosed or reported in past 6 months, or ongoing sexual relationship with a partner with HIV).[82] In the study by Beymer et al, goodness of fit was slightly better with the Los Angeles LGBT Center instrument than the CDC criteria.[131]

The 12-item SexPro instrument (score range, 1 to 20 points) was developed using persons enrolled in an (ineffective) behavioral intervention trial (1999-2001) and validated in three cohorts of participants enrolled in other clinical trials (2009-2013).[165] In addition to items on sexual risk behaviors, STIs, and illicit drug use, SexPro includes items on age, race/ethnicity, and alcohol use. In the validation cohorts (n=8,047), a cutoff score of 16 or greater on SexPro was associated with sensitivities of 64.4, 100, and 75.4 percent for incident HIV infection. Specificities were 67.4, 0, and 51.8 percent, respectively. The cohort with sensitivity of 100

percent and specificity of 0 percent only included Black participants (the proportion of Black participants in the other cohorts was 3.4% and 18.3%), who had lower SexPro scores compared with other participants. Despite the differences in diagnostic accuracy at the selected cutoff, discrimination was similar across the three validation cohorts (AUROC 0.71 to 0.73). In these cohorts, sensitivity of ARCH-MSM at a cutoff score of ≥10 ranged from 80.0 to 86.2 percent and specificity ranged from 43.2 to 61.2 percent; discrimination of ARCH-MSM (AUROC 0.74 to 0.75) was similar to the SexPro score.

The four-item Seattle PrEP Score (score range, 0 to 4 points) was developed using two large STI clinic cohorts (2001-2015).[171] In the validation cohort (n=9,234), a cutoff score of 2 or greater was associated with a sensitivity of 46.3 percent and specificity of 69.0 percent. In the combined development and validation cohorts (n=22,761), the Seattle PrEP score performed similarly to the SDET at a cutoff score of 5 or greater (sensitivity for incident HIV infection 33.1% and specificity 67.1%) in this population; three other instruments (Menza [cutoff ≥2], ARCH-MSM [cutoff ≥10], and CDC [meeting criteria for PrEP]) reported higher sensitivity (range 62.7% to 86.7%) but lower specificity (range 13.3% to 37.4%). For all five instruments, discrimination was similar (based on combined development and validation cohorts, 0.66 for Seattle PrEP score and 0.61 to 0.66 for the others [AUROC for instruments other than Seattle PrEP score not reported separately for the validation cohort]).

Evidence on how the accuracy of risk prediction instruments in MSM varied according to race or ethnicity was inconsistent. Two studies found that risk prediction instruments performed more poorly in Black MSM. In one study of MSM, the AUROC for the ARCH-MSM, SDET, and Menza instruments ranged from 0.51 to 0.62 overall, from 0.49 to 0.63 in Black MSM, and from 0.60 to 0.67 in White MSM.[142] In the other study, the AUROC for the ARCH-MSM was 0.57 in Black MSM, and similar using criteria derived from the CDC recommendations (AUROC, 0.51) or the PrEP package insert (AUROC, 0.54).[145] However, two other studies reported similar discrimination of risk prediction instruments in Black and White MSM. In one study, the AUROC of the Seattle PrEP Score was 0.64 in White MSM and 0.62 in Black MSM.[171] In the other study, the AUROC of the SexPro instrument was 0.74 in two validation cohorts of primarily (>95%) White MSM and 0.75 in a validation cohort of 100% Black MSM.[165] One study reported that discrimination of the SexPro instrument was higher in Asian (0.91) than White (0.64) MSM, but the estimate for Asian MSM was based on only six incident HIV cases and imprecise.[165]

PWID

The seven-item Assessing the Risk of Contracting HIV in Injection Drug Users (ARCH-IDUs) instrument (score range, 0 to 100 points) was developed using a cohort (1988–2008) of current and former PWID in Baltimore.[167] ARCH-IDUs is included as a tool for identifying persons who inject drugs at high risk for HIV acquisition in the 2021 CDC guideline.[175] The instrument includes seven items on age, enrollment in a methadone maintenance program, and drug use behaviors. The population in the cohort used to develop ARCH-IDUs was primarily non-Hispanic Black (93%) persons; incident HIV infection occurred in 11 percent of the development cohort.

In the sample used to develop ARCH-IDUs (n=1,904), sensitivity was 86 percent and specificity was 42 percent at a cutoff of 46 or greater, with 58 percent of the cohort meeting this threshold. The AUROC was 0.72 (CI not reported). ARCH-IDUs has not been evaluated in a separate validation cohort.

Women

One new study by Ridgeway et al evaluated a previously developed 6-item risk prediction instrument (range, 0 to 76) based on data extracted from the electronic medical record.[164] Even though the instrument included items on male sex and MSM (in addition to STI history or symptoms and age), it was evaluated in a cohort (2011-2018) of women evaluated in the emergency department. Among 21 women newly diagnosed with HIV infection in the emergency department, sensitivity of the instrument was 95 percent (20/21). Because the study only evaluated incident HIV cases, specificity was not available. In this study, all incident HIV infections except for one occurred in Black women.

General Populations of HIV-Negative Persons

Two new studies (N=5,477,291, based on derivation and validation cohorts) evaluated instruments for predicting risk of HIV Infection in general populations of HIV-negative persons.[143,151] Both instruments were developed using large health systems cohorts (2007 to 2015 and 2007 to 2014) and utilized a computerized algorithm developed with machine learning on items extracted from the electronic medical record. The proportion of Black participants in the cohorts used to develop these instruments ranged from 5.2 to 8.1 percent, the proportion of Hispanic/Latinx participants ranged from 2.9 to 5.6 percent, and the proportion of Asian participants ranged from 5.8 to 23 percent. In the cohorts used to validate the instruments, incident HIV infection occurred in 0.01 and 1.3 percent of participants.

One study evaluated a 23-item instrument (score range, 0 to 100,000) that included items on STI history or use of penicillin G, prior HIV testing, use of medications for opioid use disorder, race, gender, and primary language.[143] In the external validation cohort (n=33,404), at a cutoff of 2 or greater (indicating the top 2% of HIV risk scores), sensitivity for incident HIV infection was 98.1 percent and specificity was 26.8 percent. At a cutoff of 8 or greater, sensitivity was 91.3 percent and specificity was 44.2 percent. The AUROC was 0.77 (95% CI 0.74 to 0.79). In the other study, which evaluated a 44-item instrument, sensitivity for incident HIV infection based on classification as high or very high risk (≥0.20%) was 59.1 percent and specificity was 97.8 percent in the validation cohort (n=606,701), with an AUROC of 0.84 (95% CI 0.80 to 0.89).[151] In this study, sensitivity for incident HIV infection was similar in Black and White patients.

Key Question 4. What Are the Harms of PrEP vs. Placebo or No PrEP When Used for the Prevention of HIV Infection?

Summary

Oral PrEP vs. Placebo or No PrEP

- There was no difference between oral PrEP with TDF-FTC or TDF versus placebo or no PrEP in risk of serious adverse events (12 trials, N=18,292; RR, 0.93 [95% CI, 0.77 to 1.12]; I^2=56%).[51-55,66-68,118,137,170,172]
- Oral PrEP with TDF-FTC or TDF was associated with a trend toward increased risk of withdrawals due to adverse events versus no PrEP or placebo that was not statistically significant (4 trials, N=10,563; RR, 1.25 [95% CI, 0.99 to 1.59]; I^2=0%).[51,55,66,137,172]
- Oral PrEP with TDF-FTC or TDF was associated with increased risk of renal adverse events (primarily ≥grade 1 creatinine elevation) (12 trials, N=18,170; RR, 1.43 [95% CI, 1.18 to 1.75]; I^2=0%; absolute risk difference [ARD], 0.56% [95% CI, 0.09% to 1.04%]) versus no PrEP or placebo.[51-55,66-68,118,137,170,172] Renal abnormalities generally resolved following PrEP cessation.
- Oral PrEP with TDF-FTC or TDF was associated with increased risk of gastrointestinal adverse events (12 trials, N=18,300; RR, 1.63 [95% CI, 1.26 to 2.11]; I^2=43%; ARD, 1.95% [95% CI, 0.48% to 3.43%]) versus placebo or no PrEP;[51-55,66-68,118,137,170,172] gastrointestinal events were generally not serious and diminished over time.
- Oral PrEP with TDF-FTC or TDF was associated with a small, non-statistically significant increased risk of fracture versus placebo (7 trials, N=15,241; RR, 1.23 [95% CI, 0.97 to 1.56]; I^2=0%).[51-54,66,137,170]
- There were no differences between oral PrEP with TDF-FTC or TDF versus placebo in risk of syphilis (4 trials, N=10,775; RR, 1.08 [95% CI, 0.98 to 1.18]; I^2=0%), gonorrhea (5 trials; RR, 1.07 [95% CI, 0.82 to 1.39]; I^2=49%), chlamydia (5 trials; RR, 0.97 [95% CI, 0.80 to 1.18]; I^2=59%) or combined bacterial STIs (2 trials; RR, 1.14 [95% CI, 0.97 to 1.34], I^2=16%).[51,118,137,170,172]
- There was no difference between oral PrEP with TDF-FTC or TDF versus placebo in risk of HSV (3 trials, N=4,088; RR, 0.85 [95% CI, 0.67 to 1.07]; I^2=19%) or hepatitis C virus infection (2 trials, N=896; RR, 0.73 [95% CI, 0.25 to 2.10]; I^2=0%).[66,118,120,150,170]
- Among persons who became pregnant in PrEP trials, PrEP was not associated with increased risk of spontaneous abortion (3 trials, N=415; RR, 1.09 [95% CI, 0.79 to 1.50]; I^2=0%).[68,157,172] One trial found no differences between PrEP versus placebo in pregnancy rate, risk of preterm birth, birth anomalies, or postpartum infant mortality.[157]

Dapivirine Vaginal Ring vs. Placebo Ring

- Results for the dapivirine vaginal ring versus placebo and risk of serious adverse events were very imprecise and inconsistent (2 trials, N=4,587, RR, 1.73 [95% CI 0.60 to 4.94]; I^2=80%).[73,74]

- There were no differences between the dapivirine vaginal ring versus placebo ring in risk of STIs or incidence of pregnancy (2 trials, N=4,587).[73,74]

Evidence

Oral PrEP vs. Placebo or No PrEP

Serious Adverse Events

There was no difference between oral PrEP with TDF or TDF-FTC versus placebo in risk of serious adverse events (12 trials, N=18,292; RR, 0.93 [95% CI, 0.77 to 1.12]; I^2=56%) (**Table 8**; **Figure 12**).[51-55,66-68,118,137,170,172] Results using the profile likelihood method were similar (RR, 0.95 [95% CI, 0.78 to 1.23]) and there was no funnel plot asymmetry (Egger test p-value=0.53) (**Appendix C Figure 3**). Nine trials evaluated daily PrEP and two trials combined data for daily and intermittent/event-driven PrEP;[67,68] one trial of event-driven PrEP (IPERGAY) reported a risk of serious adverse events (RR, 1.07 [95% CI, 0.58 to 1.98]) that was similar to the pooled estimate from trials of daily PrEP (11 trials; RR, 0.92 [95% CI, 0.76 to 1.12]; I^2=59%).[66] There were also no differences between oral PrEP versus placebo in risk of serious adverse events when trials were stratified according to whether they used TDF (5 trials; RR, 0.79 [95% CI, 0.56 to 1.12]; I^2=72%)[51-55] or TDF-FTC (9 trials; RR, 1.02 [95% CI, 0.81 to 1.30]; I^2=46%; p=0.23 for interaction) (**Figure 12**).[51,54,66-68,118,137,170,172] One trial (PROUD) found TDF-FTC associated with a greater risk of serious adverse events than placebo (7.6% [21/375] vs. 2.2% [6/269]; RR, 3.42 [95% CI, 1.40 to 8.35]).[118] It differed from other trials in that it used an open-label design. Serious adverse events reported by more than one patient on TDF-FTC in PROUD included gastrointestinal events, fractures, and psychiatric events.

Withdrawals Due to Adverse Events

Withdrawals due to adverse events were reported in five trials (**Table 8**).[51,55,66,137,172] One trial (n=936)[55] reported no withdrawals with either PrEP or placebo. In the other trials, oral PrEP was associated with a small, non-statistically significant trend toward increased risk of withdrawal due to adverse events versus placebo (4 trials, N=10,563; RR, 1.25 [95% CI, 0.99 to 1.59]; I^2=0%). One trial evaluated TDF (RR, 1.00 [95% CI, 0.34 to 2.92]) and four evaluated TDF-FTC (RR, 1.27 [95% CI, 1.00 to 1.62]; p=0.67 for interaction) (**Figure 13**). The only trial to report a statistically significant increase in risk of withdrawals (either temporary or permanent) due to adverse events was the FEM-PrEP trial, which evaluated TDF-FTC (RR, 1.68 [95% CI, 1.10 to 2.56]).[172] The majority (~90%) of withdrawals in this trial were the result of laboratory abnormalities (grade 2 or higher). In FEM-PrEP, there was no difference in risk of withdrawal due to clinical adverse events, although the estimate was imprecise (RR, 3.53 [95% CI, 0.73 to 17]).

Fracture

Tenofovir exposure is associated with bone loss,[148,159,170,176] which could result in increased fracture risk. Oral PrEP with TDF or TDF-FTC was associated with a small, non-statistically significant increased risk of fracture versus placebo (7 trials, N=15,241; RR, 1.23 [95% CI, 0.97

to 1.56]; I^2=0%; ARD, 0.21% [95% CI, -0.21% to 0.62%]) (**Table 8**; **Figure 14**).[51-54,66,137,170] The meta-analysis was heavily weighted (64%) by the Bangkok Tenofovir Study of PWID, which reported a relatively high fracture rate (7.8% vs. 6.0%; RR, 1.29 [95% CI, 0.96 to 1.74]).[53] There was no statistically significant interaction between the PrEP regimen and fracture risk (p=0.50) (**Figure 14**). One trial of event-driven dosing (IPERGAY) did not find PrEP associated with an increased risk of fracture, but the estimate was imprecise (RR, 0.51 [95% CI, 0.13 to 1.99]).[66] Patients averaged 15 doses per month in IPERGAY; effects of intermittent/event-driven dosing with less frequent exposure to PrEP on fracture risk are not available. In trials for which details were available regarding the mechanism of fracture, all or almost all fractures were traumatic.[126]

Results were similar when the profile likelihood method was used for pooling (RR, 1.23 [95% CI, 0.92 to 1.58]). There were discrepancies between the number of fractures reported in journal reports of three trials (the CDC Safety Study,[52] iPrEx,[137] and Partners PrEP[51]) and the FDA review[126] of these trials (**Appendix B Tables 1–3**). However, the pooled estimate was similar when the FDA data were used in the meta-analysis in place of data reported in the journal articles (RR, 1.20 [95% CI, 0.96 to 1.52]) (**Figure 15**).

Renal Adverse Events

Oral PrEP with TDF or TDF-FTC was associated with increased risk of renal adverse events (primarily ≥grade 1 serum creatinine elevation) versus placebo (12 trials, N=18,170; RR, 1.43 [95% CI, 1.18 to 1.75]; I^2=0%; ARD, 0.56% [95% CI, 0.09% to 1.04%]) (**Table 8**; **Figure 16**).[51-55,66-68,118,137,170,172] Results were similar with the profile likelihood method (RR, 1.44 [95% CI, 1.12 to 1.79]) and no funnel plot asymmetry was present (Egger test p-value=0.29) (**Appendix C Figure 4**). A trial of event-driven PrEP (IPERGAY) reported an increased risk of renal adverse events (RR, 1.77 [95% CI, 1.06 to 2.95]) consistent with the pooled estimate from trials of daily PrEP (11 trials; RR, 1.38 [95% CI, 1.11 to 1.72]; I^2=0%).[66] There was no clear difference in risk of renal adverse events when trials were stratified according to use of TDF or TDF-FTC (p=0.31 for interaction). Serious renal events were rare, and no trial reported a difference between PrEP and placebo in risk of serious renal events or withdrawals due to renal events (**Appendix B Tables 1–3**).

Six trials[51,67,68,149,152,168] evaluated whether renal adverse events while on PrEP were persistent (**Appendix B Tables 1–3**). Three studies[51,149,168] reported a return to normal serum creatinine levels after cessation of PrEP and two others[67,68] reported normalization of creatinine level without PrEP cessation.[158] In one other trial of PWID (the Bangkok Tenofovir Study), six of seven cases of grade 2 or worse creatinine elevation resolved following PrEP cessation.[152]

Gastrointestinal Adverse Events

Oral PrEP with TDF or TDF-FTC was associated with increased risk of gastrointestinal adverse events (primarily nausea) versus placebo (12 trials, N=18,300; RR, 1.63 [95% CI, 1.26 to 2.11]; I^2=43%; ARD, 1.95% [95% CI, 0.48% to 3.43%]) (**Table 8**; **Figure 17**).[51-55,66-68,118,137,170,172] Results were similar using the profile likelihood method (RR, 1.67 [95% CI, 1.26 to 2.25]) and there was no funnel plot asymmetry (Egger test p-value=0.81) (**Appendix C Figure 5**). The risk of gastrointestinal adverse events was highest in one trial of event-driven PrEP, but the estimate

was imprecise (8.0% vs. 1.0%; RR, 8.08 [95% CI, 1.88 to 34.68]).[66] The HPTN 067/ADAPT trial, which compared different PrEP dosing strategies (daily, time-based, or event-driven), found no difference in risk of gastrointestinal events between daily and non-daily PrEP (**Appendix B Tables 1–3**).[130] When stratified according to the PrEP regimen used, the risk of gastrointestinal adverse events was increased for both TDF (5 trials; RR, 1.45 [95% CI, 1.13 to 1.85]; I^2=0%)[51-55] and TDF-FTC (9 trials; RR, 1.84 [95% CI, 1.26 to 2.70]; I^2=49%),[51,54,66-68,118,137,170,172] with no statistically significant interaction by regimen (p=0.30) (**Figure 17**). Among studies that reported rates of diarrhea[51,52,54,66,118,170,172] or vomiting[54,172] separately, none reported a significant difference between PrEP and placebo (**Appendix B Tables 1–3**). Three trials reported that the risk of gastrointestinal events diminished over time.[53,137,170] Serious gastrointestinal events were rare in the trials that reported this outcome, with no differences between PrEP and placebo (**Appendix B Tables 1–3**).[54,55,118,137,170,172]

STIs

There were no differences between PrEP versus placebo or no PrEP in risk of syphilis (4 trials, N=10,775; RR, 1.08 [95% CI, 0.98 to 1.18]; I^2=0%) (**Figure 18**), gonorrhea (5 trials, N=9,296; RR, 1.07 [95% CI, 0.82 to 1.39]; I^2=49%) (**Figure 19**), chlamydia (5 trials, N=9,296; RR, 0.97 [95% CI, 0.80 to 1.18]; I^2=59%) (**Figure 20**), or combined bacterial STIs (2 trials, N=5,291; RR, 1.14 [95% CI, 0.97 to 1.34]; I^2=16%) (**Figure 21**; **Table 9**).[51,118,137,170,172] Combined STIs were defined as gonorrhea, chlamydia, or trichomoniasis in one trial[51] and gonorrhea, chlamydia, or syphilis in the other.[118] When trials were stratified according to the PrEP regimen, TDF was associated with lower risk of chlamydia or gonorrhea versus placebo than TDF-FTC, but neither regimen was associated with increased risk, and only one trial evaluated TDF. All of the trials except for one were blinded. This could affect risk of STIs if participants who do not know whether they are taking PrEP or placebo behave differently than those who know whether or not they are taking PrEP. The open-label PROUD trial,[118] which enrolled MSM, found no statistically significant associations between PrEP versus no PrEP and risk of syphilis (RR, 1.28 [95% CI, 0.76 to 2.16]), gonorrhea (RR, 1.07 [95% CI, 0.86 to 1.34]), or chlamydia (RR, 1.32 [95% CI, 0.98 to 1.79]), although estimates were imprecise and indicated increased risk. Although the unadjusted estimate for risk of combined STIs in PROUD was statistically significant (RR, 1.20 [95% CI, 1.01 to 1.42]), the difference was no longer statistically significant after adjustment for the number of screenings (adjusted OR, 1.07 [95% CI, 0.78 to 1.46]). This is consistent with a higher rate in PROUD of condomless receptive anal intercourse with 10 or more partners among men randomized to PrEP (20%) versus deferred PrEP (12%).[118] In the nonrandomized Demo Project (a PrEP demonstration project in MSM), 26 percent of participants had an STI at baseline and approximately 50 percent had an STI while on PrEP.[177]

PrEP was not associated with increased risk of bacterial STIs when trials (open-label or blinded) were stratified according to whether they evaluated MSM or persons at risk of HIV infection via heterosexual contact (**Table 9**; **Figures 22–25**). The only trial conducted in PWID did not report risk of STI.[53] Results for bacterial STIs were similar when data were pooled using the profile likelihood method.

Based on three trials from the prior USPSTF report that could be pooled, there was no difference between PrEP versus placebo in risk of HSV infection (3 trials, N=4,088; RR, 0.85 [95% CI, 0.67 to 1.07]; I^2=19%) (**Figure 26**).[120,150,170] Two trials evaluated the risk of HSV infection based

on serology in participants who were seronegative for HSV at baseline;[120,150] the other trial did not report the method for diagnosing HSV infection.[170] When stratified according to HIV risk category, PrEP was associated with decreased risk of HSV infection versus placebo in two trials of persons at risk via heterosexual contact (RR, 0.73 [95% CI, 0.56 to 0.96]; I^2=0%)[51] but not in one trial of MSM (RR, 1.12 [95% CI, 0.80 to 1.56])[150] (**Table 9**). However, this analysis was based on few trials, and the test for a subgroup difference was not statistically significant (p=0.06). In the trial included in the prior USPSTF report of MSM, PrEP was not associated with decreased risk of a serological diagnosis of HSV infection, but was associated with lower risk of incident HSV infection with an ulcer (5.9% vs. 2.9%; p<0.05).[150] One new publication of data from IPERGAY reported risk of HSV seroconversion among MSM who were seronegative at baseline, but did not provide data to calculate RR and could not be pooled with the prior trials.[132] It found no association between on-demand PrEP versus placebo and risk of HSV-1 (n=108, HR 2.08, 95% CI 0.63 to 7.92) or HSV-2 (n=218, HR 1.16, 95% CI 0.43 to 3.33) seroconversion.

Hepatitis C Virus Infection

There was no difference between PrEP versus placebo or no PrEP in risk of hepatitis C virus infection, but only two trials (N=896) reported this outcome, and the estimate was imprecise (RR, 0.73 [95% CI, 0.25 to 2.10]; I^2=0%)[66,118] (**Figure 27**). Both trials (PROUD and IPERGAY) evaluated PrEP with TDF-FTC in MSM. There were 6 cases of hepatitis C virus infection in one trial[118] and 8 cases in the other.[66]

Hepatitis B Virus Infection

One trial (VOICE) reported one case of incident hepatitis B virus infection among 1,009 patients randomized to placebo and no cases among 1,007 patients randomized to TDF.[54] Incident hepatitis B virus infection was otherwise not reported. All trials except for two excluded patients with active hepatitis B virus infection. In one trial (Study of TDF), of 56 patients with active hepatitis B infection at baseline (based on hepatitis B surface antigen positive status), the risk of grade 1 asparate or alanine transaminase elevations (≤42 U/L) following discontinuation of study drug was 4.3% (1/23) for those randomized to TDF and 9.1% (3/33) for those randomized to placebo.[55] In the other trial (iPrEx), no cases of hepatitis flare occurred following discontinuation of TDF-FTC in five patients with chronic hepatitis B virus infection.[169]

Pregnancy-Related Outcomes

No trial of PrEP enrolled pregnant persons, and persons who became pregnant during the course of the trial were withdrawn from participation. Three trials reported on pregnancy outcomes in persons who were withdrawn from PrEP because of pregnancy.[68,157,172] In one trial, only one pregnancy occurred among persons randomized to PrEP;[68] in the other two trials, 74 and 192 pregnancies occurred.[51,172] All of the trials were conducted in Africa and evaluated women at increased risk of HIV infection via heterosexual activity. Among persons who became pregnant in the trials, PrEP was not associated with increased risk of spontaneous abortion (N=415, RR, 1.09 [95% CI, 0.79 to 1.50]; I^2=0%) (**Appendix B Tables 1–3**; **Figure 28**). When stratified according to the PrEP regimen used, TDF was not associated with increased risk, but it was only evaluated in one trial (RR, 0.83 [95% CI, 0.50 to 1.37]).[157] TDF-FTC was associated with a trend toward increased risk of spontaneous abortion that was not statistically significant (RR, 1.32

[95% CI, 0.86 to 2.01]; I^2=0%).[68,157,172] There was no statistically significant interaction between the PrEP regimen and risk of spontaneous abortion (p=0.17). The Partners PrEP trial found no differences between PrEP versus placebo in pregnancy rate, risk of preterm birth, birth anomalies, or postpartum infant mortality, and the FEM-PrEP trial found no difference in risk of any adverse pregnancy outcome (**Appendix B Tables 1–3**).[157]

Dapivirine Vaginal Ring vs. Placebo Ring

Two trials of the dapivirine vaginal ring versus placebo ring reported adverse events. Results for serious adverse events were very imprecise (2 trials, N=4,587; RR 1.73, 95% CI 0.60 to 4.94, I^2=80%; **Figure 29**).[73,74] In addition, marked statistical heterogeneity was present, with one trial finding no increase in risk of serious adverse events (4.0% vs. 3.6%, RR 1.09, 95% CI 0.74 to 1.60) and the other finding an increased risk (2.9% vs. 0.9%, RR 3.16, 95% CI 1.34 to 7.44). In the trial reporting increased risk, the most common serious adverse events were various infections (1.1%) and injuries (0.6%) that did not appear related to use of PrEP. One trial (n=1,959) found no differences between the dapivirine ring versus placebo in risk of any STI (RR 1.06, 95% CI 0.96 to 1.16).[74] Pooled analyses of the two RCTs found no differences between the dapivirine vaginal ring versus placebo and risk of chlamydia (N=4,587; RR 0.98, 95% CI 0.89 to 1.07, I^2=0%), gonorrhea (N=4,587; RR 1.01, 95% CI 0.80 to 1.27, I^2=63%), or trichomoniasis infection (N=4,587; RR 1.06, 95% CI 0.92 to 1.23, I^2=0%) (**Figures 30–32**).[73,74] One trial reported no difference in risk of syphilis (1.3% vs. 0.8%).[74] In both trials, pregnancy incidence was similar for the dapivirine ring and placebo (3.9 vs. 4.0 per 100 person-years and 1.6 vs. 2.0 per 100 person-years). Neither trial reported congenital abnormalities.

Event-Driven vs. Daily Oral PrEP

One small, new, crossover trial (n=119) found event-driven oral PrEP associated with decreased risk of any adverse event versus daily oral PrEP (8% [10/119] vs. 31% [37/119], RR 0.27, 95% CI 0.14 to 0.52).[144] All adverse events were grade 1 except for in one patient, who reported grade 2 symptoms. The most common adverse events were diarrhea, headache, lethargy, dizziness, dyspepsia, and nausea. There was no difference between regimens in change in creatinine clearance (data not provided). Due to the crossover design of the trial, it was not able to compare effects of event-driven versus daily oral PrEP on risk of STIs.

Key Question 5. What Are the Harms of Newer PrEP Regimens (Oral TAF-FTC, Injectable Cabotegravir, or the Dapivirine Vaginal Ring) vs. TDF-FTC?

Summary

Daily Oral TAF-FTC vs. TDF-FTC

Based on one trial (n=5,387)[162]:

- No differences between TAF-FTC versus TDF-FTC in risk of serious adverse events (7% vs. 7%), discontinuation due to adverse events (1% vs. 2%), or any adverse event (94% vs. 94%).
- No differences between TAF-FTC versus TDF-FTC in rates of any renal adverse event (10% vs. 10%) or renal adverse events leading to discontinuation (0.07% vs. 0.2%).
- No difference between TAF-FTC versus TDF-FTC in the risk of fracture (2% vs. 2%); however, among persons 25 years of age or older, TAF-FTC was associated with greater percent change from baseline than TDF-FTC in hip bone mineral density (+0.6% vs. -1.0%, p<0.001) and spine bone mineral density (+0.9% vs. -1.4%, p<0.001).
- TAF-FTC was associated with smaller reduction from baseline versus TDF-FTC in low density lipoprotein cholesterol (median -0.05 vs. -0.18 mmol/L, p<0.0001) and greater weight gain (median +1.7 vs. +0.5 kg, p<0.0001).

Long-Acting Injectable Cabotegravir vs. Daily Oral TDF-FTC

Based on two trials (N=7,786)[70,88]:

- No differences between long-acting injectable cabotegravir versus daily oral TDF-FTC in risk of serious adverse events (5.3% vs. 5.3% and 2.0% vs. 2.0%) or grade 3 or higher adverse events (31.9% vs. 33.6% and 17.1% vs. 17.4).
- No differences between cabotegravir versus TDF-FTC in risk of grade 2 or 3 renal (decreased creatinine clearance) or liver (increased alanine or aspartate transaminase) events, risk of discontinuation due to liver-related adverse events, or risk of STIs.
- Cabotegravir was associated with increased weight gain versus TDF-FTC (mean differences 0.86 and 0.4 kg).
- Cabotegravir was associated with increased risk of injection site reactions (most commonly, pain) versus TDF-FTC (81.4% vs. 31.3% and 38.0% vs. 10.8%) that were usually mild and diminishing following the initial injection.
- In one trial that enrolled women, pregnancy incidence was low with cabotegravir and TDF-FTC (1.5 [95% CI, 1.0 to 2.2] vs. 1.0 [95% CI, 0.6 to 1.6] per person-years), with no congenital abnormalities observed.[88]

Evidence

Daily Oral TAF-FTC vs. TDF-FTC

The DISCOVER trial (n=5,387)[121] found no difference between TAF-FTC versus TDF-FTC in risk of serious adverse events (7.5% vs. 6.9%) or discontinuation of study drug due to adverse events, which was uncommon (1.5% vs. 1.9%).[162] The types of serious adverse events varied and most did not appear related to PrEP (e.g., appendicitis, suicidal ideation or attempt, hepatitis A, pneumonia, depression, cellulitis, acute kidney injury, or atrial fibrillation). Rates of any adverse event (94% vs. 94%) were very similar; the most common non-STI adverse event was diarrhea (18% vs. 17%). There were also no differences in rates of sexually transmitted infections (rectal or urethral chlamydia, rectal or urethral gonorrhea, or syphilis) (**Appendix B Tables 1–3**).

There were also no differences between TAF-FTC versus TDF-FTC in rates of any renal adverse event (10% vs. 10%) or renal adverse events leading to discontinuation (0.07% vs. 0.2%). Regarding bone adverse events, there was no difference in the risk of fracture (2.2% vs. 2.2%) or nontraumatic fracture (1 vs. 2 cases; <1% in each arm). However, among persons 25 years of age or older, TAF-FTC was associated with greater percent change from baseline than TDF-FTC in hip bone mineral density (+0.6% vs. -1.0%, p<0.001) and spine bone mineral density (+0.9% vs. -1.4%, p<0.001).

TAF-FTC was associated with smaller reduction from baseline versus TDF-FTC in low density lipoprotein cholesterol (median -0.05 vs. -0.18 mmol/L, p<0.0001) and greater weight gain from baseline versus TDF-FTC (median +1.7 vs. +0.5 kg, p<0.0001).

Long-Acting Injectable Cabotegravir vs. Daily Oral TDF-FTC

In HPTN 083 and 084 (N=7,786), there were no differences between long-acting injectable cabotegravir versus daily oral TDF-FTC in risk of serious adverse events (5.3% [120/2280] vs. 5.3% [121/2282] and 2.0% [33/1614] vs. 2.0% [33/1610]) or grade 3 or higher adverse events (31.9% [727/2280] vs. 33.6% [767/2282] and 17.1% (276/1614) vs. 17.4% [280/1610]) (**Appendix B Tables 1–3**).[70,88] There were also no differences in risk of grade 2 or 3 renal (decreased creatinine clearance) or liver (increased alanine or aspartate transaminase) events, risk of discontinuation due to liver-related adverse events, or risk of incident rectal or urethral gonorrhea, rectal or urethral chlamydia, or syphilis infections. In both trials, cabotegravir was associated with increased weight gain versus TDF-FTC, which occurred early during treatment (mean differences 0.86 and 0.4 kg). Injection site reactions (most commonly, pain) were more frequent with cabotegravir than TDF-FTC (81.4% vs. 31.3% and 38.0% vs. 10.8%). Injection site reactions were usually mild and occurred most commonly with the first injection, with diminishing frequency over time. In one trial that enrolled women (HPTN 084), pregnancy incidence was similar and low with cabotegravir and TDF-FTC (1.5 [95% CI 1.0 to 2.2] vs. 1.0 [95% CI 0.6 to 1.6] per 100 person-years), with no congenital abnormalities observed.[88]

Contextual Questions

Contextual Question 1. What Are Rates of Adherence to and Persistence of PrEP and Factors Associated With Increased or Decreased Adherence in U.S. Primary Care Settings?

Adherence, or medication compliance, refers to the degree to which patients take medications as directed (e.g., every day for oral daily PrEP). The prior USPSTF report[2] found a strong association between increased adherence and greater PrEP effectiveness. In six placebo-controlled trials in which adherence was 70 percent or greater, the pooled RR of PrEP for preventing HIV infection was 0.27 (95% CI, 0.19 to 0.39; I^2=0%).[51,52,66,67,118,170] Additional subgroup and modeling analyses also support the association between increased adherence and greater PrEP effectiveness. One analysis based on trial data estimated a 96 percent reduction in HIV infection risk among MSM taking at least four oral PrEP doses a week,[178] suggesting important benefits even when adherence is incomplete.

Methods for measuring adherence include drug levels (plasma, dried blood spot levels, or urine), self-report, pill count, and others. Some studies have shown lower levels of adherence based on drug levels than by self-report or pill counts,[54,128,141,179,180] although other evidence indicates more concordance.[118] Some discrepancies between drug levels and self-reported adherence or pill counts could be related to use of financial incentives or other benefits for trial participation (patients in such a trial might have concerns about trial dismissal and loss of financial compensation or access to care as a result of low adherence) or social desirability bias (patients might overreport adherence to avoid disappointing study personnel with whom they have developed relationships).[181] Dried blood spot samples measuring intracellular drug concentrations of TFV-DP (the active moiety of tenofovir) reflect longer-term cumulative drug exposure compared with tenofovir plasma levels, correlating with the number of doses taken in the last several weeks (plasma levels indicate dosing within the last week).

Persistence refers to continuation of treatment for the prescribed length of time.[182] Persistence and adherence are distinct concepts; among patients with PrEP persistence, adherence may be incomplete or fluctuate. Persistence is a necessary condition for PrEP effectiveness, though patients may re-start PrEP following periods of non-persistence. Definitions and methods for measuring persistence vary and include temporary or permanent discontinuation of PrEP, lapses in prescription coverage that exceed specified thresholds, or non-retention in PrEP care.

In the United States, evidence on adherence is primarily available for daily oral PrEP in populations of MSM (**Appendix D Table 1**). In five observational studies of primarily MSM, adherence rates ranged from 22 to more than 90 percent, based on TFV-DP dried blood spot levels of 700 fmol/punch or greater (consistent with an average of ≥4 pills/week over the last 1 to 2 months).[177,183-186] One study (n=557) found that the proportion of patients meeting the adherence threshold ranged from 80 to 86 percent from week 4 to 48 (proportion meeting the adherence threshold on all samples, 62 percent),[177] and another study (n=301) found that adherence was 83 percent at week 4 and 66 percent at week 48.[186] A smaller study (n=50) found that 90 percent (19/21) of patients met the adherence threshold at a mean PrEP duration of 4.4

months.[185] Two other studies (n=200 and 72) using dried blood spot samples reported lower adherence rates.[183,184] Both focused on younger MSM (mean ages 20 and 16 years) than the studies described above (mean age >30 years). The proportion of patients meeting the 4 or more doses/week threshold was approximately 50 percent at week 12, decreasing to 34 and 22 percent at week 48. The proportion of patients with dried blood spot levels of 350 fmol/punch or greater (consistent with ≥2 doses/week) was 72 and 59 percent at week 12, decreasing to 49 and 26 percent at week 48.

Several U.S. studies reported adherence in MSM using methods other than dried blood spot samples. Two studies described above found adherence rates based on self-report were similar to rates based on dried blood spot testing.[177,185] Another observational study (n=267)[187] found that 92 percent of patients reported taking four or more pills in the last week at 3 and 6 months. An RCT of a group-based behavioral HIV prevention intervention in young MSM (n=20 randomized to PrEP) found tenofovir detected in 63 percent of plasma samples among those randomized to PrEP at week 4, decreased to 20 percent at week 24.[141] Another RCT of MSM (n=373) utilized medication event monitoring system data.[52] Adherence was 79 percent based on doses taken and 93 percent based on pill count.

An RCT (n=179) of MSM (97%) and transgender women (2%) enrolled at a U.S. site compared adherence with daily, intermittent, and event-driven oral PrEP, based on TFV-DP dried blood spot levels of 326 fmol/punch or greater (consistent with ≥2 doses/week; 2 doses per week associated with an estimated reduction in risk of HIV acquisition of 76%[178]).[136] During weeks in which sex was reported, adherence was higher for daily (49%) than intermittent (31%) or event-driven (17%) PrEP. Adherence was also higher for daily PrEP than intermittent or event-driven PrEP based on event monitoring system data (65% vs. 46% vs. 41% of tablets used/recommended, respectively).

Among U.S. MSM, evidence on factors associated with higher or lower adherence suggests differences in adherence based on race/ethnicity, socioeconomic status or other social determinants, and presence of higher-risk behaviors. One study (n=557; mean age 34 to 35 years) of MSM (98%) and transgender women (1.4%) found Black race associated with lower adherence compared with White race (adjusted OR, 0.28 [95% CI, 0.12 to 0.64]).[177] Latino, Asian, and "other" race/ethnicity were also associated with decreased likelihood of adherence, but estimates were imprecise and differences were not statistically significant. The study also found having stable housing (renting or owning) associated with higher adherence versus less stable housing (living with friends or family, public housing, or homeless) (adjusted odds ratio [OR], 2.02 [95% CI, 1.14 to 3.55]) and having condomless receptive anal sex with two or more partners (vs. 0 or 1 partner) in the past 3 months associated with higher adherence (adjusted OR, 1.82 [95% CI, 1.14 to 2.89]). There were no clear associations between age, educational level, PrEP awareness, income level, health insurance status, depression, and alcohol or drug use and adherence to PrEP. A study of younger (ages 18 to 22 years) MSM (n=200) found that those who reported engaging in recent sex without condoms had higher TFV-DP levels than those who did not report this behavior (p=0.01).[184] There was a similar but statistically nonsignificant trend toward higher TFV-DP levels among participants who reported condomless receptive anal sex with their last sexual partner. Patients who did not like taking pills were more likely to be

nonadherent (p=0.02). Evidence on differences in adherence among MSM by mode of PrEP administration is addressed in Contextual Question 2.

Evidence on adherence with PrEP in U.S. populations other than MSM is limited. A large observational study (n=1,086, indication for PrEP not reported), which assessed adherence based on prescription refill data, found the median proportion of days covered in the first year was 0.74 (interquartile range, 0.40 to 0.92).[188] In this study, older age (ages 50 to 64 vs. <35 years; adjusted OR, 2.00 [95% CI, 1.37 to 2.92]), being men (vs. women; adjusted OR, 3.39 [95% CI, 1.37 to 8.42]) and White race (vs. Black race; adjusted OR, 2.02 [95% CI, 1.43 to 2.87]) were associated with increased adherence.[188] Other factors, including comorbid substance use disorder or depression, low socioeconomic status, rural living, and region of the United States, were not significantly associated with adherence. A small (n=29) study evaluated PrEP adherence among people (72% men, 93% heterosexual) with opioid use disorder and receiving HCV treatment. It found that the proportion of patients with dried blood spot levels consistent with ≥4 doses/week was 68% at week 24, declining to 25% at week 36. Estimates based on dried blood spot levels were substantially lower than adherence based on self-report, which was 71% at 12 weeks and 88% at 48 weeks.

Evidence on PrEP persistence in U.S. populations indicates that discontinuations are frequent (**Appendix D Table 1**). However, interpretation is complicated by differences in the methods used to measure persistence and the populations assessed. A large (n=13,906; 95% men) observational study of persons in an integrated health system found that among those who initiated PrEP, 52.5% (95% CI 48.9% to 55.7%) discontinued PrEP at least once, defined as >120 days without PrEP based on pharmacy refill data.[107] At 2 years, the proportion who had discontinued PrEP was 38.4% (95% CI 37.2% to 39.6%). Among those who discontinued at least once, the proportion who reinitiated PrEP was 60.2% (95% CI 52.2 to 68.3%). The highest rates of discontinuation occurred in the first two years after initiating PrEP. In unadjusted analyses, factors associated with increased likelihood of discontinuation were younger age (<45 years, HR 2.17, 95% CI 1.92 to 2.38), Black race (vs. White race, HR 1.36, 95% CI 1.17 to 1.57), Latino ethnicity (vs. White non-Latino, HR 1.33, 95% CI 1.22 to 1.46), being a woman (HR 1.99, 95% CI 1.67 to 2.38), greater neighborhood deprivation (vs. highest quintile, HR 1.40, 95% CI 1.26 to 1.57 for lowest quintile), and having a substance use disorder (HR 1.23, 95% CI 1.09 to 1.39). Another large study (n=7,148; 97% men) of PrEP users in a national pharmacy database found rates of persistence (defined as at least 16 days of PrEP filled per 30-day period for at least three-quarters of a 12 or 24 month period) were 56 percent in year 1 and 41 percent in year 2.[189] Factors associated with increased likelihood of persistence were older age (for 50+ years vs. 18 to 24 years, adjusted OR 2.77, 95% CI 2.25 to 3.41), being a man (adjusted OR 2.46, 95% CI 1.77 to 3.41), having commercial insurance (vs. government, adjusted OR 1.96, 95% CI 1.69 to 2.27; vs. cash/other, adjusted OR 1.69, 95% CI 1.33 to 2.13), and having a lower copay (≤$20 vs. >$20, adjusted OR 1.64, 95% CI 1.45 to 1.85). Another large study (n=11,807; 98% men) reported persistence (defined as no gap in refills >30 days) of 54.0 percent in a commercially insured cohort and 29.9 percent in a Medicaid-insured cohort.[190] As in the prior two studies, being a man and older age were associated with increased likelihood of persistence; among Medicaid-insured patients, Black race was associated with decreased likelihood of persistence versus White race (4.7% vs. 7.3%, p=0.003). A study of Veterans Affairs patients (n=1,086; 96% men) found that 44 percent discontinued PrEP in the first year (defined as a >120 day gap).[188]

Discontinuation was more common among younger persons (<35 vs. 50-64 years, 51.5% vs. 39.2%, p=0.008), Black compared with White persons (52.4% vs. 41.6%, p=0.05), and women versus men (80.0% vs. 42.8%, p<0.001). The above studies were based on analyses of administrative or pharmacy databases; information regarding indication for PrEP was not available. A smaller study (n=271, 86% men, 81% MSM) of persons using PrEP in two health centers found that 47.2 percent discontinued PrEP (defined as missing more than 2 quarterly visits with no additional visits by the end of follow-up) and 11.4 percent had intermittent care (missing at least 2 quarterly visits but then reinitiating care).[191] Factors associated with decreased risk of discontinuation included older age (adjusted OR 0.97, 95% CI 0.94 to 1.00) and being an MSM (vs. non-MSM, adjusted OR 0.26, 95% CI 0.10 to 0.64); estimates for race/ethnicity and having a partner with HIV were imprecise.

In six U.S. studies (n=50 to 693) of primarily or exclusively MSM, discontinuation rates (variably defined) ranged from 15% to 69% (**Appendix D Table 1**).[177,185,187,192-194] In the largest (n=663) study, factors associated with decreased time to discontinuation were younger age (vs. 30 to 39 years, adjusted HR for 18 to 24 years 2.0, 95% CI 1.4 to 2.9; adjusted HR for 25 to 29 years 2.2, 95% CI 1.6 to 3.1), being a transgender woman (vs. cisgender man, adjusted HR 2.0, 95% CI 1.2 to 3.4), and having more mental health disorders (per additional disorder, adjusted HR 1.2, 95% CI 1.1 to 1.4). Another study (n=267) found no clear association between age, race/ethnicity, educational level, being a man who has sex with men, income, or insurance status and likelihood of retention in care, though some estimates were imprecise.[187]

Evidence on rates of and factors associated with PrEP persistence in populations other than MSM was very limited. A study (n=51) of transgender men (80%) or women (20%) found that among those who ever received PrEP, 49 percent (25/51) had discontinued.[195] A small (n=21) study of heterosexual women initiated on PrEP found that 61 percent (13/21) were retained in care (defined as a clinic visit within 1 month) at 3 months and 37.5 percent (8/21) were retained at 6 months.[196] A small study (n=29) of people using PrEP with opioid use disorder receiving HCV treatment found that retention decreased from 86.2 percent (25/29) at week 4 to 31.0 percent (9/29) at week 36.

Contextual Question 2. How Does Adherence to and Persistence of PrEP Vary According to Mode of Administration (e.g., Oral, Injectable, or Vaginal Ring)?

Two head-to-head trials compared injectable cabotegravir versus daily oral TDF-FTC.[70,88] The method used to assess adherence differed for the two modalities. For cabotegravir, adherence was based on "coverage," defined as no delay of longer than two weeks between scheduled injections. For TDF-FTC, adherence was measured using dried blood spot levels consistent with ≥4 doses/week. In HPTN 083 (n=4,570; U.S. 37%), which enrolled 87 percent MSM and 12 percent transgender women, coverage with injectable cabotegravir was 91.5 percent of person-years, compared with adherence with oral TDF-FTC of 72.3 percent based on dried blood spot samples.[70] In HPTN 084 (n=3,898), which was conducted in women in Africa, coverage with injectable cabotegravir was 93.0 percent of person-years, compared with adherence with oral TDF-FTC of 42 percent based on dried blood spot samples.[88] In both trials, discontinuation rates

with cabotegravir and TDF-FTC were similar (19.5% vs. 20.3% in HPTN 083 and 5.3% vs. 6.8% in HPTN 084). Because participants in these trials were blinded to receipt of cabotegravir or TDF-FTC (via a placebo injection or tablet), generalizability to clinical practice is uncertain.

Evidence comparing adherence and persistence using the dapivirine ring versus oral PrEP is very limited. Published trials of the dapivirine ring used a placebo comparator. Interim results from one crossover trial, which compared the dapivirine ring versus daily oral PrEP in young (16 to 21 years) women in Africa, have been reported as a conference abstract.[197] "High" adherence (defined as dapivirine levels indicating release of 3.0 mg/28 d) was observed in 50.2 percent (687/1368 timepoints) of ring users (based on residual drug levels) and 22.4 percent (294/1310 timepoint) of oral PrEP users (based on dried blood spot levels).

Contextual Question 3. What Is the Risk of Infection With Antiretroviral Drug–Resistant HIV in Persons Using PrEP, and What Is the Effect of Infection With PrEP-Related, Antiretroviral Drug–Resistant HIV on Treatment Outcomes?

Ten placebo-controlled RCTs, all included in the prior USPSTF review, reported rates of antiretroviral drug resistance in persons randomized to oral PrEP with TDF or TDF-FTC (N=8,661) (**Appendix D Table 2**).[51-55,66,118,137,170,172] One trial evaluated event-driven PrEP[66] and the other nine trials evaluated daily PrEP. Five trials evaluated PrEP with TDF alone[51-55] and seven trials evaluated TDF-FTC;[51,66,137,172] two trials[51,54] evaluated both regimens. The most commonly reported mutations were the tenofovir resistance mutations K65R and K70E and the emtricitabine mutations M184I and M184V (both tenofovir and emtricitabine are nucleoside reverse transcriptase inhibitors).

Resistance rates were low with oral PrEP. Among all patients randomized to PrEP, 0.06 percent (2/3,149) of patients on TDF (4 trials)[51-54] and 0.3 percent (14/5,085) of patients on TDF-FTC (7 trials)[51,54,66,118,137,170,172] were identified as having incident HIV infection with a drug resistance mutation. Among patients with incident HIV infection, 1.1 percent (3/282) had a tenofovir resistance mutation.[51,53-55,66,118,137,170,172] Seven of the trials reported no cases of tenofovir resistance mutations (N=198),[53,54,66,118,137,172] and two trials reported one or two cases (n=10[170] and n=35[51]). All three cases were attributed to undiagnosed baseline HIV infection and involved M184V and K65R mutations (including one case of multiple resistance mutations to K65R, M184V, and A62V).[51,170] No other case of multidrug resistance was identified in patients randomized to PrEP.

In six trials of PrEP with TDF-FTC, 8 percent (14/174) of patients diagnosed with HIV infection after initiating PrEP were diagnosed with emtricitabine resistance mutations (M184I or M184V).[51,54,66,118,137,170,172] The number of cases of emtricitabine resistance in each trial ranged from 0 to 4. Nine of the 14 cases of emtricitabine resistance occurred in persons who were infected with HIV upon trial enrollment, including 1 case of multiple resistance mutations described above.

Data on drug resistance mutations in patients using oral PrEP were also available from the iPrEX-OLE observational study,[198] which enrolled patients (n=1,225) from the United States, South Africa, South America, and Thailand, and four U.S.-based observational studies (total N=696) (**Appendix D Table 2**).[177,183-185] All of these studies evaluated PrEP with daily TDF-FTC. Among a total of 1,936 patients receiving PrEP across the observational studies, two were diagnosed with an antiretroviral drug resistance mutation (0.1%). In iPrEx-OLE, one of 28 patients (3.6%) diagnosed with HIV infection had the M184V mutation.[198] Among the four U.S.-based studies, one of 10 patients diagnosed with HIV infection while on PrEP was found to have M184V and multiple thymidine analog mutations.[185]

Data to compare risk of antiretroviral resistance associated with different oral PrEP regimens are limited. For event-driven PrEP, one placebo-controlled trial (n=400) reported two cases of HIV infection among patients randomized to PrEP, with no resistance mutations identified;[66] a head-to-head trial (n=119) of daily versus event-driven PrEP was not designed to evaluate HIV incidence or antiretroviral resistance.[144] The DISCOVER Trial (n=5,387) compared oral TAF-FTC versus TDF-FTC.[121,162] Among 20 patients who were infected with HIV infection and had resistance testing results, an M184V or M184I resistance mutation was detected in four patients. All of the infections occurred in patients randomized to TDF-FTC who were suspected of having an infection at baseline.

Two placebo-controlled trials (ASPIRE and the Ring Study) not included in the prior USPSTF report provided data on resistance mutations with the dapivirine vaginal ring.[73,74] Dapivirine is a nonnucleoside reverse transcriptase inhibitor (NNRTI). Across both trials, the proportion of patients randomized to dapivirine with an NNRTI resistance mutation was 0.8 percent (22/2,620). In ASPIRE, the rate of NNRTI resistance mutations among patients with incident HIV infection was similar in patients randomized to the dapivirine ring versus those randomized to placebo (11.8% [8/68] vs. 10.4% [10/96], p=0.80).[73] Among dapivirine ring patients, there were two cases of the K103N mutation, two cases of the V90I mutation, three cases of the E138A mutation, and one case each of the K101E, K103S, V106M, V108I, E138G, V179D, and H221Y mutations. In the Ring Study, the rate of NNRTI resistance mutations was also similar between the dapivirine ring and placebo arms (18.2% [14/77] vs. 16.1% [9/56], p=0.75). Dapivirine was associated with a nonstatistically significant increased risk of E138A resistance mutations versus placebo (11.7% [9/77] vs. 1.8% [1/56], p=0.07); other specific NNRTI resistance mutations (A98G, K103N, K101E, V106M, V090I, V108I, E138Q, Y181C, Y188C, H221Y) were less common (occurring in 1 to 5 patients across both arms).[74] In open label extensions of these trials (N=2,397), NNRTI resistance mutations (K103N, E138A, A98G, V179D, V106M, K101E) occurred in 20% (7/35) and 29% (5/17) of patients with incident HIV infection.[111,112]

Two new trials (HTPN 083 and 084) provided data on resistance mutations among persons randomized to injectable cabotegravir versus daily oral TDF-FTC.[70,88] Cabotegravir is an integrase strand transfer inhibitor (INSTI). Across both trials, among all patients randomized to cabotegravir, the proportion with an INSTI resistance mutation was 0.1 percent (4/3874). In HPTN 083, INSTI resistance mutations were observed in 4 of 9 (44.4%) incident HIV cases in whom resistance testing was available (resistance testing unavailable for 4 incident HIV infections); one such mutation was identified in a patient with baseline infection.[70] In HPTN 084,

there were no cases of INSTI resistance mutations in four individuals with incident HIV infections.[88] Neither trial reported any cases of INSTI resistance mutation acquired following cessation of cabotegravir, during the pharmacological tail period. Among individuals randomized to TDF-FTC across both trials, the proportion with antiretroviral resistance mutations was 0.1 percent (5/3870). In HPTN 083, among individuals randomized to TDF-FTC, nucleoside reverse transcriptase inhibitor resistance mutations (K65R, M184V and M184I) with or without a nonnucleoside reverse transcriptase inhibitor mutation were identified in four of 39 (10.3%) incident cases.[70] In HPTN 084, one of 36 (2.8%) patients randomized to TDF-FTC with incident infection had an M184V (nucleoside reverse transcriptase inhibitor) resistance mutation and "several" participants (specific data not provided) had a nonnucleoside reverse transcriptase inhibitor resistance mutation (primarily K103N).[88]

Evidence on effects of acquiring antiretroviral resistant HIV infection while receiving PrEP on clinical outcomes is very limited but suggests that virological suppression with antiretroviral therapy remains achievable. One study reported that among five patients previously exposed to PrEP and diagnosed with HIV infection with an M184V or M184I mutation, four had an undetectable viral load 3 months after starting antiretroviral therapy, with one patient lost to followup.[199] All patients received TDF and FTC with either darunavir and cobicistat or dolutegravir. Another study found that among patients diagnosed with HIV infection, 52 reported recent PrEP exposure.[200] Of these, 30 percent (13/52) had an M184V or M184I infection, 3.8 percent (2/52) had another nucleoside reverse transcriptase inhibitor resistance mutation (L74V or M41L and/or L210W and/or T215Y/F), and 9.6 percent (5/52) had a nonnucleoside reverse transcriptase inhibitor resistance mutation (3 K103N/S, 1 V108V/I, and 1 G190A/S/E); there were no protease inhibitor resistance mutations. All 39 individuals with a viral load >200 copies/mL at baseline who received antiretroviral therapy achieved an undetectable viral load at 24 weeks. All patients were started on tenofovir-based antiretroviral therapy, with the third agent boosted darunavir, bictegravir, dolutegravir, or raltegravir; 43 percent of patients were switched off boosted darunavir to an integrase inhibitor combination within 3 months from antiretroviral therapy initiation based on clinic protocol. Results were not reported separately for patients with antiretroviral resistance mutations. No study was designed to evaluate effects of infection with antiretroviral resistant HIV infection while on PrEP on long-term clinical outcomes. When PrEP-selected mutations occur, some data indicates the mutations will become undetectable in the absence of antiretroviral therapy but "archived" mutations (those that reemerge following exposure to antiretroviral therapy) are possible.[201]

Contextual Question 4. What Factors (e.g., Race and Ethnicity, Age, Sex, Gender, Sexual Orientation, HIV Risk Category, Socioeconomic Status, Cultural Factors, Educational Attainment, or Health Literacy) Are Associated With Disparities in Utilization of PrEP?

National CDC surveillance data indicate that in 2019 (the last year with reliable data); PrEP coverage (the proportion of persons with PrEP indications who were prescribed PrEP) was higher among men (25.5%) than women (9.3%); higher among White persons (60.5%) than

Black (7.9%) or Hispanic/Latinx (13.8%) persons; and lower among persons 16 to 24 years of age (15.0%) compared with adults ≥25 years of age (19.6% to 26.6%).[103] The surveillance data did not report utilization by HIV risk category and did not control for other factors that could impact utilization. Additional data on disparities in utilization of PrEP in the United States were available from a recent (searches through 2019) meta-analysis of 95 surveys[93] (N=95,854), six large recent additional studies (three nationwide surveys [n=4,475,[202] n=10,504,[203] n= 4,056[204]], and three retrospective cohorts [n=13,906,[107] n=23,312,[205] n=25,886[206]]. Two smaller studies focused on specific factors associated with PrEP utilization in MSM[207,208] and one study focused on the association between insurance status and PrEP utilization.[104] Evidence primarily focused on disparities in utilization among MSM; data on HIV risk categories other than MSM were limited. Although evidence indicates disparities in PrEP utilization related to age, sexual orientation, socioeconomic status, and educational attainment, evidence on disparities related to race and ethnicity were somewhat inconsistent. Data on disparities related to gender were limited, and data on disparities related to health literacy were lacking. A challenge in interpreting data on PrEP utilization is the intersectionality between multiple factors potentially associated with disparities.

The meta-analysis included 95 surveys of self-reported PrEP use in U.S. populations at higher risk for HIV infection; 46 surveys collected data from 2015-2017, subsequent to the publication of the Centers for Disease Control and Prevention guideline on PrEP. In 2015-2017, the overall proportion of respondents reporting PrEP use was 11.3%, whereas from 2004-2014, the proportion of respondents with PrEP use ranged from 0.3% to 3.2%. Eighty studies reported PrEP use in MSM, 26 studies in Black persons, 19 in Hispanic/Latinx persons, and 19 studies in youth. Few studies reported PrEP use in PWID (k=6), transgender women (k=9) and cisgender or unspecified women (k=4). From 2015-2017, MSM were more likely to report PrEP use (pooled prevalence [PP] 13.9%, 95% CI 8.8 to21.1) than non-MSM (PP 5.3%, 95% CI 3.7 to 7.5) and other groups at high risk for HIV acquisition, including PWID (PP 3.7%, 95% CI 0.8 to 16.1) and transgender women (PP 11.2%, 95% CI 5.8 to 20.6). Youth, even when including MSM, reported relatively low PrEP use (PP 7.3%, 95% CI 4.7 to 11.2). Hispanic/Latinx (PP 11.5%, 95% CI 7.1 to 18.1) and Black persons (PP 9.9%, 95% CI 8.3 to 11.8) reported PrEP use at rates similar to the overall proportion. The meta-analysis was not limited to surveys of individuals at high HIV acquisition risk; although surveys generally focused on populations frequently at risk for HIV acquisition (e.g., MSM, PWID, or persons attending STI clinics or in other higher-risk settings), they did not necessarily exclude individual respondents within those populations at lower risk. The meta-analysis had other limitations including reliance on self-report data, potential overlap among surveyed populations, high statistical heterogeneity among included studies (even when restricting analysis to only include recent surveys), and inclusion of some studies (k=19) assessed as having high risk for bias.

Eight additional studies published after the systematic review also reported disparities in PrEP utilization in different U.S. populations. Five studies reported factors associated with PrEP utilization in MSM; each accounted for confounders such as demographic factors, geographic location, HIV risk factors, income, and education. A survey of 4,475 MSM (891 considered PrEP-eligible), found no difference in utilization by race/ethnicity (Black versus White adjusted prevalence ratio [aPR] 1.09, 95% CI 0.88 to 1.37; Hispanic versus White aPR 0.91, 95% CI 0.76 to 1.09) but did find differences in utilization based on age <25 years versus ≥25 years (aPR

0.44, 95% CI 0.35 to 0.55), rural versus urban MSM (aPR 0.45, 95% CI 0.33 to 0.62) and insured versus uninsured MSM (aPR 2.98, 95% CI 1.93 to 4.59).[202] Another survey of 10,504 people at high risk of HIV acquisition (predominantly MSM) compared current PrEP users and PrEP-naïve individuals.[203] It found no differences in PrEP utilization by race/ethnicity (vs. White persons, adjusted odds ratio [aOR] for Black race 0.92, 95% CI 0.71 to 1.18; for Latino ethnicity aOR 0.95, 95% CI 0.83 to 1.09; for Asian race aOR 0.90, 95% CI 0.77 to 1.05) and no difference in utilization between MSM and transgender women (aOR= 1.27, 95% CI 0.41 to3.88). However, increasing age (aOR 1.2, 95% CI 1.16 to 1.24) and higher education (aOR 1.91, 95% CI 1.65 to 2.20) were associated with increased likelihood of PrEP use while bisexual orientation (aOR 0.67, 95% CI to 0.62 to 0.72), low income (aOR 0.47, 95% CI 0.37 to 0.59), housing instability (aOR 0.79, 95% CI 0.65 to 0.96) and residence in a state without Medicaid expansion (aOR 0.62, 95% CI 0.5 to 0.76) were associated with decreased likelihood of PrEP. utilization. A survey of 4,056 MSM with likely PrEP indications found that White MSM were more likely than Latino or Black MSM to use PrEP (White versus Hispanic aPR 1.2, 95% CI 1.1 to 1.3; White versus Black aPR 1.4, 95% CI 1.2 to 1.6).[204] One study (n=368) found MSM at increased risk for HIV acquisition with an HIV-positive main partner were more likely to use PrEP than those without an HIV-positive main partner (OR =3.12; 95% CI=1.05–9.31)[207] and one study (n=863) found certain forms of intimate partner violence associated with decreased PrEP use.[208]

Two large, recent retrospective studies described PrEP use in general U.S. populations eligible for PrEP. In a retrospective review of 13,906 individuals referred to PrEP or with a PrEP-coded encounter within a single healthcare system, Black and Latino patients were slightly less likely than Asian patients to initiate PrEP compared to White patients (vs. White patients, HR for Black patients 0.87, 95% CI 0.80 to 0.95; for Latinx patients HR 0.90, 95% CI 0.86 to 0.95; and for Asian patients HR 1.06, 95% CI 1.00 to1.12).[107] Some disparities in utilization were also identified for younger (age ≤45) versus older persons (HR 1.09, 95% CI 1.02 to 1.1), women versus men (HR 0.71, 95% CI 0.64 to 0.80), people with a substance use disorder versus no substance use disorder (HR 0.88, 95% CI 0.81 to 0.95.), people of lower versus higher socioeconomic status (HR 0.93, 95% CI 0.87 to 0.99) and people with public versus private insurance (HR 0.96, 95% CI 0.86 to1.07). A retrospective review of 23,312 patients within the Veteran Health Administration (8,001 patients with indication for PrEP based on diagnosis of gonorrhea or early syphilis) also found some disparities in PrEP initiation by race (White vs. Black, OR 1.7, 95% CI 1.0 to2.7) and age (<35 years vs. 35-49 years, OR1.3, 95% CI 0.8 to2.0), though estimates were imprecise and not statistically significant. In this study, men were more likely to initiate PrEP than women (OR 6.2, 95% CI 2.5 to15.2) and urban residence was associated with increased likelihood of PrEP initiation than rural residence (OR 5.0, 95% CI 1.8 to 13.5).[205] A retrospective review of 25,886 people (8,063 with a PrEP indication) found no difference in likelihood of PrEP prescriptions between Black versus White patients (aPR 0.92, 95% CI 0.84 to 1.00) or Hispanic versus White patients (aPR 1.10, 95% CI 0.97 to 1.23).[206] Among PWID, non-MSM were less likely to be prescribed PrEP than MSM (aPR 0.72, 95% CI 0.56 to 0.91). A systematic review of 10 studies published between 2013 and 2020 reported infrequent PrEP use among PWID, ranging from 0 to 3%.[209] One study found being insured associated with increased likelihood of PrEP utilization versus being uninsured (adjusted OR 4.49, 95% CI 1.68 to 12.01).[104]

Data on transgender identity and PrEP use are limited. One study of 863 people started on PrEP found that the likelihood of PrEP use was lower in transgender women than MSM (aPR 0.52, 95% CI 0.32 to 0.85);[206] similarly, a survey also found transgender women (n=369) were less likely to use PrEP than MSM (n=399) (Prevalence Ratio [PR] 0.36, 95% CI 0.28 to 0.47).[210] Data on other factors such as transactional sex, cultural factors, and health literacy and disparities in PrEP utilization were lacking. Perceived stigma regarding PrEP has been associated with decreased likelihood of PrEP initiation in transgender women as well as women not identifying as transgender.[211,212]

Contextual Question 5. What Is the Effectiveness of Primary Care Interventions to Increase Utilization of PrEP and Decrease Disparities in Utilization?

Five randomized trials[213-217] and one non-randomized study[218] evaluated interventions relevant to U.S. primary care settings to increase utilization of PrEP in persons at higher risk of HIV infection. Sample sizes ranged from 50 to 164 (**Appendix D Table 3**). Four trials evaluated MSM;[213-216] among these trials, one also included transgender women,[213] one focused on young MSM,[214] and three trials[213-215] focused on Black populations. One other trial[217] evaluated persons interested in PrEP without restricting to a specific risk category and the non-randomized study[218] evaluated women with substance use disorders in addiction treatment. The interventions varied in intensity and methods, but generally involved counseling and education; other approaches included peer mentoring and a patient-centered decision aid. All studies were conducted in the United States and participants were recruited from STI, addiction treatment, and other outpatient clinics; using social network applications; or at community events, community organizations, and public venues.

Four trials of HIV-negative MSM at higher risk of HIV infection found interventions associated with increased uptake of PrEP.[213-216] Three trials focused on Black MSM and one of these focused on younger MSM, suggesting that the interventions could potentially reduce disparities in PrEP utilization among these populations. However, the trials were not designed to directly measure impacts on disparities in PrEP utilization. One trial (n=146, median age 26 years) of Black MSM and Black transgender women presenting in STI clinics found an intervention based on the information-motivation-behavioral skills model (administered by a social work interventionist in a 60 minute face-to-face session) associated with increased likelihood of PrEP initiation at 3 months versus usual services (24% vs. 11%, p=0.05 based on self-report; 20% vs. 11%, p=0.15 based on electronic medical record linked data).[213] A smaller (n=50) trial of young (16 to 25 years, mean age 22 years) Black MSM recruited using social networking applications evaluated a personalized comprehensive client-centered counseling and education intervention (administered by a staff member who self-identified as a Black MSM) versus standard PrEP education.[214] The comprehensive counseling and education intervention was associated with increased likelihood of PrEP initiation at 3 months (24% vs. 0%, p=0.02). Another trial (n=80) of older (mean age 44 years) Black MSM recruited from public venues, community organizations, and community events compared an intervention consisting of peer mentoring and group behavioral/educational activities with a customized needs assessment and incentivized referrals to health and support services versus the needs assessment and incentives alone. The addition of

peer mentoring and group activities was associated with a non-statistically significant increase in use of PrEP at 6 months (22% vs. 9%, p>0.05).[215] The fourth trial (n=86, mean age 32 years) evaluated MSM of various races/ethnicities (65% White, 10% Black, 5.8% Asian; 26% Latinx) attending STI clinics. Versus usual care, it found a brief (15 to 20 minute) motivational interviewing intervention administered by an STI counselor followed by a brief (<10 minute) telephone booster associated with increased likelihood of further discussing PrEP with a prescriber (OR 6.0, 95% CI 2.3 to 15.6), attending the prescriber appointment (OR 3.6, 95% CI 1.5 to 8.9), and PrEP receipt (OR 3.6, 95% CI 1.5 to 8.9).[216]

Evidence on the effectiveness of interventions to increase uptake of PrEP in populations other than MSM is limited. One trial (n=61) of adults (mean age 40 years; 34% Black, 11% White non-Hispanic, 43% Hispanic) attending outpatient clinics and interested in PrEP evaluated a strengths-based case management intervention administered by a patient navigator in one 45-to-60 minute session and up to 4 additional followup visits or phone/text message contacts.[217] In this trial, 15 percent of participants were women, 3.2 percent reported injection drug use, and 52 percent reported sexual orientation as gay or bisexual. The strengths-based case management intervention was associated with an increased likelihood of PrEP initiation at 12 weeks versus usual care that was not statistically significant (40% vs. 29%, p=0.37). One non-randomized study (n=164, mean age 40 years; 16% Black, 75% White) of women in addiction treatment found use of a decision aid tailored to this population and setting associated with increased likelihood of seeing a provider for PrEP that was of borderline statistical significance (15.7% vs. 6.2%, p=0.05).[218]

Contextual Question 6. What Is the Effectiveness of PrEP Delivered Using Telehealth vs. Office-Based PrEP?

Telehealth modalities could support uptake and adherence to PrEP, particularly in rural communities and other populations with limited access or other barriers to traditional office-based health services.[84,219] Telehealth for PrEP encompasses a variety of modalities, including various provider-to-patient and provider-to-provider (e.g., telementoring or "e-Consults") approaches. However, evidence on the effectiveness of PrEP delivered using telehealth versus office-based PrEP is very limited. One small (n=48) observational study conducted in Washington state of men and transgender women who have sex with men with risk factors for HIV infection evaluated a telehealth approach to facilitate PrEP initiation.[220] In this clinic, in-person visits with a physician to initiate PrEP were offered one day a week. Patients who could not attend clinic on that day or who did not wish to wait were offered a telehealth approach, in which the physician was present through interactive videoconference; however, patients still attended clinic for in-person counseling with an HIV counselor and diagnostic testing. Ten patients received the telehealth approach. There were no differences between the telemedicine and standard office-based approach in the proportion of participants prescribed PrEP (70% vs. 79%), the proportion attending the first follow-up visit at 1 month (83% vs. 85%), or adherence at 1 month (median missed doses 2 vs. 1). However, among patients not linked to a primary care provider, only 40 percent (2/5) of telehealth participants attended the 3-month followup visit, compared with 87 percent (20/23) of standard care participants. The telehealth participants reported missing 10 and 14 doses in the prior month, compared with a median of 2 (IQR 0 to 2)

for standard care participants. Given the observational nature of the study, these differences were ascribed to confounding related to the reasons for initially selecting the telehealth approach. No cases of HIV infection occurred in either group.

No published randomized trials of telehealth versus office-based PrEP were identified. However, two U.S. trials are scheduled for completion in May 2022,[221-223] and one other U.S. and one Canadian trial are estimated to be completed in the summer of 2023.[224,225] One trial (n=396) compares a home-based support system (self-testing, centralized laboratory processing, and electronic behavioral monitoring) for followup in MSM on PrEP, versus standard office-based follow-up visits, targeting enrollment of 50 percent of persons ages 18 to 34 years (18 to 49 years eligible) and 50 percent Black persons.[223] This intervention (PrEP@Home) is intended to replace three of four annual followup visits, and was previously found to be highly acceptable to patients in an uncontrolled pilot study.[226] The other trial (n=217) compares a home-based system (ePrEP) for initiation as well as followup of PrEP among young, rural MSM (age 18 to 29 years) versus standard office-based care.[221,222] The ePrEP intervention consists of video teleconsultations, secure messaging, behavioral risk surveys, and self-testing with centralized laboratory processing. In both trials, the primary outcome is adherence based on blood spot sample levels for TFV-DP; the ePrEP trial will also assess initiation and retention of PrEP. The PrEPTECH trial (n=400) aims to test the effectiveness of website providing access to PrEP to U.S. adolescent and adult MSM and adult transgender women.[224] Via the website, participants will have access to laboratory testing for PrEP eligibility delivered to their home, telehealth care, and PrEP prescriptions delivered through an online pharmacy, and the primary outcome will be self-report PrEP initiation. The Canadian Virtual PrEP (VPrEP) cross-over trial (n=142) will compare delivery of PrEP through the Freddie® mobile Health (mHealth) platform, where communication could occur over a number of days and minimizes the need for in-person interactions, versus standard delivery, with the primary outcome patient preference of the model of delivery.[225] Both of these trials will also measure adherence.

Chapter 4. Discussion

Summary of Review Findings

This report synthesizes evidence on effects of PrEP on risk of HIV infection, harms, and other clinical outcomes; the diagnostic accuracy of instruments for identifying potential candidates for PrEP; and contextual issues related to utilization, adherence, persistence, and antiretroviral drug resistance. **Table 10** summarizes the evidence reviewed for this report.

As described in the prior USPSTF review, oral PrEP with TDF or TDF-FTC was associated with decreased risk of acquiring HIV infection compared with placebo or no PrEP (11 trials, RR 0.46, 95% CI 0.33 to 0.66, I^2=67%).[51-55,66-68,118,137,170,172] The absolute difference in risk of HIV infection was about 2 percent after 4 months to 4 years, for a number needed to treat with oral PrEP to prevent 1 case of HIV infection of about 50. In three trials conducted in the United States and Europe, each of which evaluated MSM (HIV incidence, 4% to 8% with placebo or no PrEP), the pooled absolute difference was larger at about 5 percent after 9 months to 2 years (range, 4% to 6%), for a number needed to treat with PrEP to prevent one case of incident HIV infection of about 20.[52,66,118] Effects of PrEP on HIV infection risk were very similar for TDF alone (RR, 0.49 [95% CI, 0.28 to 0.84]; I^2=58%) and TDF-FTC (RR, 0.44 [95% CI, 0.27 to 0.72]; I^2=74%). However, TDF is not FDA-approved for use as PrEP and is no longer recommended as an alternative regimen in the 2021 CDC guideline.[84] Although statistical heterogeneity was present in the pooled estimate, this was not related to use of TDF alone or TDF-FTC. On the other hand, there was a strong association between the degree of study-level adherence and estimates of effectiveness, when adherence was analyzed as either a categorical or continuous variable. In six trials in which adherence was 70 percent or greater, the pooled RR was 0.27 (95% CI, 0.19 to 0.39; I^2=0%), with no statistical heterogeneity.[51,52,66,67,118,170]

Additional analyses also support an association between higher oral PrEP adherence and greater effectiveness, including within-study stratified analyses of trial participants stratified according to PrEP adherence level and analyses on the association between tenofovir levels in persons using PrEP and risk of HIV infection.[51,53,54,135,137,153,170,172] Modeling based on trial data indicates that PrEP is highly effective in MSM taking four doses per week (estimated reduction in risk, 96%), and reduction in risk is substantial even at two doses per week (reduction in risk, 76%),[178] suggesting important benefits of PrEP despite incomplete adherence. These findings also suggest the potential use of event-driven (targeted at periods of higher HIV risk) or intermittent (regular nondaily) dosing strategies in this population. One trial (IPERGAY) found event-driven PrEP in MSM associated with substantially reduced risk of HIV infection versus no PrEP (RR, 0.14 [95% CI, 0.03 to 0.63]).[66] IPERGAY evaluated a population of MSM with relatively frequent sexual intercourse (median, 10 episodes per month) and dosing of PrEP (median, 15 doses per month), potentially reducing applicability to populations in which dosing is less frequent. However, a post hoc subgroup analysis of IPERGAY found that among adherent patients, event-driven PrEP among those who used 15 or fewer doses per month and those who used more than 15 pills per month appeared similarly effective, with no cases of incident HIV infection in either group.[129]

The applicability of evidence on effects of adherence and event-driven or intermittent dosing from studies of MSM to other populations is uncertain. Tenofovir accumulates rapidly and at high concentrations in rectal compared with vaginal tissue, which could reduce the effectiveness of nondaily dosing in women, in whom the primary mode of transmission is through receptive vaginal intercourse. A modeling study estimated that 98 percent or greater of the population achieved protective mucosal tissue levels by the third day of exposure with TDF-FTC, although six doses/week were required to protect the lower female genital tract, compared with two doses/week to protect colorectal tissue.[227] On the other hand, simian studies have shown protective effects of tenofovir alafenamide from rectal simian HIV challenge despite low rectal mucosal concentrations, suggesting limited correlation between rectal or genital mucosal concentrations of tenofovir and protection from HIV infection.[228] No study evaluated effectiveness of intermittent or event-driven dosing in women or PWID.

Findings regarding effectiveness of oral PrEP were robust in subgroup and stratified analyses based on HIV risk category (MSM, PWID, or persons at risk of HIV infection via heterosexual contact), study duration, study quality, age, and sex. However, evidence in PWID was limited to one trial conducted in Thailand in which most patients received directly observed therapy and sterile syringes were not provided (RR, 0.52 [95% CI, 0.29 to 0.92]),[53] and all trials of persons at risk via heterosexual contact were conducted in Africa, which might reduce applicability to U.S. practice. Effects of PrEP were stronger in trials conducted in the United States, Europe, and Canada (RR, 0.13 [95% CI, 0.05 to 0.32]) than in studies conducted in Africa, Asia, or internationally (RR, 0.54 [95% CI, 0.37 to 0.79]); this could be related to high adherence in the North American and European trials or differences across countries in HIV epidemiology and management (e.g., differences in the proportion of partners with HIV treated with ART). No study evaluated effectiveness of PrEP according to a sexual partner with HIV's use of ART or viral load.[52,66,118] However, the 2021 CDC guideline notes that persons with HIV with a consistently undetectable viral load pose effectively no risk for HIV transmission to sexual partners. No randomized trial of PrEP enrolled adolescents, but in 2018 TDF-FTC was approved by the FDA for PrEP in adolescents weighing at least 35 kg. This decision was informed by a PrEP demonstration study in MSM ages 15 to 17 years that found a similar safety profile for TDF-FTC compared with the safety profile observed in adults.[183]

Evidence on beneficial effects of oral PrEP on clinical outcomes other than HIV infection was sparse. Oral PrEP was associated with a statistically nonsignificant reduction in mortality risk versus no PrEP or placebo (RR, 0.81 [95% CI, 0.59 to 1.11]; I^2=0%), and trials were not designed to address this outcome.[51-55,66,67,118,137,170,172] No trial reported effects of PrEP on quality of life, although observational and qualitative research suggests that PrEP may reduce anxiety or worry about getting HIV.[229-231]

Although oral PrEP was associated with some harms, most appeared relatively mild and reversible with PrEP discontinuation. PrEP was not associated with an increased risk of serious adverse events,[51-55,66-68,118,137,170,172] and there was a statistically nonsignificant increased risk of withdrawal due to adverse events (RR, 1.25 [95% CI, 0.99 to 1.59]).[51,55,66,137,172] PrEP was associated with increased risk of gastrointestinal events (RR, 1.63 [95% CI, 1.26 to 2.11]; ARD, 1.95%),[51-55,66-68,118,137,170,172] that generally improved with longer duration of therapy. Consistent with renal effects of tenofovir, oral PrEP was also associated with an increased risk of renal

insufficiency (RR, 1.43 [95% CI, 1.18 to 1.75]; ARD, 0.56%),[51-55,66-68,118,137,170,172] which generally appeared to be mild and resolved with cessation of PrEP. Our finding of an increased risk of renal adverse events was consistent with another review that found oral PrEP associated with increased risk of grade 1 creatinine elevation or worse versus placebo (OR, 1.39 [95% CI, 1.09 to 1.71]).[232] Consistent with effects of tenofovir on bone loss, PrEP was associated with a statistically nonsignificant increase in risk of fracture (RR, 1.23 [95% CI, 0.97 to 1.56]);[51-54,66,137,170] results of the fracture meta-analysis were heavily weighted by the Bangkok Tenofovir Study of PWID.[53] These findings are consistent with a recent systematic review that found oral PrEP associated with greater bone mineral density decline than placebo, with no statistically significant increase in risk of fractures.[233] Studies with longer-term followup would be helpful for clarifying fracture risk, given the relatively short followup in the trials (4 months to 4 years) and potential long-term effects of tenofovir on bone density and fracture risk. Based on currently available shorter-term data, effects of PrEP on fracture risk appear small (ARD, 0.21%). One small new crossover trial found event-driven oral PrEP associated with decreased risk of short-term, mild adverse events, but was not designed to assess more serious or longer-term harms.[144]

A large new trial (DISCOVER) found oral daily TAF-FTC to be noninferior to TDF-FTC for incident HIV infection in primarily MSM (2% transgender women), and potentially associated with increased efficacy (RR 0.53, 95% CI 0.23 to 1.26).[121,162] TAF-FTC was associated with positive short-term effects on bone mineral density versus TDF-FTC and negative effects on lipid parameters and weight gain, without differences in clinical adverse events including renal events and fractures, which require longer-term study. TAF-FTC is not approved for PrEP in women at risk for acquiring HIV infection from receptive vaginal sex because effectiveness has not been evaluated in this situation, and it is not recommended in the 2021 CDC guideline for this population.[84]

Among persons using oral PrEP, the rate of resistance mutations to tenofovir or emtricitabine appears low. Most cases of antiretroviral resistance occurred in persons who were infected with HIV at baseline, reinforcing the importance of clinical history and HIV testing to rule out HIV infection before initiating PrEP. Evidence to determine the effects of PrEP-selected antiretroviral resistance mutations on clinical outcomes is not available, but is likely to depend on the specific resistance mutation(s) present, impact on effectiveness of first-line ART, and availability of alternative (non-first-line) ART regimens, if needed.[234] Patients with the most common PrEP-selected nucleoside reverse transcriptase inhibitor resistance mutations (K65R, M184I, M184V) can frequently be treated with INSTI or protease-inhibitor based regimens, with limited evidence indicating high rates of virological suppression in persons with these mutations.[199,200] Furthermore, the number of HIV cases averted by PrEP appears to be substantially higher than the number of cases of antiretroviral resistance caused. Based on data from the Partners PrEP trial, there were an estimated 123 cases of HIV infection averted, compared with five cases of drug resistance.[146]

A concern about PrEP has been the potential for behavioral risk compensation. There was no association between PrEP and increased risk of bacterial STIs in RCTs.[51,118,137,170,172] However, in most trials, patients were blinded to receipt of PrEP, which might affect sexual behaviors differently than when patients know they are using PrEP, as in clinical practice. One open-label trial (PROUD) found nonstatistically significant associations between PrEP and STIs in MSM, consistent with the higher prevalence of risky sexual behaviors among men randomized to PrEP that was observed in this trial.[118] In addition, participants in randomized trials may differ from

the general population of PrEP users, who may be at higher risk for STIs.[177] A systematic review that included PROUD, the U.S. demonstration study, and other open-label, nonrandomized studies found PrEP associated with an increased risk of rectal chlamydia (4 studies; OR, 1.59 [95% CI, 1.19 to 2.13]), but no statistically significant association between PrEP and risk of chlamydia at any site (5 studies; OR, 1.23 [95% CI, 1.00 to 1.51]), STIs overall (8 studies; OR, 1.24 [95% CI, 0.99 to 1.54]), syphilis (6 studies; OR, 1.12 [95% CI, 0.86 to 1.47]), or gonorrhea (5 studies; OR, 1.13 [95% CI, 0.78 to 1.64]).[235] The nonrandomized studies had methodological shortcomings, including use of a before-after study design, failure to adjust for differential STI testing rates, and use of self-report to determine STI rates before initiation of PrEP. Some data suggest that persons who engage in riskier behaviors tend to be more adherent to PrEP (see Contextual Question 1),[53,177,184] which might result in greater benefits in terms of reduction in HIV incidence that could offset negative effects related to any increase in risky behaviors (e.g., STIs). There was no association between PrEP and risk of HSV infection,[120,150,170] although some trials[120,170] found decreased risk or a trend toward decreased risk, consistent with antiviral effects of tenofovir on HSV.[119,120] Cases of acute hepatitis C virus infection have been reported in U.S. MSM using PrEP,[236] but data from randomized trials are too limited to determine effects on risk of hepatitis C virus infection.[66,118] In patients with chronic hepatitis B virus infection, very limited evidence suggests that cessation of oral PrEP is not associated with hepatitis flare.[55,169] However, almost all randomized trials excluded patients with hepatitis B virus infection at baseline and some trials provided hepatitis B virus vaccination to eligible patients. One trial reported one case of incident hepatitis B virus infection,[54] though this outcome was not a specified outcome in any trial.

Alternative PrEP regimens that do not require daily administration could improve utilization and adherence. One alternative to oral PrEP in women is the dapivirine vaginal ring, which was not addressed in the 2019 USPSTF review. The dapivirine vaginal ring was associated with decreased risk of infection versus a placebo ring in African women at increased risk of HIV infection (2 trials, RR, 0.71 [95% CI 0.57 to 0.89]), and had a favorable safety profile.[73,74] However, efficacy versus placebo for preventing HIV infection was lower with the dapivirine vaginal ring than observed in trials of oral PrEP. Open-label extension studies suggest greater adherence and effectiveness in women enrolled in the RCTs who chose to continue with the dapivirine ring, but utilized simulated control groups.[111,112] The dapivirine ring has not been FDA-approved and has been withdrawn from the manufacturer from further FDA review.

Another alternative to oral PrEP is long-acting injectable cabotegravir, which involves a bimonthly injection. Long-acting injectable cabotegravir was associated with greater reduction in risk of HIV infection than oral TDF-FTC in one new trial of MSM and transgender women (0.6% vs. 1.7%; RR, 0.33 [95% CI, 0.18 to 0.62][70] and one new trial of African women at high risk of HIV infection (0.3% vs. 2.3%; RR, 0.11 [95% CI, 0.04 to 0.31]).[88] Cabotegravir was associated with increased risk of injection site reactions that were usually mild and decreased in frequency following the initial injection, and weight gain (<1 kg). A potential concern with cabotegravir is the prolonged pharmacologic tail (period of declining drug levels) when injections are discontinued or delayed. Low drug levels during the pharmacologic tail could select for antiretroviral drug resistance mutations if HIV infection is acquired.[237,238] Resistance to one integrase strand transfer inhibitor such as cabotegravir is of concern because it may result in cross-resistance with other integrase strand transfer inhibitors, potentially limiting the use of

first-line antiretroviral therapy regimens. Although randomized trials of cabotegravir reported a low incidence of INSTI resistance mutations among persons randomized to this regimen, one trial[70] reported a high proportion of patients with incident HIV infection had an INSTI mutation. No cases of INSTI resistance mutations acquired following cessation of cabotegravir during the pharmacologic tail period were identified. Longer-term implementation and other studies are required to clarify incidence and consequences of INSTI resistance mutations acquired in persons using cabotegravir for PrEP. Cabotegravir is FDA-approved for use in at-risk adults and adolescents (≥35 kg) to reduce the risk of sexually acquired HIV infection.[75]

Data on effects of PrEP in pregnancy remains limited. Trials excluded pregnant persons and discontinued PrEP in persons who became pregnant. Among persons who became pregnant in the trials, oral PrEP was not associated with increased risk of spontaneous abortion[68,157,172] or other adverse pregnancy outcomes. Observational studies also indicate no increased risk of adverse pregnancy outcomes among persons with prenatal exposure to oral PrEP.[239,240] A systematic review of persons infected with HIV or hepatitis B virus who received tenofovir during pregnancy (not for PrEP) found mild to moderate maternal and infant harms that were not considered to be tenofovir-related, no increased risk of growth or bone abnormalities in infants exposed in utero, and no increased risk of congenital abnormalities.[241] FDA labeling information and perinatal antiretroviral treatment guidelines permit use of TDF-FTC (an FDA pregnancy category B drug) during pregnancy.[84] Although the FDA-approved label recommends that nursing mothers not breastfeed if they are taking TDF-FTC and data on safety in breastfeeding infants are lacking, the 2021 CDC guideline[84] notes limited exposure via breast milk. Evidence on safety of cabotegravir for PrEP in pregnant or breastfeeding persons is very sparse, although one trial[88] reported no congenital abnormalities in infants with in utero exposure to PrEP.

Understanding PrEP uptake, adherence, and persistence in U.S. primary care and primary care–applicable settings could be useful for assessing applicability of RCTs, which were primarily conducted in low-income settings, and inform efforts for successful implementation of PrEP. Available evidence primarily focused on use of oral PrEP. Disparities in oral PrEP utilization have been reported, with decreased utilization among PWID, transgender women, and adolescents.[93] Some studies have found disparities in utilization by race/ethnicity,[107,204,205] though findings were inconsistent. Evidence on primary care interventions to increase utilization was limited but suggested that behavioral and educational interventions tailored to specific populations (e.g., young and/or Black MSM) can increase utilization, potentially reducing disparities.[213-216] Evidence on effects of telehealth for PrEP on utilization and other outcomes is extremely limited, though RCTs are in progress. Studies of U.S. MSM found that adherence based on documentation of highly protective drug levels varied widely (22% to 90%), with lower levels of adherence in younger MSM; adherence also tended to decrease over time.[177,183-186] Other factors associated with decreased adherence include non-White race, lower socioeconomic status, presence of other adverse social determinants; a factor associated with increased adherence was presence of higher-risk behaviors, indicating that patients may vary adherence according to degree of risk.[242] In MSM, discontinuation of oral PrEP is frequent, and appears related to factors similar to those associated with decreased adherence.[177,185,187,192-194] One RCT of U.S. MSM found higher adherence with daily than intermittent or event-driven PrEP.[136] Evidence on PrEP utilization, adherence, and persistence in populations other than MSM (e.g., PWID, persons at risk due to vaginal intercourse, transgender persons) remains limited.

However, trials of MSM and transgender women and women at risk due to vaginal intercourse indicate that long-acting injectable cabotegravir is associated with higher adherence (based on lack of delayed or discontinued injections) than oral PrEP (based on protective dried blood spot levels).[70,88]

Instruments that are accurate for predicting risk of incident HIV infection could help inform decisions regarding eligibility for PrEP. Five instruments for predicting incident HIV infection in MSM found moderate discrimination (AUROC estimates ranged from 0.60 to 0.73),[140,155,165,166,171] though some instruments require further validation. All studies applied instruments retrospectively and some instruments were developed using data from older cohorts in which the effects of factors associated with HIV incidence (e.g., nitrates, amphetamines) may differ from contemporary populations. In general populations of HIV-negative persons, two large studies found two new instruments had moderate to high discrimination (AUROC 0.77 and 0.84) for predicting incident HIV infection.[143,151] Both instruments utilized a computerized algorithm on items extracted from the electronic medical record.

Limitations

Our review had limitations. As statistical heterogeneity was anticipated in pooled analyses, we used the DerSimonian and Laird random-effects model to pool studies. The DerSimonian and Laird random-effects model may result in CIs that are too narrow when heterogeneity is present, particularly when the number of studies is small.[125] Therefore, we repeated analyses in which statistical heterogeneity was present using the profile likelihood method; these sensitivity analyses resulted in similar findings. To explore statistical heterogeneity, we also performed sensitivity and subgroup analyses based on adherence level, study quality, duration of followup, HIV risk category, PrEP regimen, and geographic setting. Although statistical heterogeneity remained present in some analyses, results consistently favored PrEP, although estimates varied according to level of adherence and geographic setting. We did not have access to individual patient data. Therefore, our findings are based on analyses of study-level data and our ability to analyze subgroup effects was restricted to published reports. We excluded non-English–language articles, which could result in language bias. However, some research suggests that English-language restriction has little effect on the conclusions of systematic reviews of non-complementary medicine topics, and we did not identify large non-English trials of PrEP versus placebo in other systematic reviews.[243,244] We only assessed for publication bias using statistical and graphical methods to assess for small sample effects when there were at least 10 studies, as research indicates that such methods can be misleading with smaller numbers of studies.[127] Funnel plot asymmetry was present (**Appendix C Figure 1**) for the outcome of HIV infection and a test for small sample effects was statistically significant. Although small sample effects may be due to publication bias, graphical and statistical tests can be difficult to interpret in the presence of other factors that could influence study results, such as differences across trials in geographic setting, adherence levels, HIV risk category, and other factors. We identified no unpublished trials of PrEP in searches on a clinical trials database (clinicaltrials.gov). Our primary analyses were based on data reported in journal publications. In three trials included in the FDA medical review of PrEP with tenofovir and emtricitabine, there were some discrepancies between the journal articles and the FDA report for numbers of HIV cases and fractures.[126] In the iPrEx trial, more HIV infections in both the PrEP and placebo arms were

reported in the FDA review than in the journal publication.[137] A sensitivity analysis that used the FDA data resulted in similar results for iPrEx (RR, 0.58 [95% CI, 0.41 to 0.82]) compared with results in the journal publication (RR, 0.53 [95% CI, 0.36 to 0.77]) and no change in the pooled estimate (RR, 0.45 [95% CI, 0.30 to 0.66]). Similarly, although there were some discrepancies in fractures rates between the journal publications and the FDA review of the iPrEx, Partners PrEP, and CDC Safety Study trials, a sensitivity analysis using FDA data did not affect the estimate for fracture risk. Although publication and reporting bias may be associated with industry funding, few PrEP trials reported receipt of industry support, with support in those trials primarily consisting of provision of study drugs. Stratified analyses did not indicate better results for PrEP in trials that reported some industry support. However, some trials that received donated study drugs may not have reported it, which could have resulted in some misclassification.

Emerging Issues/Next Steps

Alternative PrEP regimens that are easier to tolerate, do not require daily administration, are not associated with adverse renal and gastrointestinal effects, do not select for drug resistance, and achieve protective levels could increase the effectiveness of PrEP, improve the balance of benefits to harms, and facilitate greater uptake of PrEP. In addition to oral TAF-FTC, the dapivirine vaginal ring and long-acting injectable cabotegravir, which were not evaluated in the prior USPSTF review but added for this report, other PrEP regimens that have been studied include oral maraviroc,[113-115] tenofovir vaginal gel,[54,116,117] and injectable rilpivirine. However, these regimens have not been approved by the FDA, have limited evidence of effectiveness or evidence of low effectiveness, and are not recommended in clinical practice guidelines. Trials of long-acting (every 6 months) injectable lenacapavir (an HIV-1 capsid inhibitor) for PrEP are currently in progress, with expected completion in 2027.[245,246]

PrEP could also be delivered as a biodegradable, long-acting subcutaneous implant.[247] A potential advantage of implants over long-acting injectable formulations is that they could be removed if needed without a prolonged pharmacological tail period. However, a review of nonclinical animal model studies of TAF hemifumarate subcutaneous implants identified safety and tolerability issues judged sufficiently concerning by the Gates Foundation to no longer pursue clinical development.[248] Islatravir, a nucleoside reverse transcriptase translocation inhibitor, has been evaluated in oral and implant formulations for PrEP but studies have been put on clinical holds by the FDA due to observations of decreases in total lymphocyte and CD4+ T-cell counts in some patients receiving islatravir.[249] Broadly neutralizing HIV-1 monoclonal antibodies were not effective for reducing risk of HIV acquisition in initial trials,[250] though further research is underway.[251]

Emerging areas to improve uptake of PrEP include use of telehealth for PrEP (see Contextual Question 6), same-day PrEP initiation,[252] and various behavioral, educational, peer support/mentoring, decision aids, and other interventions (see Contextual Question 5).

Relevance for Priority Populations

In the U.S., HIV disproportionately affects racial/ethnic minorities, in particular Black and Hispanic persons. One trial found no difference in effectiveness of PrEP between Hispanic and non-Hispanic persons,[137] and trials found PrEP to be effective in diverse racial/ethnic populations worldwide. Among PrEP-eligible individuals, PrEP coverage is substantially higher among White compared to Black or Hispanic/Latinx individuals, suggesting potential disparities in utilization.[253] As described in Contextual Question 4, however, evidence indicating presence of disparities in utilization by race/ethnicity are somewhat inconsistent and may be attenuated after controlling for other factors associated with PrEP utilization, such as age, sex and gender, socioeconomic status, and other social determinants. Regardless, race and ethnicity are often correlated with the presence of social determinants that drive disparities in PrEP utilization.

Although PrEP was associated with decreased risk of HIV infection in women at high risk of acquisition via heterosexual contact, all trials of this population were conducted in Africa. As described in Contextual Question 4, some data suggest disparities in the United States with regard to implementation of PrEP in women. Data on the number of pregnant or lactating women on PrEP in the United States are not available, but use in these populations is likely to be low.

Data on PrEP in transgender women remains limited, though one survey using a national probability sample found that PrEP was only utilized in 3 percent of respondents who had sex with cisgender men and/or transgender women.[106] Barriers to PrEP use in transgender individuals include lack of knowledge, unfavorable attitudes toward PrEP, and stigma.[106,212,254] Although it is unlikely that there are significant drug interactions between gender-affirming hormone treatments and PrEP,[255] some evidence indicates small interaction effects of uncertain clinical significance.[256,257] Randomized trials that included transgender women have not been powered to evaluate effectiveness in transgender individuals. A post hoc analysis of iPrEx[137] found that PrEP was effective in MSM (HR, 0.50 [95% CI, 0.34 to 0.75]) but not in transgender women (HR, 1.1 [95% CI, 0.5 to 2.7]), although the interaction was not statistically significant (p=0.09),[134] precluding reliable conclusions regarding decreased effectiveness in transgender women. In the iPrEx trial, adherence was lower in transgender women than in MSM, particularly among those who reported receptive anal intercourse without a condom. In addition, there was an association between TFV drug level detectability and decreased risk of HIV infection, highlighting adherence as a potentially important implementation challenge in transgender individuals. The DISCOVER trial, which compared TAF-FTC versus TDF-FTC, enrolled 2 percent transgender women; no cases of HIV infection occurred in this group in either arm.[121,162] In HPTN 083, which enrolled 13% transgender women who have sex with men, efficacy was similar in MSM (HR 0.35, 95% CI 0.18 to 0.68) and transgender women (HR 0.34, 95% CI 0.08 to 1.56), suggesting cabotegravir as a potential option in transgender persons with suboptimal adherence on oral PrEP.[70] No PrEP trial enrolled transgender men and data on the prevalence of HIV infection in this population are lacking.[258]

Evidence on the effectiveness of PrEP in persons at risk due to injection drug use remains limited. One Asian trial found oral PrEP to be effective in PWID.[53] Uptake of PrEP in PWID appears relatively low (see Contextual Question 4), though surveys indicate opportunities to improve utilization, based on the proportion expressing willingness to take PrEP.[259,260]

The FDA has approved daily oral TDF-FTC, daily oral TAF-FTC, and injectable cabotegravir in adolescents weighing at least 35 kg who otherwise meet indications for use of these regimens as PrEP. Although 22 percent of new HIV Infections in 2018 occurred in adolescents, data on PrEP initiation from the manufacturer indicated that less than 5 percent of individuals receiving new PrEP in 2012 were adolescents, indicating marked underutilization.[261] In addition to decreased uptake, other barriers to implementation of PrEP in adolescents include lower adherence and persistence (see Contextual Question 1) and potential privacy issues (e.g., for adolescents who may receive PrEP while on their parents' insurance plan).

Future Research

Research is needed to clarify the comparative effectiveness and harms of alternative PrEP regimens, including oral TDF-FTC, oral TAF-FTC, and injectable cabotegravir; to determine the comparative effectiveness and harms of daily versus event-driven or intermittent oral PrEP; and to identify effective interventions to improve PrEP uptake, adherence, and persistence (including telehealth approaches and same-day PrEP initiation). Studies comparing TAF-FTC and TDF-FTC should have sufficient power and duration to evaluate whether short-term differences in renal function, bone mineral density, lipid parameters, and weight gain are associated with differences in long-term clinical outcomes. In addition, studies are needed to determine whether TAF-FTC is effective in populations other than MSM, including women at risk due to vaginal intercourse. For cabotegravir, longer-term follow-up and implementation studies are needed to assess adherence in clinical practice and the durability of observed benefits as well as the risk of and clinical consequences of integrase strand transfer inhibitor resistance mutations.

Randomized trials and implementation studies of PrEP in U.S. populations of women at high risk via vaginal intercourse and PWID would be useful to verify the applicability of trials conducted in low-income settings to the United States, including the effectiveness of PrEP in primary care settings. Studies should measure adherence and evaluate the association between adherence and effectiveness, particularly among persons with HIV exposure through cervico-vaginal tissue or blood (i.e., injection drug use). Research is needed to confirm the safety and effectiveness of PrEP during pregnancy or lactation and in gender nonconforming persons, the effectiveness and long-term safety (e.g., bone effects) of PrEP in adolescents, and to understand effects of PrEP on quality of life (including sexual health). To accurately assess effects of PrEP in different populations, studies should collect accurate information on sex and gender identity. Studies on factors associated with adherence and methods for increasing PrEP uptake, adherence, and persistence would be very helpful for guiding strategies for successful implementation, particularly in populations with low adherence, such as adolescents and various racial/ethnic groups, and other underserved populations based on socioeconomic status, insurance status, educational level, health literacy, and other social determinants of health.

Additional research would help to further clarify effects of PrEP related to behavioral risk compensation. Open-label studies, including observational studies that include a concurrent no-PrEP comparison group or compare alternative PrEP regimens and account for differential STI testing rates, would be helpful for understanding behavioral risk compensation effects in clinical practice. Research is also needed to clarify whether oral PrEP confers protective effects against

HSV and how any observed effects on HSV affect HIV acquisition risk; determine effects of PrEP on hepatitis C virus infection, particularly in populations at high risk of hepatitis C virus (e.g., PWID, MSM); and determine whether PrEP reduces risk of hepatitis B infection[262] (due to the antiviral effects of tenofovir and emtricitabine) and verify the safety of PrEP in persons with chronic hepatitis B virus infection.

Research is also needed to further develop and validate instruments for identifying persons at high risk of acquiring HIV infection, particularly for populations other than MSM. Studies should perform validation in independent cohorts, ideally using more current cohorts with prospective application of risk assessment instruments and assessment of HIV incidence, and should be applicable to diverse racial/ethnic groups. For identifying persons eligible for PrEP among general populations of uninfected individuals, studies are needed to verify the accuracy and impact of automated computerized algorithms using electronic medical records data.[143,151]

Conclusions

In adults at increased risk of HIV infection, oral PrEP with TDF or TDF-FTC is associated with decreased risk of HIV infection compared with placebo or no PrEP, although effectiveness decreases with inadequate adherence. TAF-FTC was non-inferior to TDF-FTC in MSM and long-acting injectable cabotegravir was associated with decreased risk of HIV infection versus TDF-FTC in MSM or transgender women and women at higher risk for HIV infection. Instruments for predicting risk of incident HIV infection have moderate discrimination in MSM and moderate to high discrimination in general populations of persons without HIV infection.

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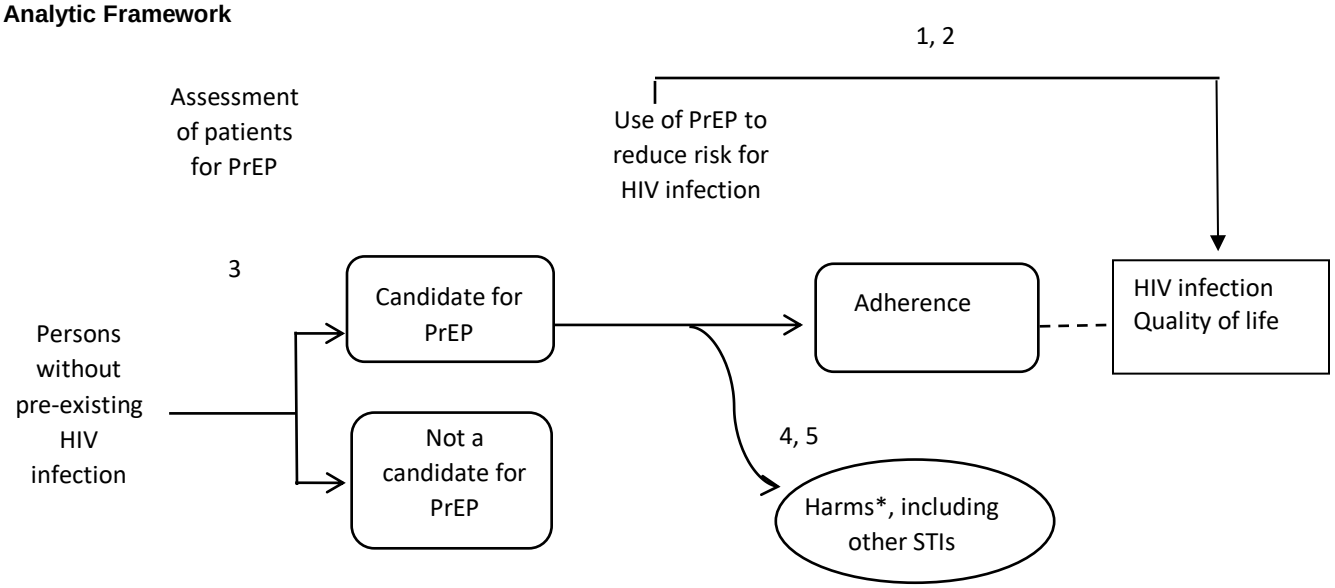
Figure 1. Analytic Framework and Key Questions

Analytic Framework



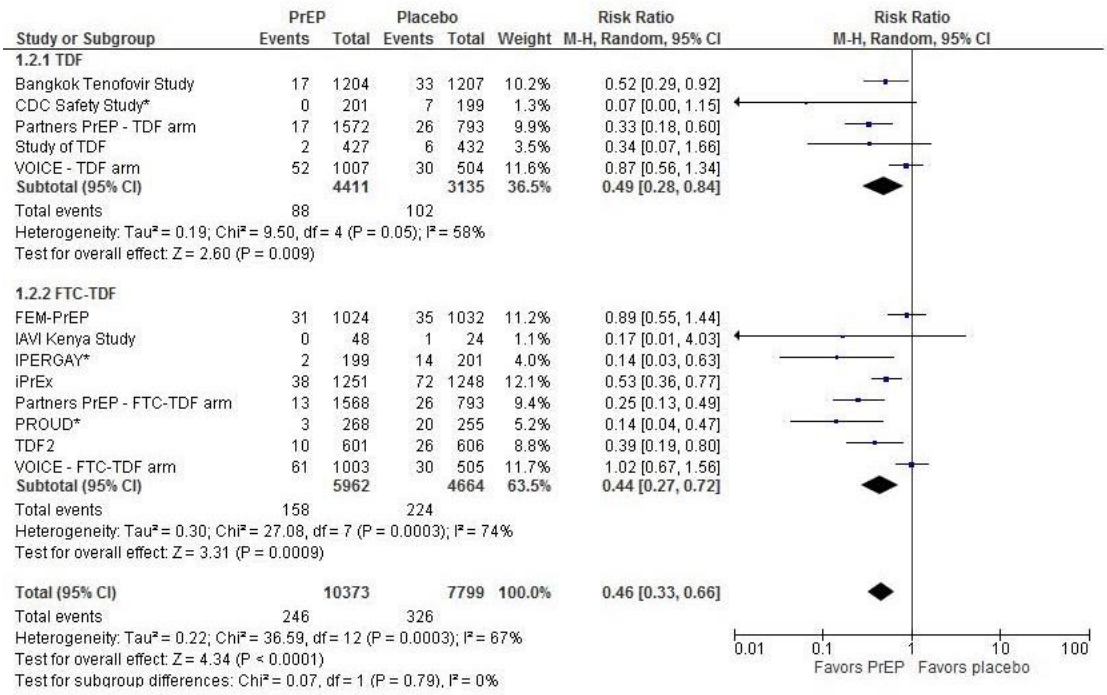
*****Harms also include renal dysfunction, adverse effects on bone, pregnancy-related outcomes, infection with antiretroviral drug-resistant HIV, gastrointestinal harms, headaches, and discontinuation due to adverse events.

Key Questions

1. What are the benefits of PrEP in persons without pre-existing HIV infection vs. placebo or no PrEP (including deferred PrEP) on the prevention of HIV infection and quality of life?
    a. How do the benefits of PrEP differ by populations of interest (e.g., defined by age, sex, gender identity, race and ethnicity, and HIV risk category)?
    b. How do the benefits of PrEP differ by dosing strategy or regimen?
2. What are the benefits of newer PrEP regimens (oral TAF-FTC, injectable cabotegravir, or the dapivirine vaginal ring) vs. TDF-FTC?
3. What is the diagnostic accuracy of provider or patient risk assessment tools in identifying persons at increased risk of HIV acquisition who are candidates for PrEP?
4. What are the harms of PrEP vs. placebo or no PrEP when used for the prevention of HIV infection?
5. What are the harms of newer PrEP regimens (oral TAF-FTC, injectable cabotegravir, or the dapivirine vaginal ring) vs. TDF-FTC?

Abbreviations: HIV=human immunodeficiency virus; PrEP=pre-exposure prophylaxis; STIs=sexually transmitted infections; TAF-FTC=tenofovir alafenamide-emtricitabine; TDF-FTC=tenofovir disoproxil fumarate-emtricitabine.

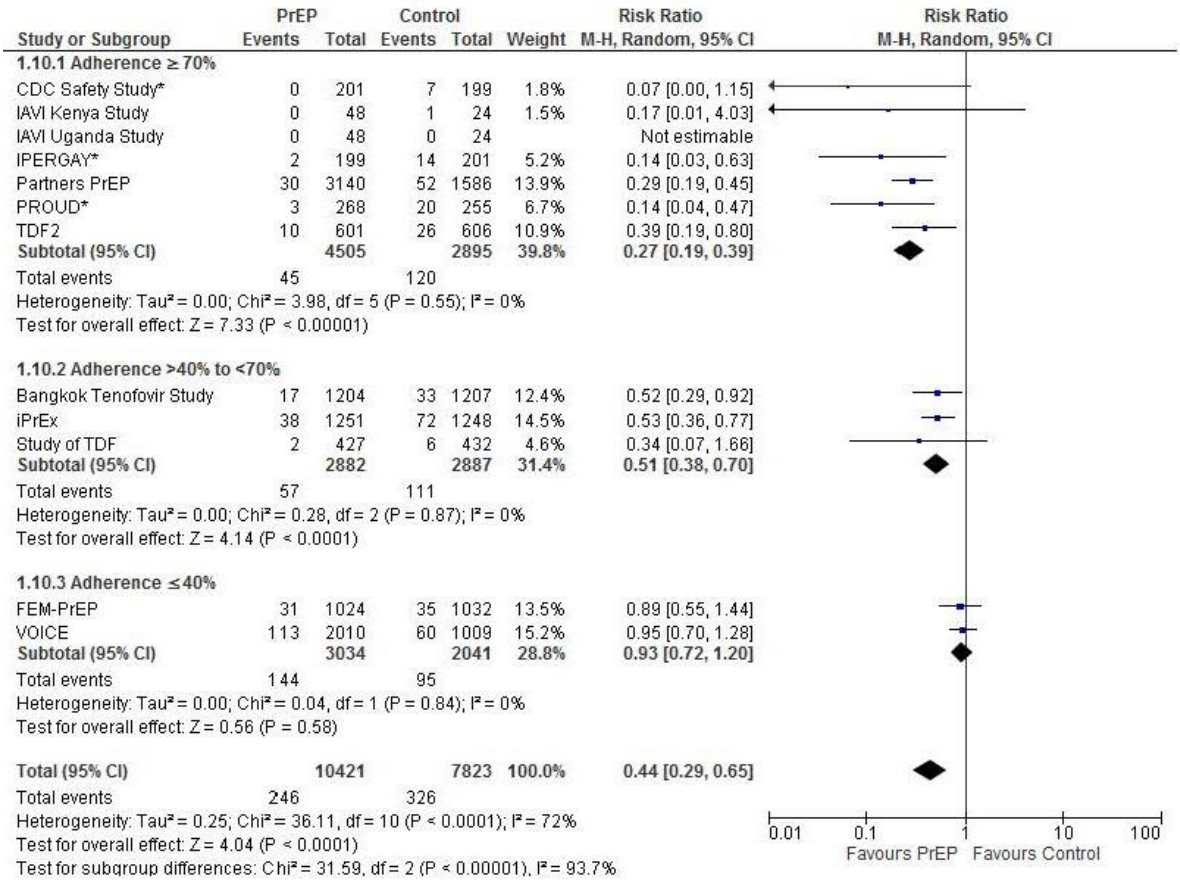
Figure 2. Meta-Analysis: HIV Infection Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; IAVI=International AIDS Vaccine Initiative; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

Figure 3. Meta-Analysis: HIV Infection Stratified by Adherence

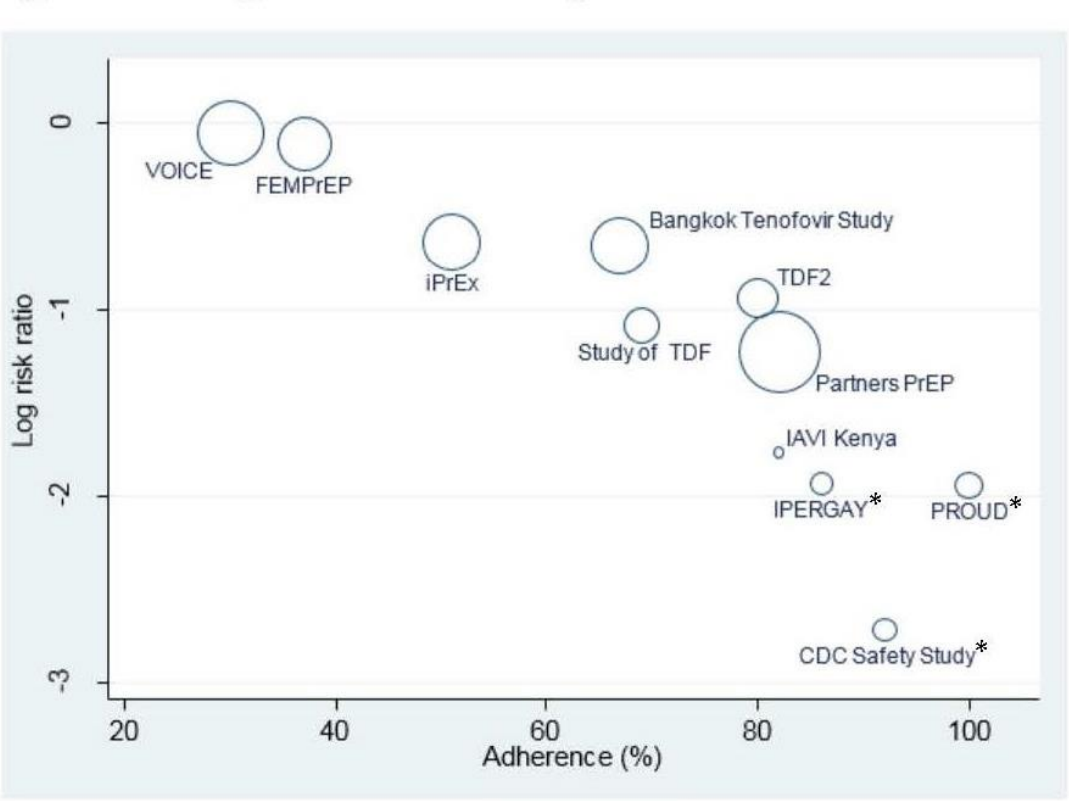


Note: Based on plasma testing, unless otherwise noted**.**

*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; IAVI=International AIDS Vaccine Initiative; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

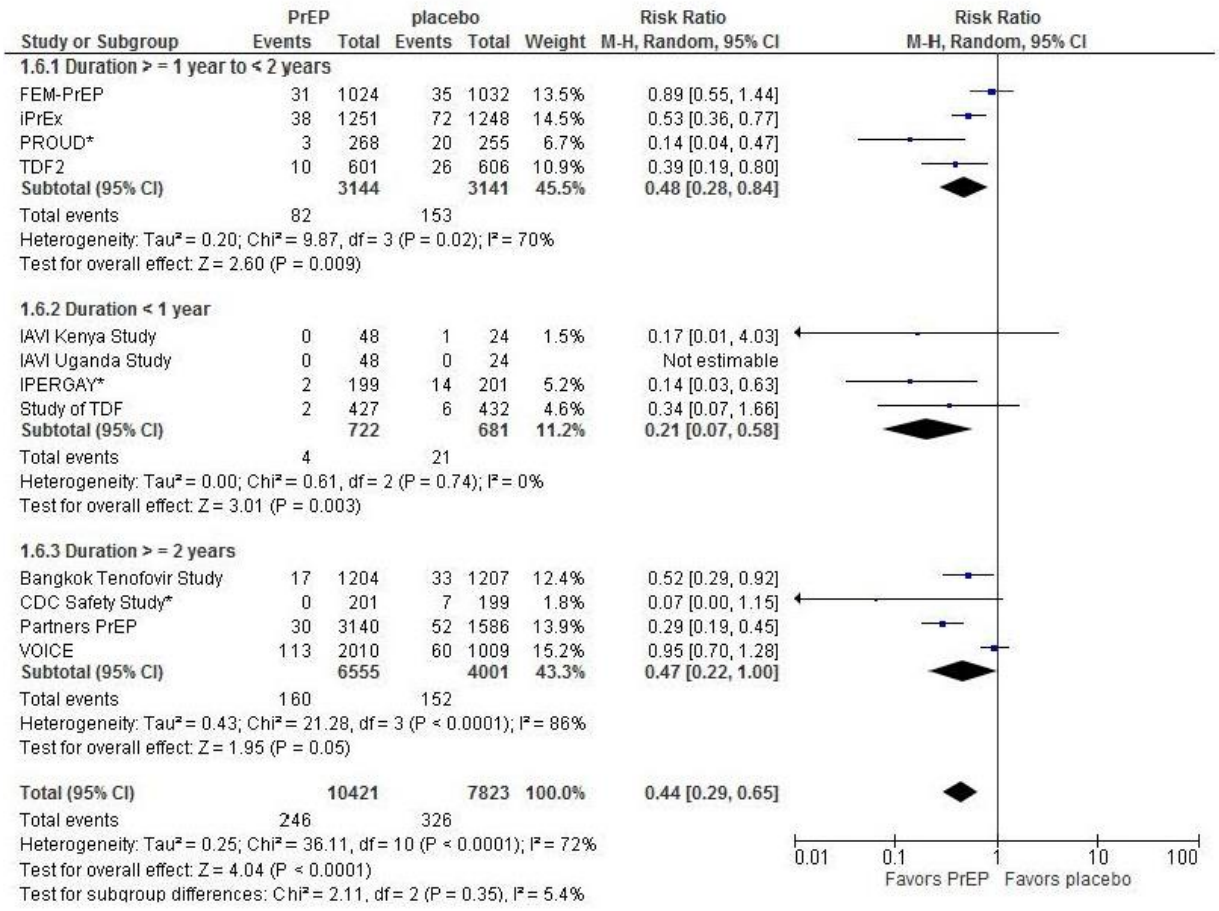
Figure 4. Meta-Regression: PrEP Efficacy vs. Adherence



*U.S, Canada, or Europe.

Abbreviations: FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; IAVI=International AIDS Vaccine Initiative; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

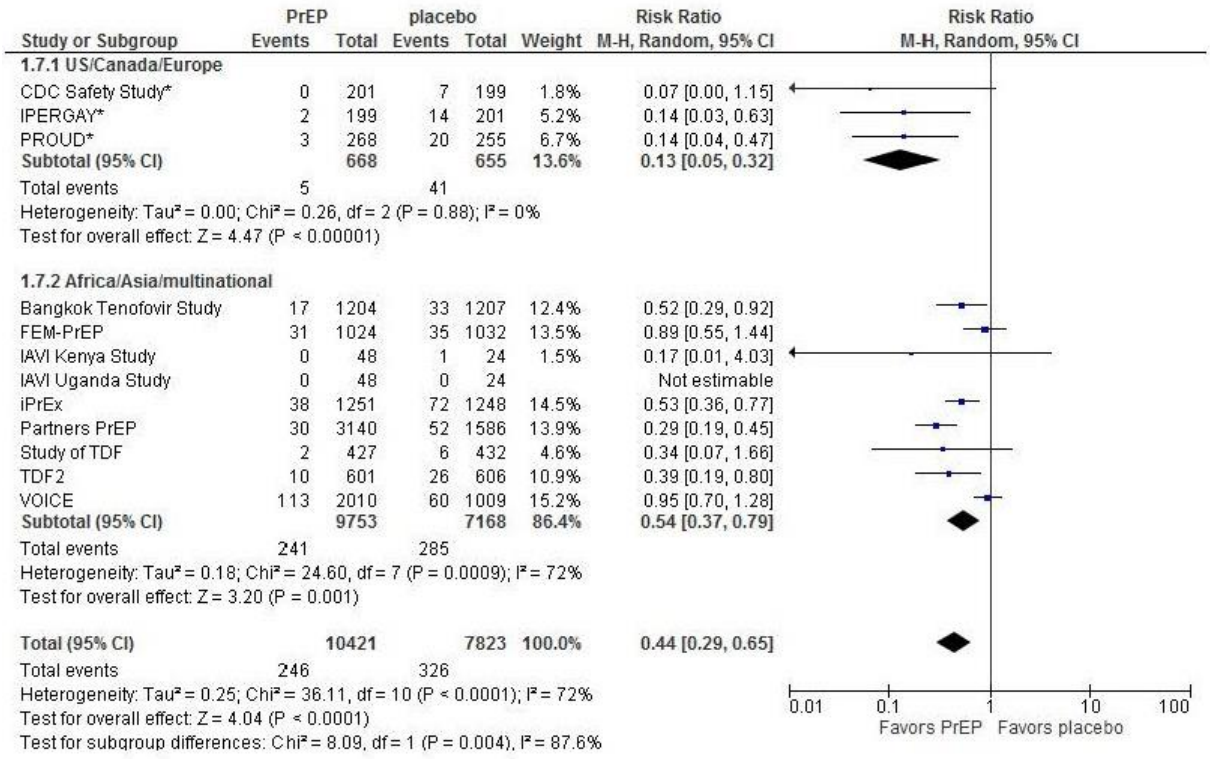
Figure 5. Meta-Analysis: HIV Infection Stratified by Study Duration



*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; IAVI=International AIDS Vaccine Initiative; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

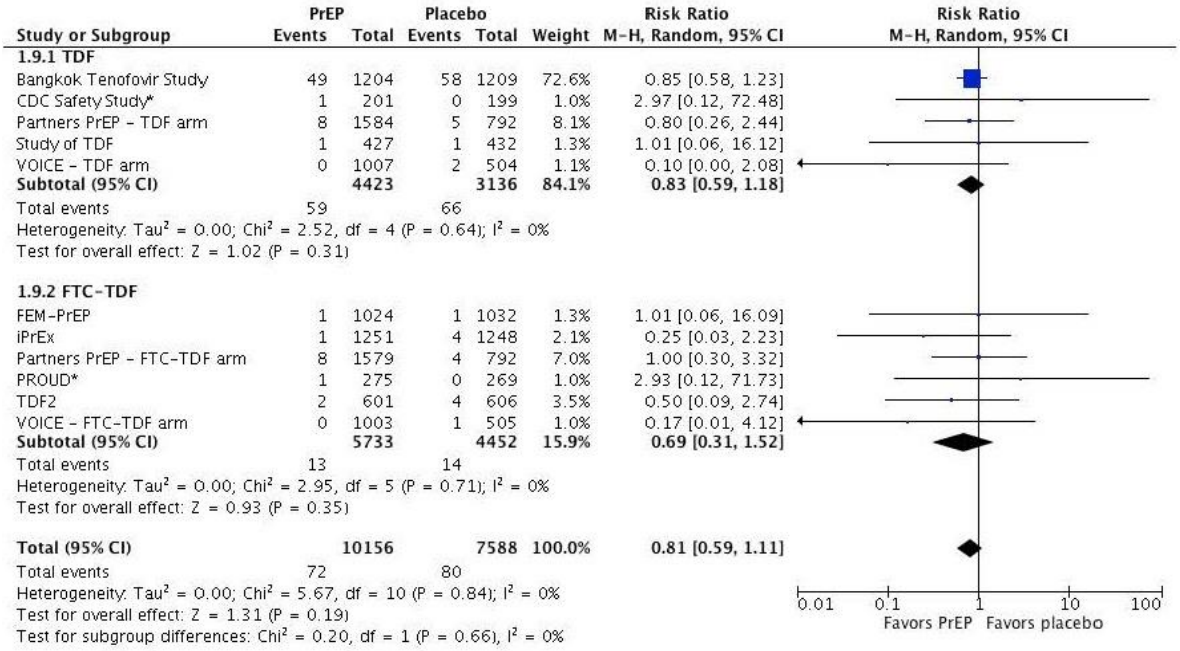
Figure 6. Meta-Analysis: HIV Infection Stratified by Geographic Setting



*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; IAVI=International AIDS Vaccine Initiative; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

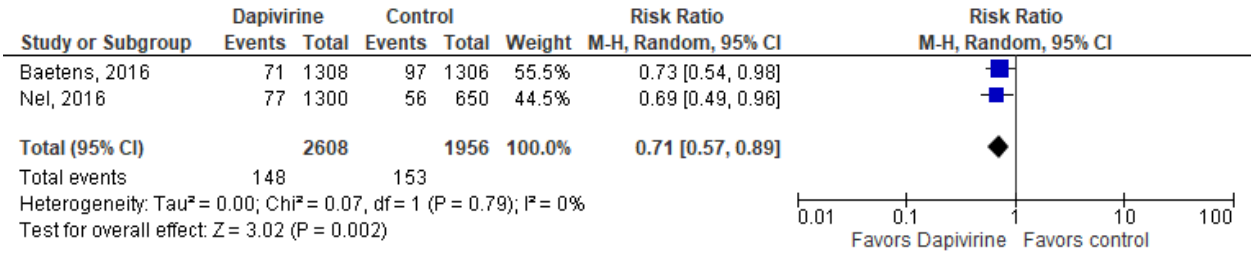
Figure 7. Meta-Analysis: Mortality Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis trial for HIV Prevention Among African Women; FTC=emtricitabine; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate Or Deferred; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

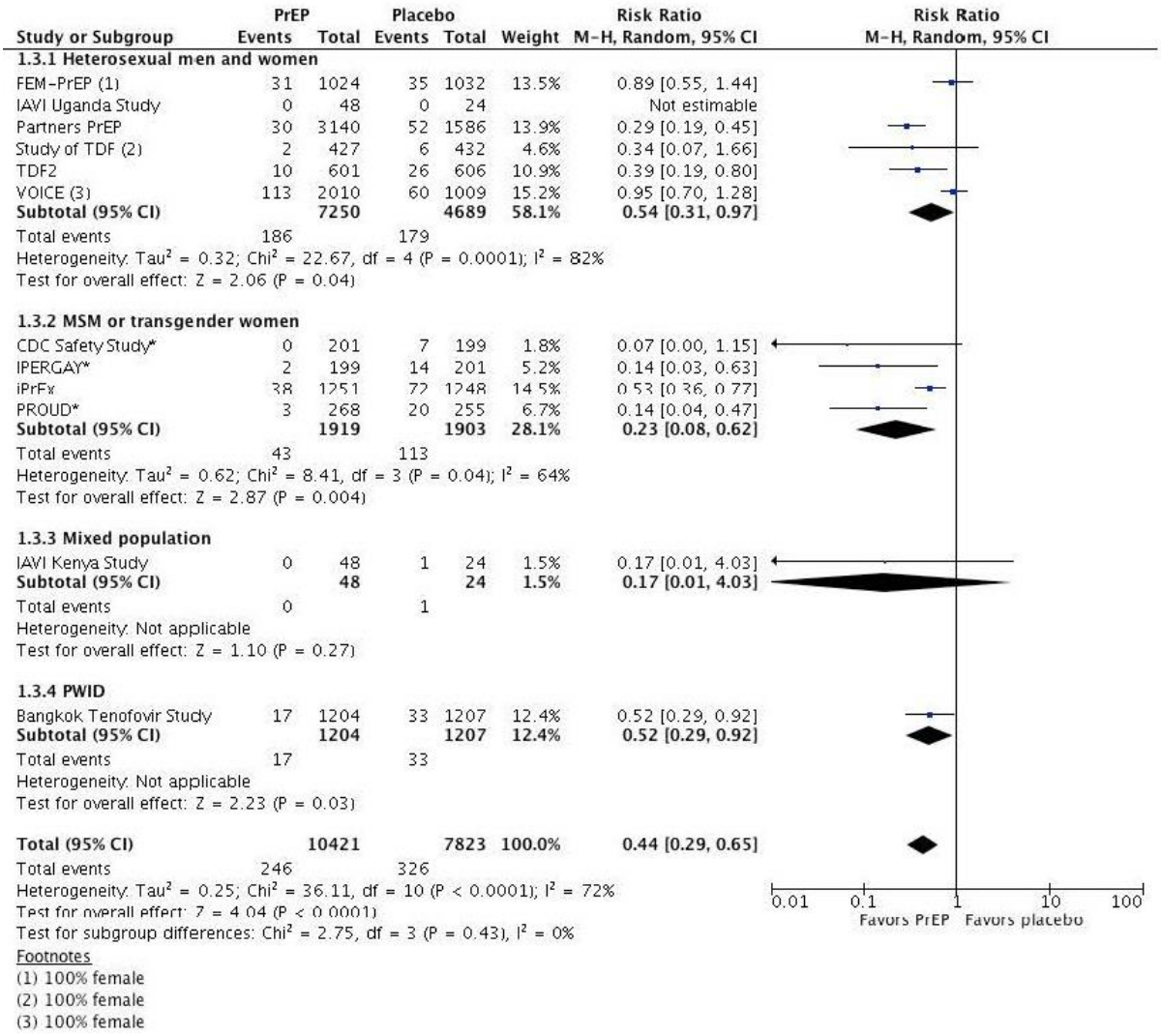
Figure 8. Dapivirine vs. Placebo: HIV Infection



RD: -2.23% (95% CI, -3.75% to -0.74%)

Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel-Haenszel; RD=risk difference.

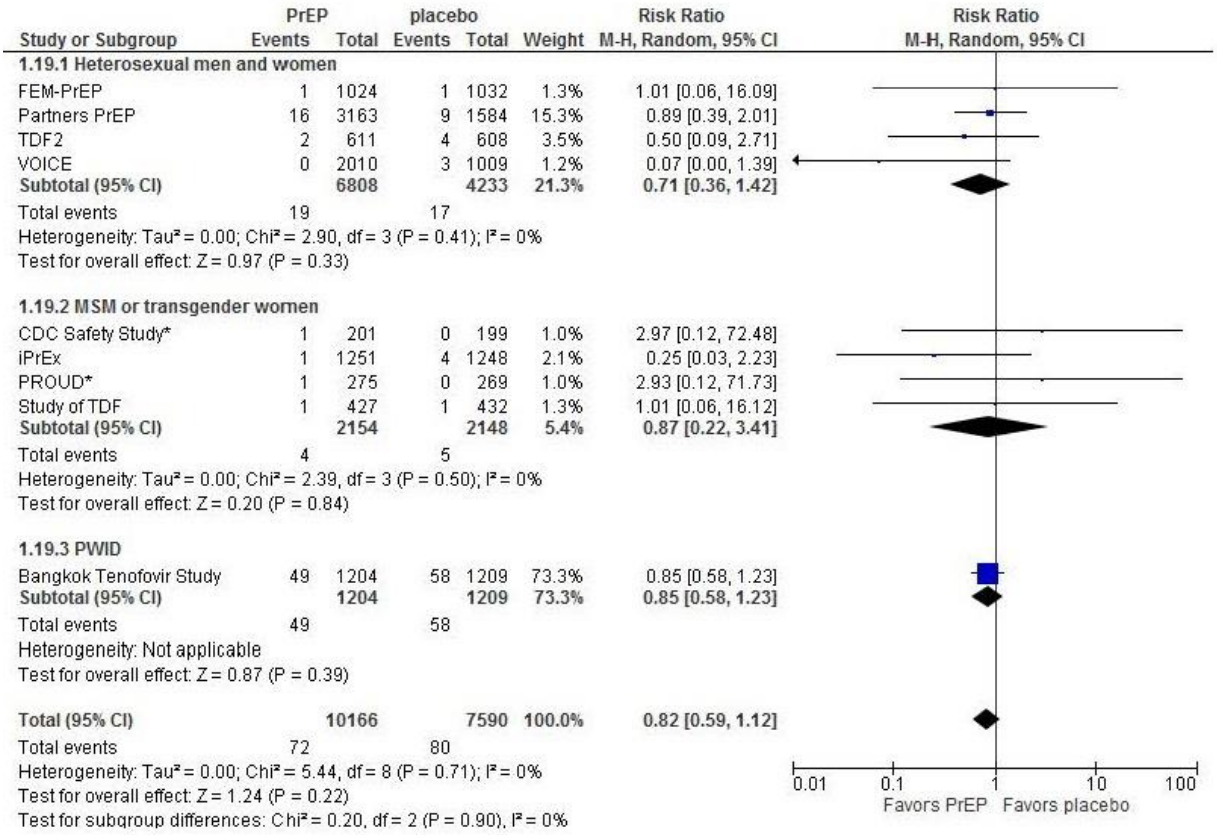
Figure 9. Meta-Analysis: HIV Infection Stratified by HIV Risk Category



*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; IAVI=International AIDS Vaccine Initiative; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; MSM=men who have sex with men; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

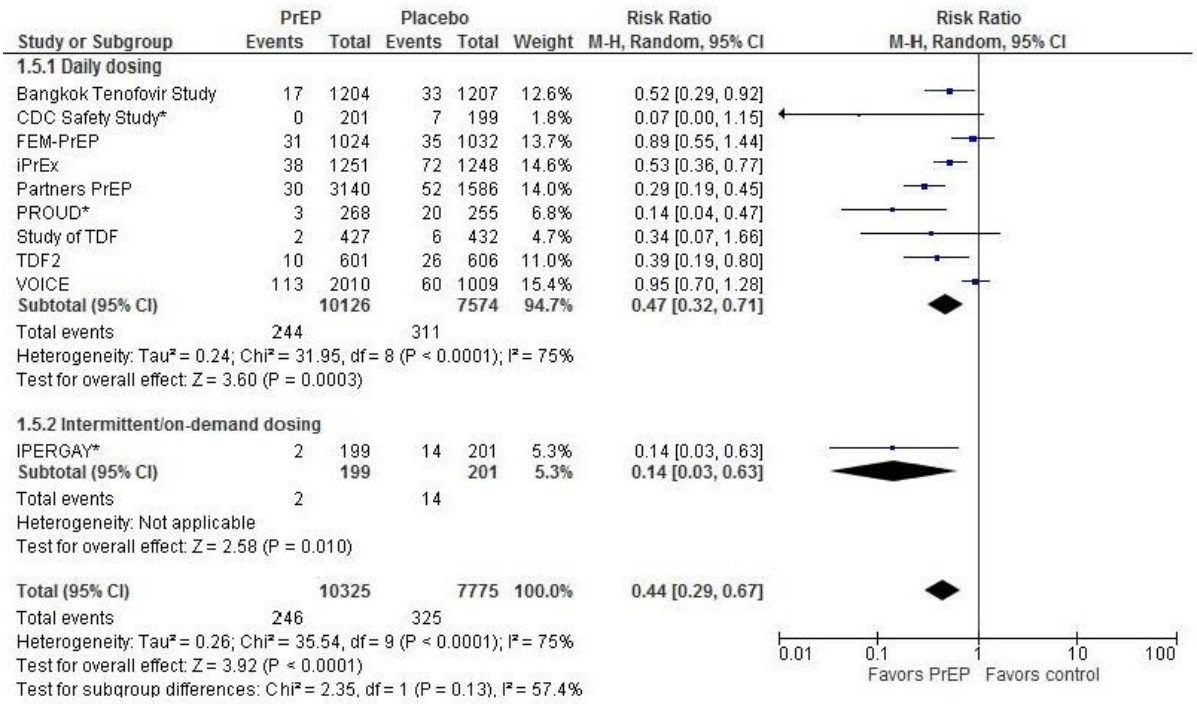
Figure 10. Meta-Analysis: Mortality Stratified by HIV Risk Category



*U.S, Canada, or Europe.

Abbreviatons: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; MSM=men who have sex with men; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; PWID=persons who inject drugs; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF2=Study of Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

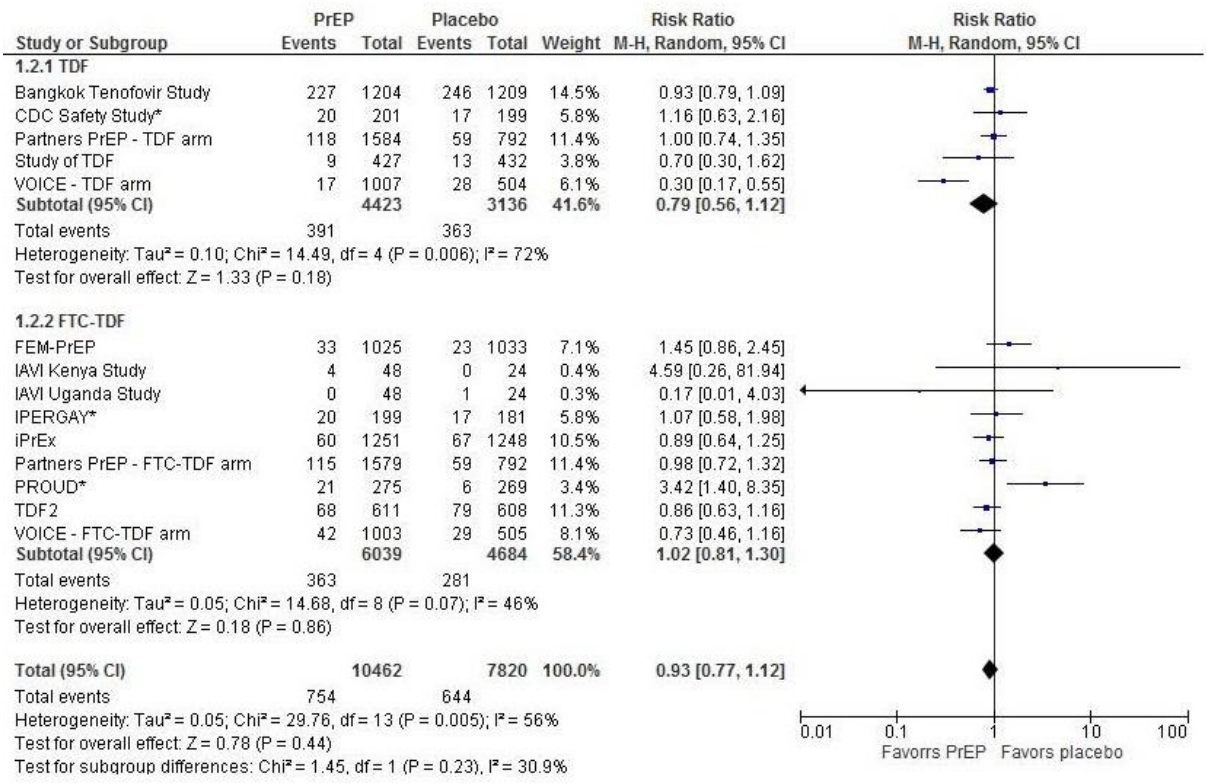
Figure 11. Meta-Analysis: HIV Infection Stratified by Dosing Strategy



*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

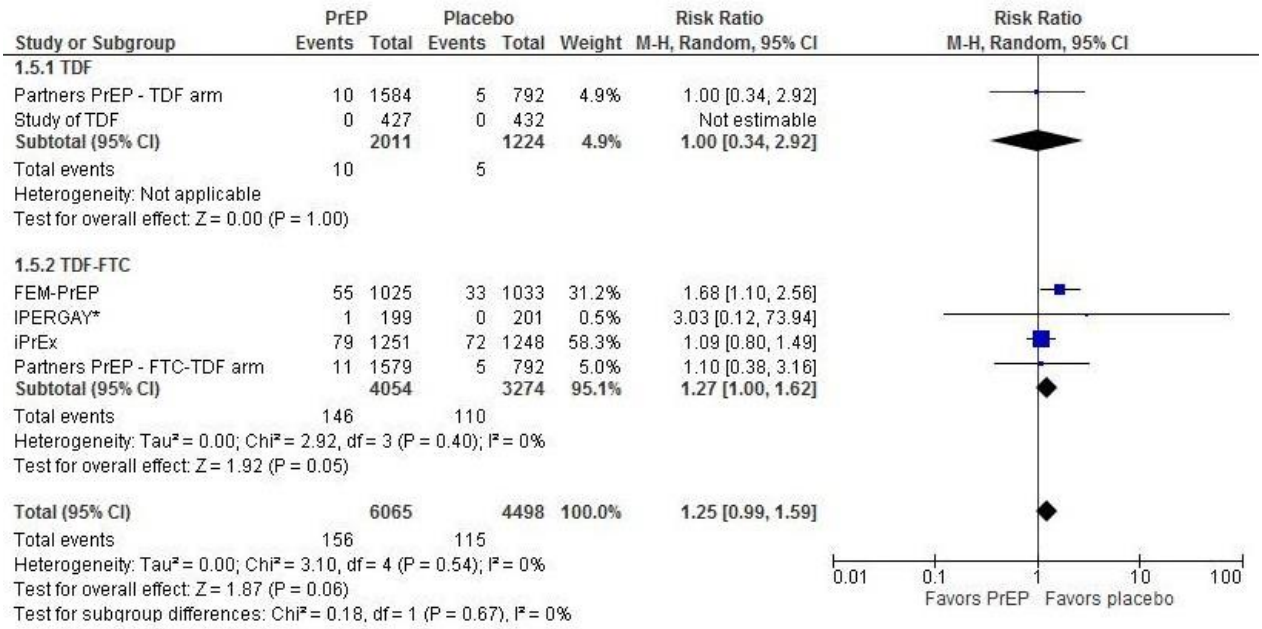
Figure 12. Meta-Analysis: Serious Adverse Events Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; IAVI=International AIDS Vaccine Initiative; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

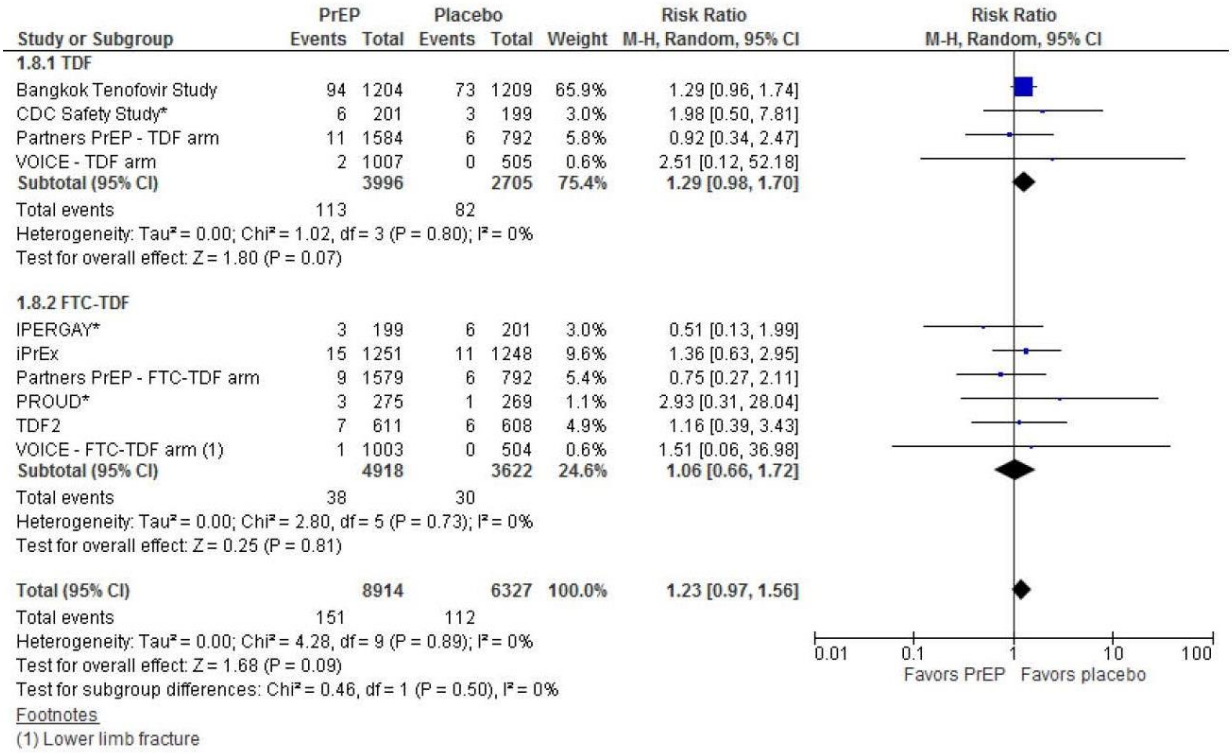
Figure 13. Meta-Analysis: Withdrawals Due to Adverse Events Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; M-H=Mantel-Haenszel test; iPrEx=Pre-Exposure Prophylaxis Initiative; PrEP=pre-exposure prophylaxis; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF=tenofovir disoproxil fumarate; U.S.=United States.

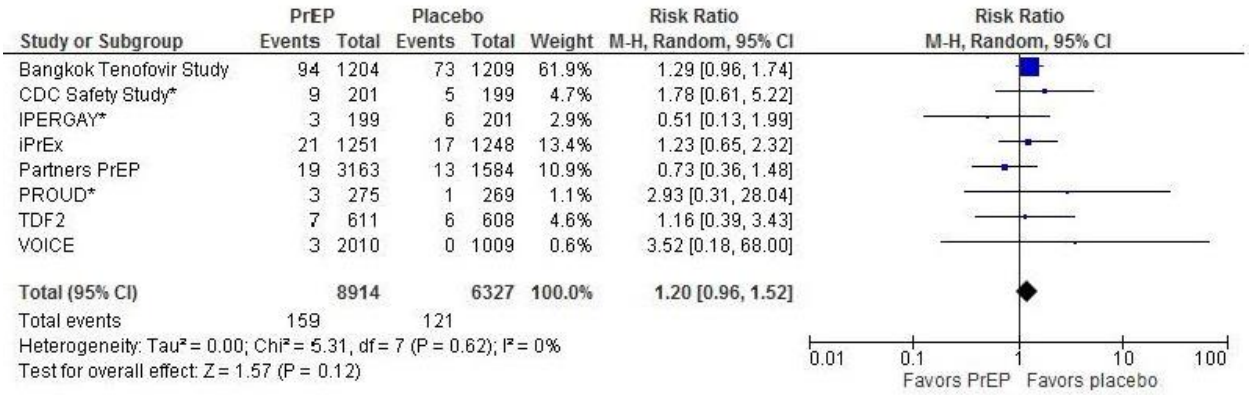
Figure 14. Meta-Analysis: Fracture Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FTC=emtricitabine; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

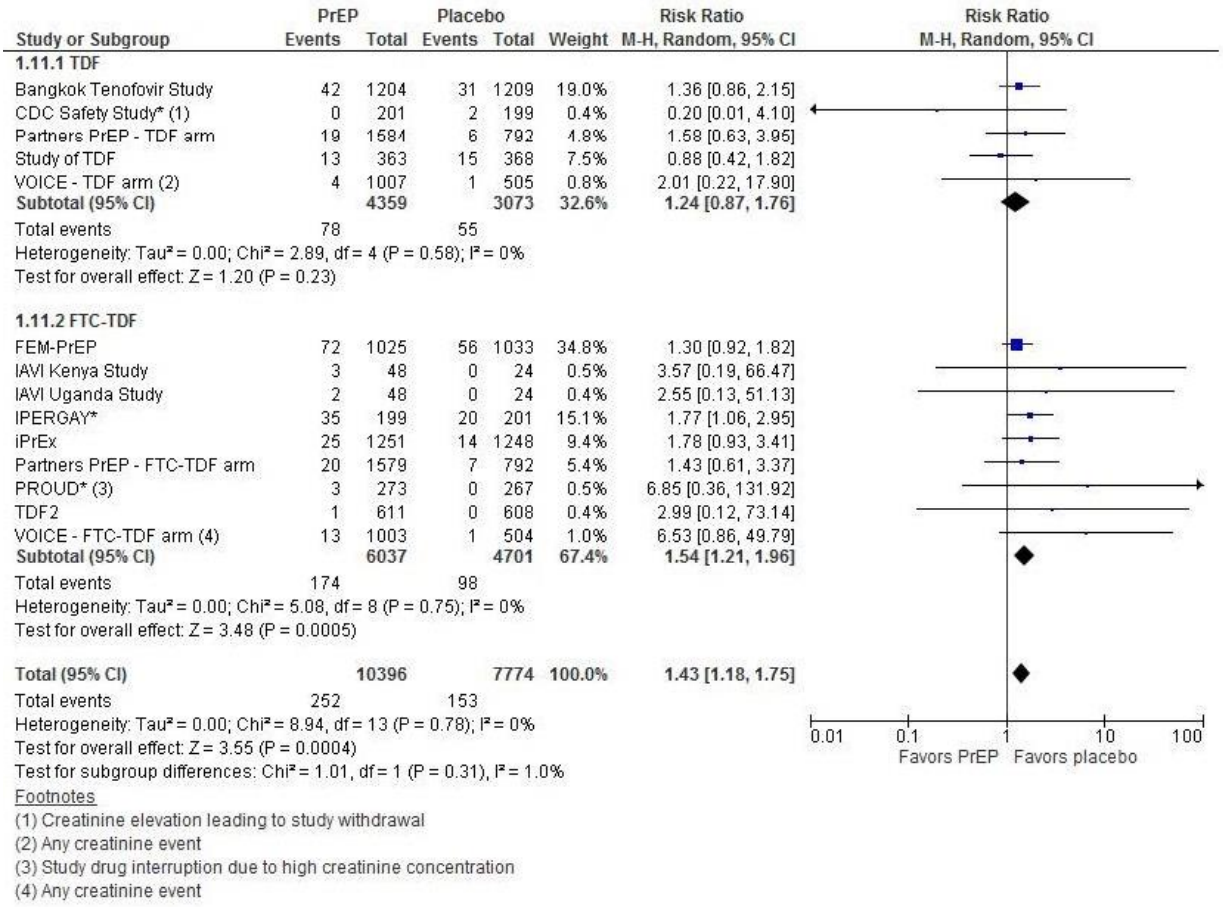
Figure 15. Meta-Analysis: Fracture Using FDA Data (iPrEx, Partners PrEP, CDC Safety Study)



*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval, df=degrees of freedom; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test, PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

Figure 16. Meta-Analysis: Renal Adverse Events Stratified by Study Drug

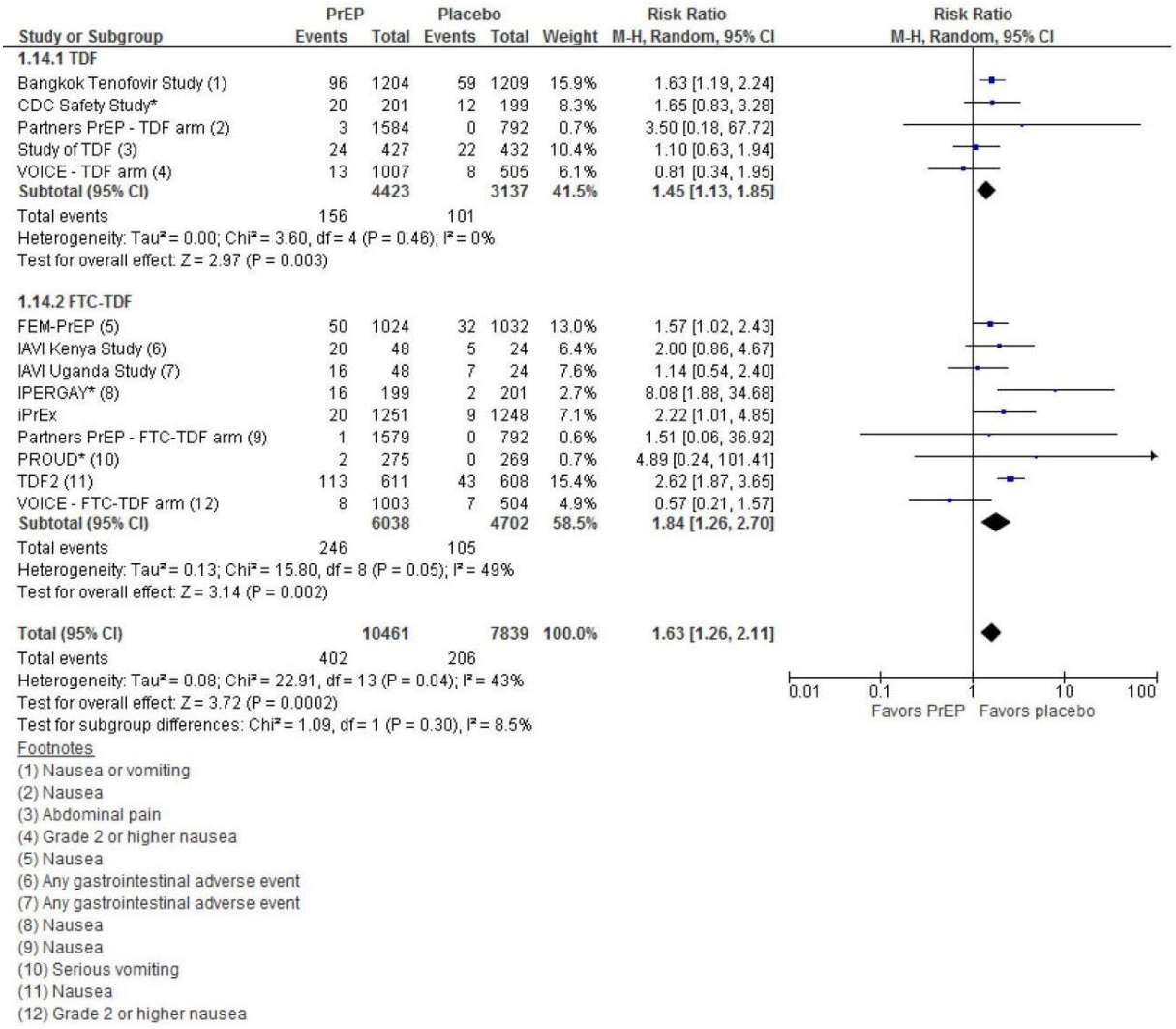


Note: Defined as ≥grade 1 serum creatinine elevation unless otherwise noted.

*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; IAVI=International AIDS Vaccine Initiative; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

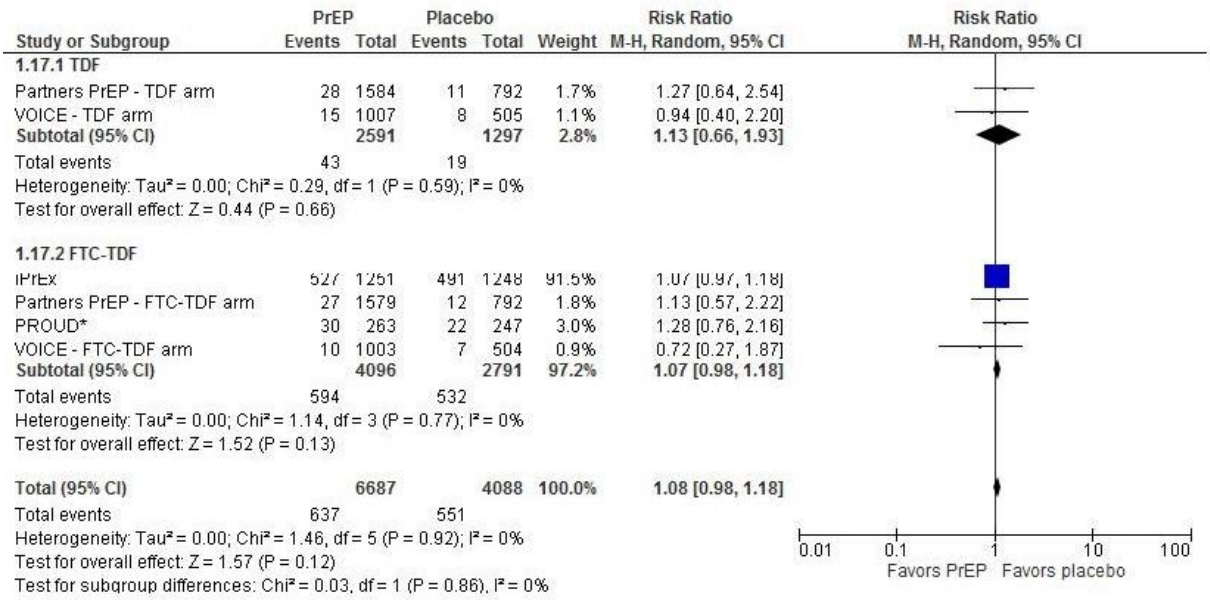
Figure 17. Meta-Analysis: Gastrointestinal Adverse Events Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; IAVI=International AIDS Vaccine Initiative; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; Study of TDF=Study of Tenofovir Disoproxil Fumarate; TDF=tenofovir disoproxil fumarate; TDF2= Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

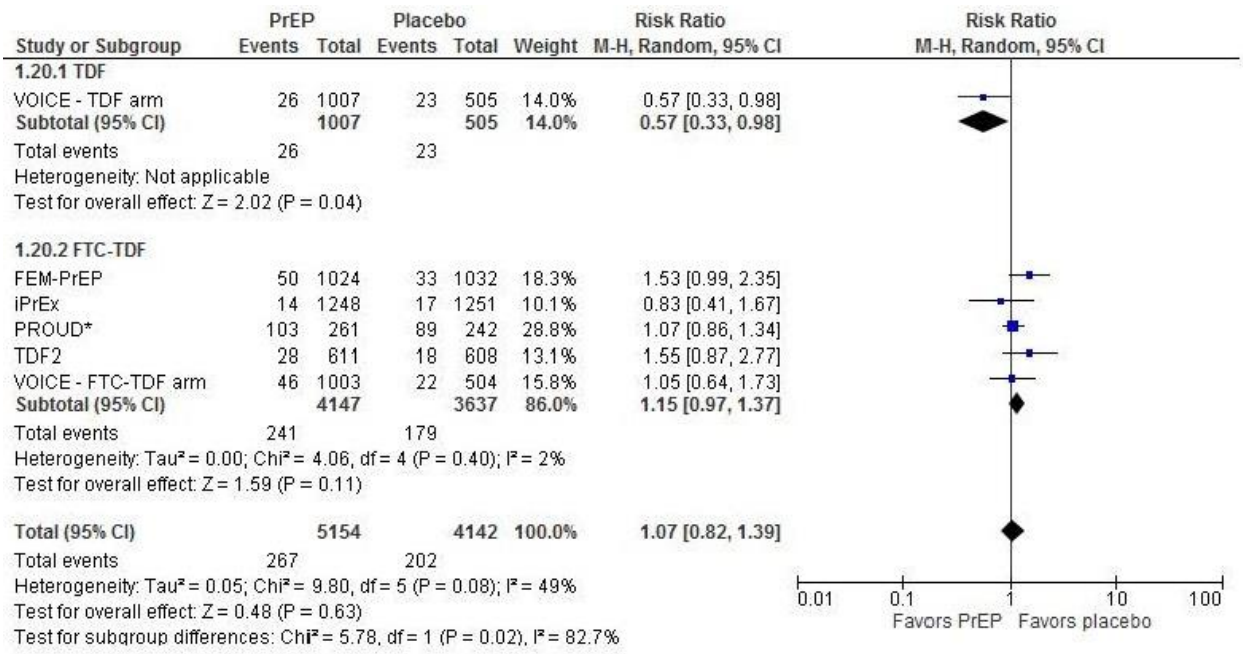
Figure 18. Meta-Analysis: Syphilis Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; FTC=emtricitabine; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; TDF=tenofovir disoproxil fumarate; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

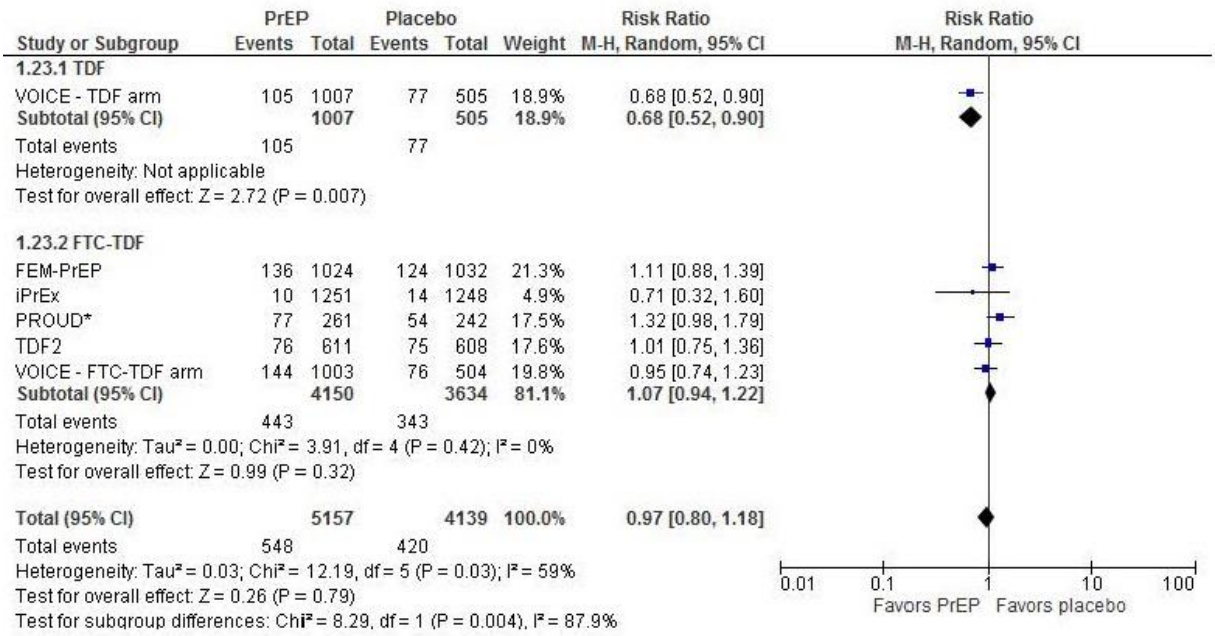
Figure 19. Meta-Analysis: Gonorrhea Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; TDF=tenofovir disoproxil fumarate; TDF2= Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

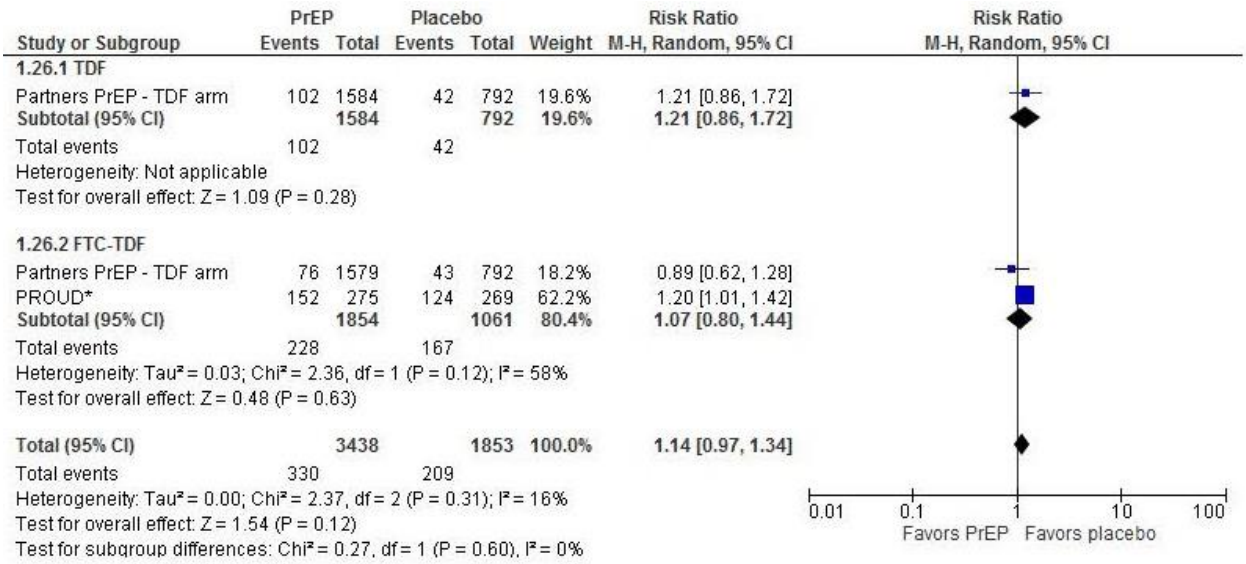
Figure 20. Meta-Analysis: Chlamydia Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; TDF=tenofovir disoproxil fumarate; TDF2= Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

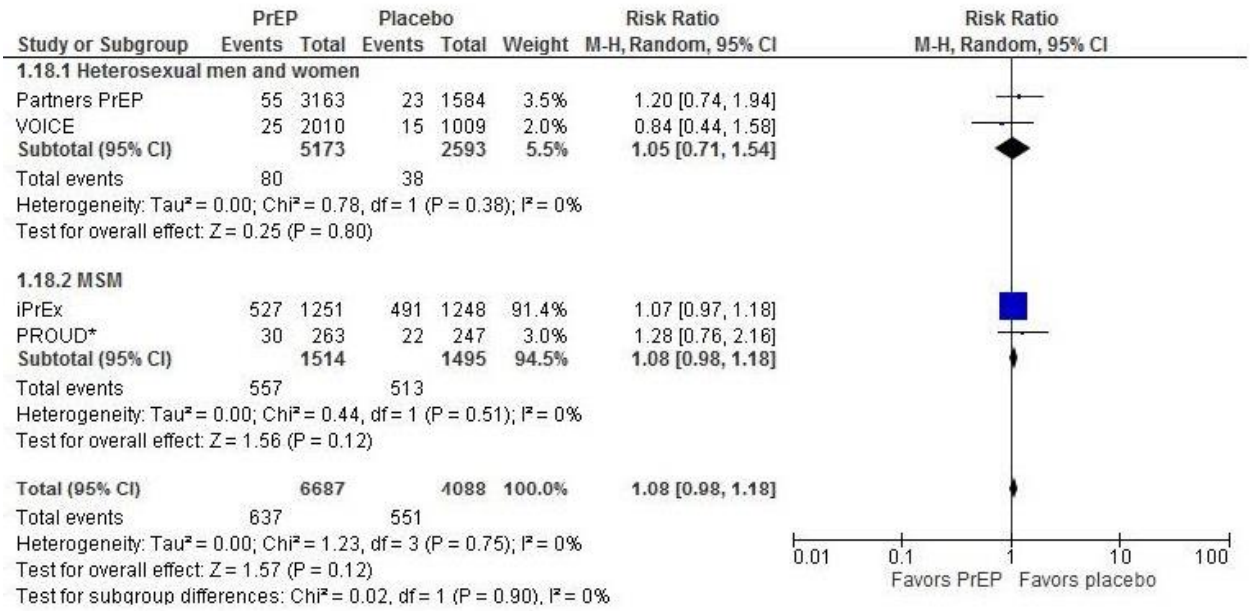
Figure 21. Meta-Analysis: Combined Bacterial STIs Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; FTC=emtricitabine; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; TDF=tenofovir disoproxil fumarate; U.S.=United States.

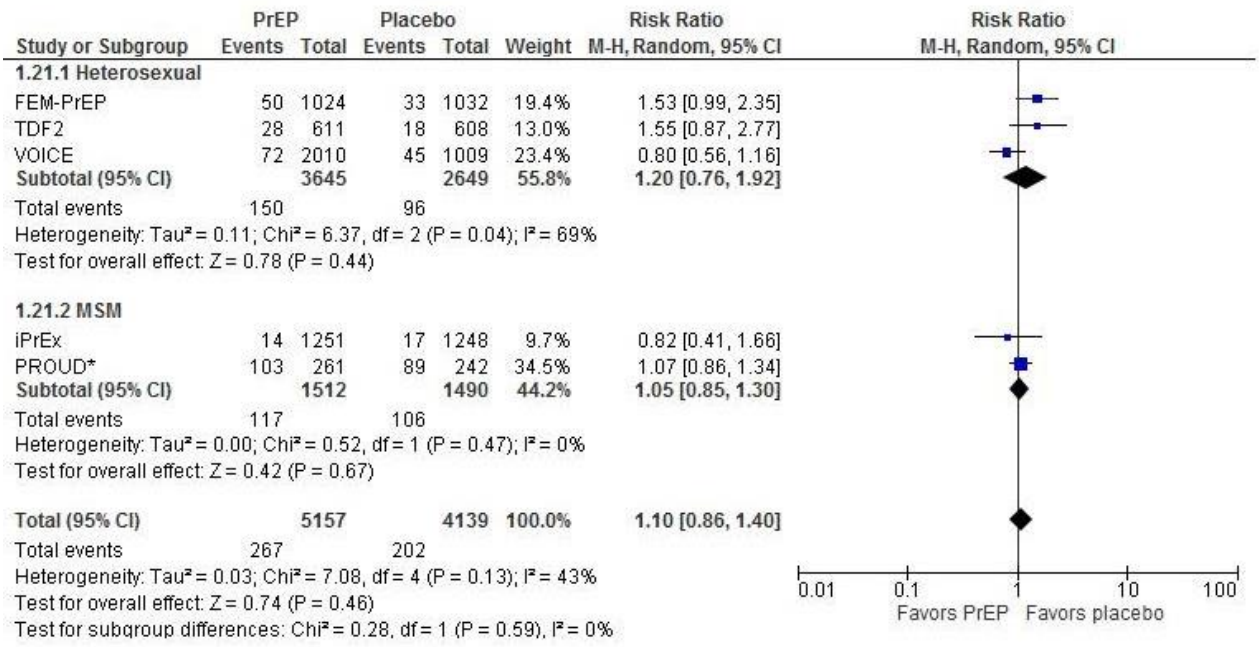
Figure 22. Meta-Analysis: Syphilis Stratified by HIV Risk Category



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenzel test; MSM=men who have sex with men; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; TDF=tenofovir disoproxil fumarate; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

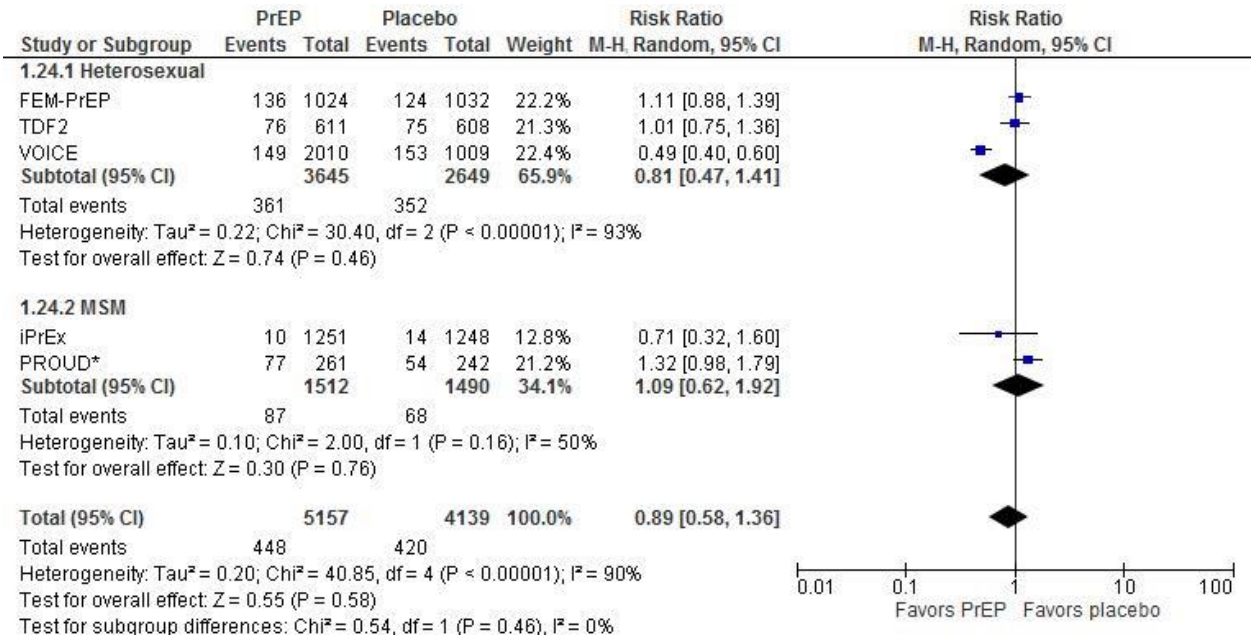
Figure 23. Meta-Analysis: Gonorrhea Stratified by HIV Risk Category



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; MSM=men who have sex with men; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; TDF2=Tenofovir Disoproxil Fumarate Study 2; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

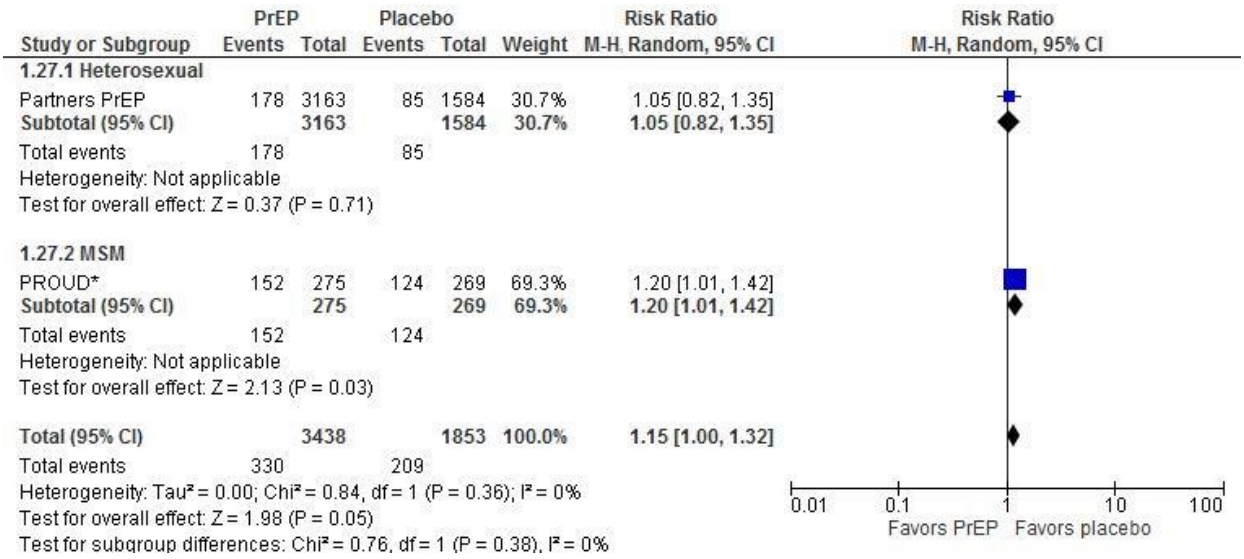
Figure 24. Meta-Analysis: Chlamydia Stratified by HIV Risk Category



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; MSM=men who have sex with men; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

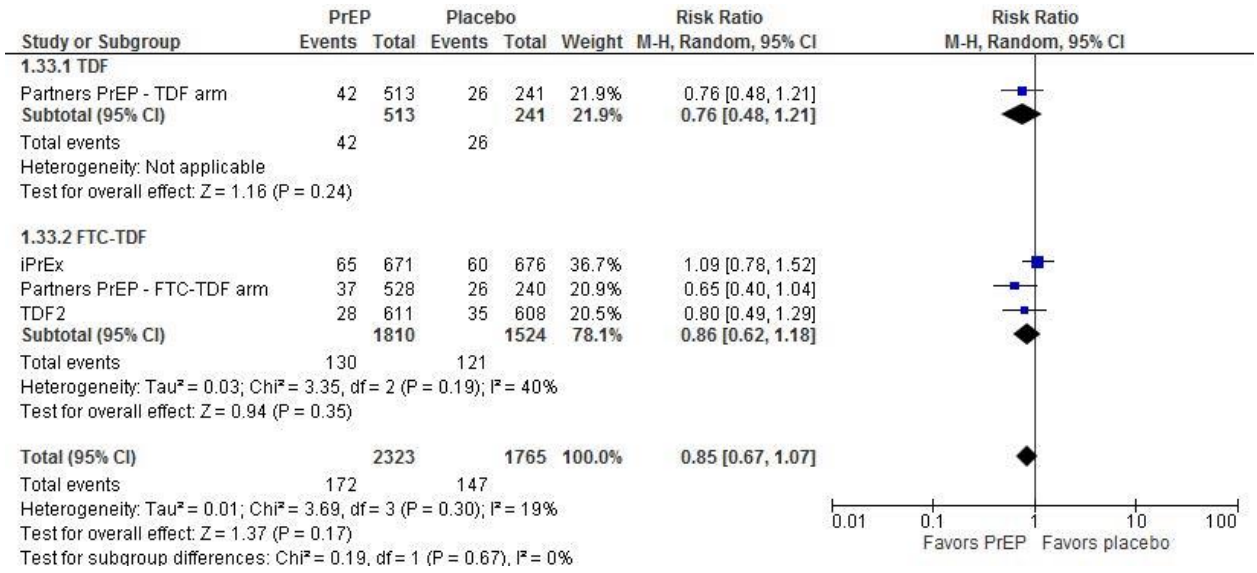
Figure 25. Meta-Analysis: Combined Bacterial STIs Stratified by HIV Risk Category



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; M-H=Mantel-Haenszel test; MSM=men who have sex with men; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; U.S.=United States.

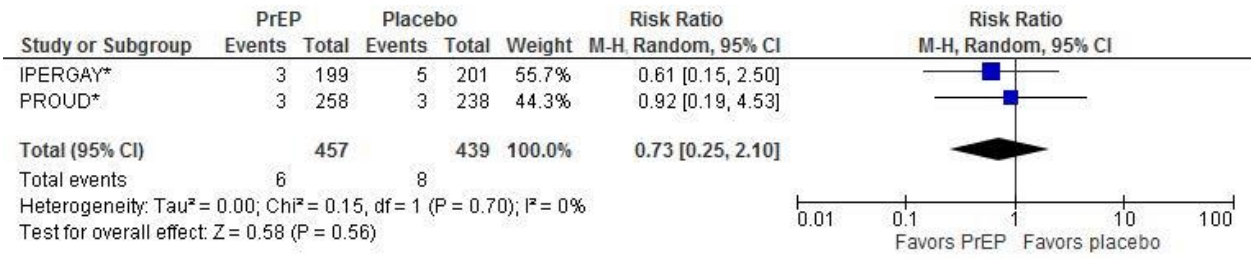
Figure 26. Meta-Analysis: Herpes Simplex Virus Infection Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; FTC=emtricitabine; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States

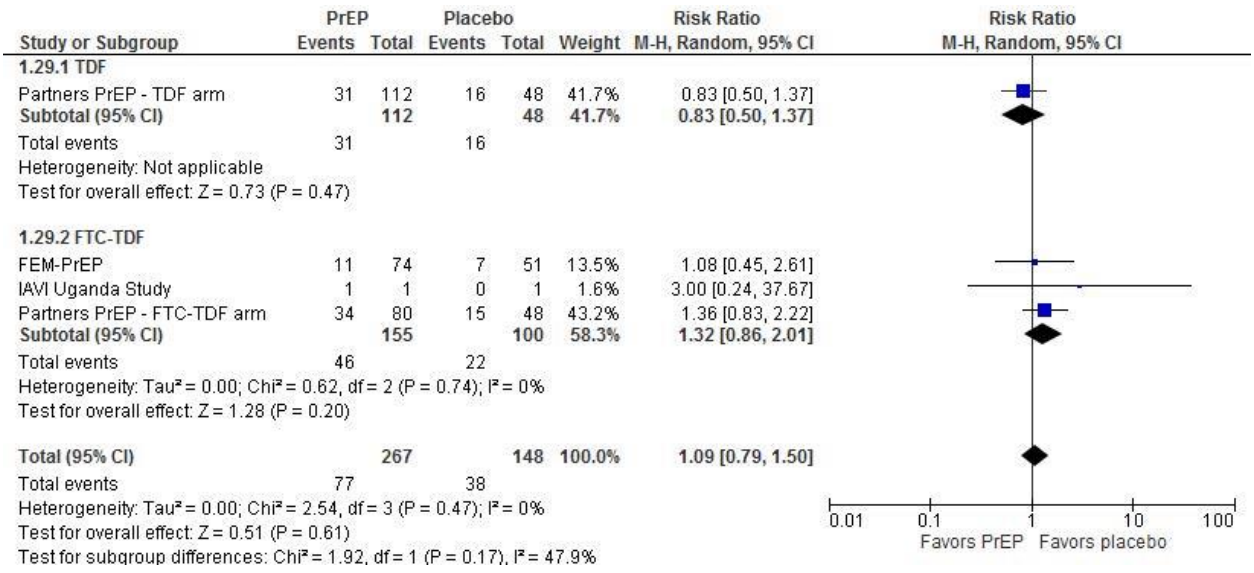
Figure 27. Meta-Analysis: Hepatitis C Virus Infection



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; U.S.=United States.

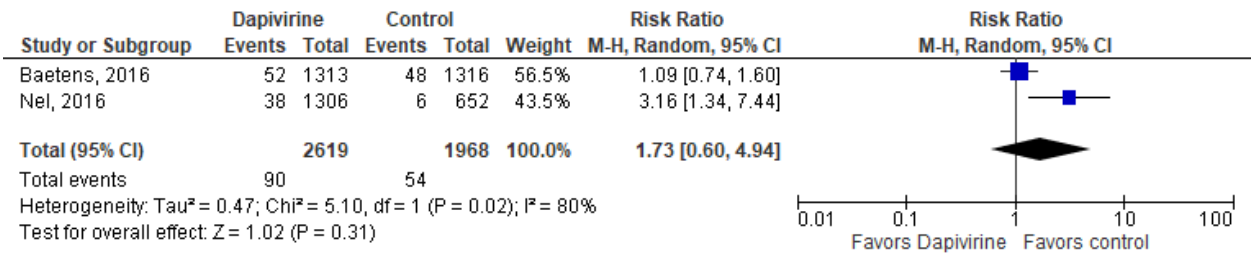
Figure 28. Meta-Analysis: Spontaneous Abortion Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; df=degrees of freedom; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; IAVI=International AIDS Vaccine Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate; U.S.=United States.

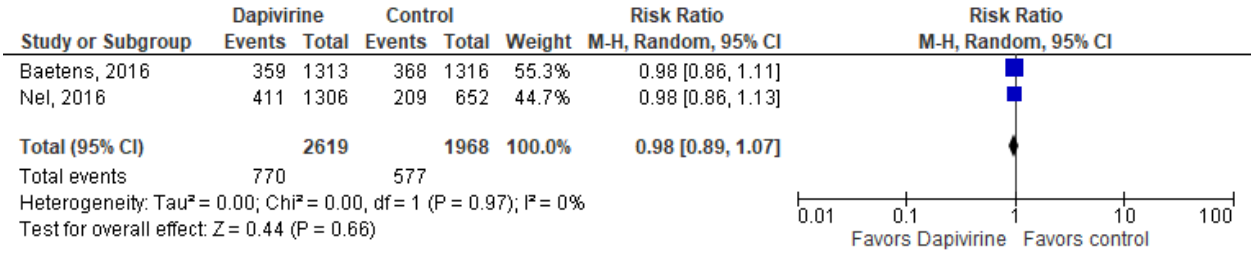
Figure 29. Dapivirine vs. Placebo: Serious Adverse Events



RD: 1.20% (95% CI, -0.59% to 2.99%)

Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel-Haenszel; RD=risk difference.

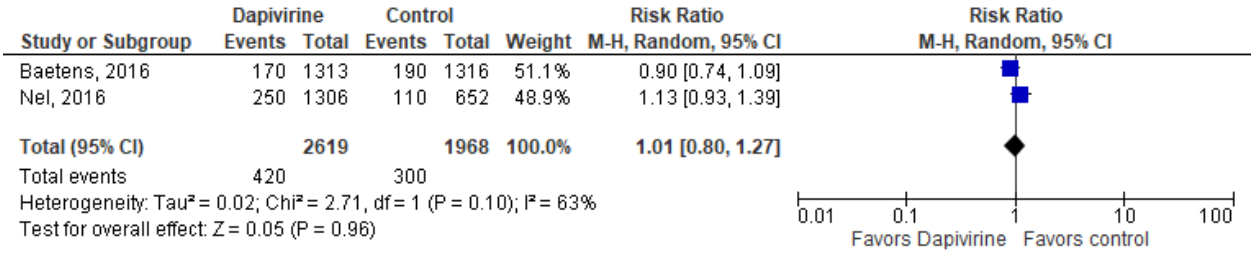
Figure 30. Dapivirine vs. Placebo: Chlamydia



RD: -0.61% (95% CI, -3.30% to 2.09%)

Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel-Haenszel; RD=risk difference.

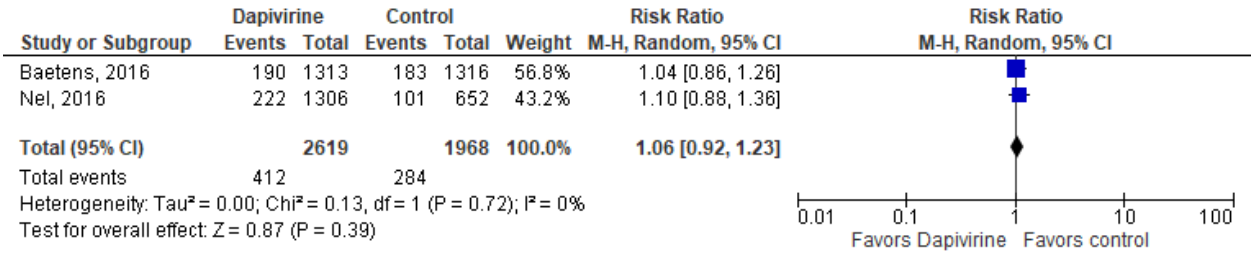
Figure 31. Dapivirine vs. Placebo: Gonorrhea



RD: 0.19% (95% CI, -3.50% to 3.87%)

Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel-Haenszel; RD=risk difference.

Figure 32. Dapivirine vs. Placebo: Trichomoniasis



RD: 0.92% (95% CI, -1.19% to 3.03%)

Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel-Haenszel; RD=risk difference.

Table 1. Summary of Guidance on Use of PrEP

Organization	Guidance for	Details
U.S. Public Health Service/CDC, 2021[84]	Sexually-active adults and adolescents	Anal or vaginal sex in past 6 months AND any of the following: • HIV-positive sexual partner (especially if partner has an unknown or detectable viral load) • Bacterial STI in past 6 months • History of inconsistent or no condom use with sexual partner(s)
	Persons who inject drugs	• HIV-positive injecting partner OR • Sharing injection equipment
IAS-USA, 2020[87]	Individuals at risk for HIV infection	• Initiation of PrEP is recommended as soon as feasible for individuals who have chosen to use it • Tenofovir disoproxil fumerate/emtricitabine once daily is recommended for oral PrEP • For MSM, a double dose (2 pills) of tenofovir disoproxil fumerate/emtricitabine is recommended on the first day • For MSM with or at risk for kidney dysfunction, osteopenia, or osteoporosis, daily tenofovir alafenamide/emtricitabine is recommended • Oral PrEP dosing using the 2-1-1 (or on-demand) method is recommended only for MSM • Injectable cabotegravir every 8 weeks is recommended as PrEP for cisgender men and transgender women who have sex with men
WHO, 2016[89] and 2021[80]	Individuals at substantial risk for HIV infection	• Oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches • Provisional definition of substantial risk is defined as HIV incidence higher than 3 per 100 person-years in the absence of PrEP • HIV incidence higher than 3 per 100 person-years has been identified among some groups of MSM, transgender women in many settings, and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection. Individual risk varies within groups at substantial risk, depending on individual behavior and the characteristics of sexual partners. • The WHO now also recommends the dapivirine vaginal ring as a new choice for women at substantial risk of HIV infection[80]

Abbreviations: IAS=International AIDS Society; PrEP=pre-exposure prophylaxis; STI=sexually transmitted infection; TDF-FTC=tenofovir disoproxil fumarate-emtricitabine, WHO=World Health Organization.

Table 2. Study Characteristics of Placebo-Controlled RCTs of PrEP

Type of PrEP	Study name Author, year* Country Duration of followup Quality	Interventions†	HIV risk group(s) Risk-based inclusion criteria	Patient characteristics	Adherence (method for measuring adherence)
Oral PrEP Versus Placebo or No PrEP	Bangkok Tenofovir Study Choopanya, 2013[53] Thailand 4 years (mean) Good	A. TDF 300mg (n=1,204) B. Placebo (n=1,209)	PWID: Injection drug use in the previous 12 months	A vs. B Age 20 to 29: 43% vs. 43% Age 30 to 39: 38% vs. 37% Age 40 to 49: 15% vs. 15% Age 50 to 60: 5% vs. 5% Male: 80% vs. 80%. Race: NR	67% (plasma, tenofovir detectable)
	FEM PrEP Van Damme 2012[172] Kenya, South Africa, Tanzania 1 year Good	A. TDF-FTC 300/200mg (n=1,062) B. Placebo (n=1,058)	High-risk women: >1 vaginal sex acts in previous 2 weeks or >1 sex partner in the previous month	A vs.B Age (mean): 24 vs. 24 years Female: 100% Race: NR	37% (plasma, tenofovir level ≥10 ng/mL [consistent with dose in last 48 hours])
	CDC Safety Study Grohskopf 2013 U.S.[52] 2 years Good	A. TDF 300 mg (n=201) B. Placebo (n=199)	MSM: Biological male engaging in anal sex with another man in the previous 12 months	A vs. B Age (mean): 38 vs. 37 years Male: 100% vs. 100% White: 79.6% vs. 66.8% African American: 23% vs. 37% Asian/Pacific Islander: 10% vs. 4% Other race: 8% vs. 25%	93% (pill count)
	IAVI Uganda Study Kibengo 2013[68] Uganda 4 months Good	A. TDF-FTC 300/200mg (n=24) B. Intermittent TDF-FTC (n=24) C. Daily placebo (n=12) D. Intermittent placebo (n=12)	High-risk heterosexual men and women: Unprotected vaginal sex with ART-naive HIV-infected partner in the previous 3 months	A vs. B vs. C vs. D Age (mean): 33 vs. 33 vs. 33 vs. 33 years Female: 50% vs. 46% vs. 67% vs. 42% Race NR	98% (MEMS [daily dosing])
	IAVI Kenya Study Mutua 2012[67] Kenya 4 months Good	A. TDF-FTC 300/200mg (n=24) B. Intermittent TDF-FTC (n=24) C. Daily placebo (n=12) D. Intermittent placebo (n=12)	MSM and high-risk women: Current or previous STI, multiple episodes of unprotected vaginal or anal sex, or engaging in transactional sex in the previous 3 months	A vs. B vs. C vs. D Age (mean): 26 vs. 26 vs. 27 vs. 28 years Female: 12% vs. 0% vs. 8% vs. 8% Race: NR	82% (MEMS [daily dosing])

Table 2. Study Characteristics of Placebo-Controlled RCTs of PrEP

Type of PrEP	Study name Author, year* Country Duration of followup Quality	Interventions†	HIV risk group(s) Risk-based inclusion criteria	Patient characteristics	Adherence (method for measuring adherence)
Oral PrEP Versus Placebo or No PrEP	IPERGAY Molina 2015[66] France, Canada 9 months (median) Good	A. On-demand TDF-FTC 300/200mg (n=199) B. Placebo (n=201)	MSM: Unprotected anal sex with at least two partners in the previous 6 months	A vs. B Age (median): 35 vs. 34 years (IQR 29-43) Female: 0% White: 94% vs. 89%; other races NR	86% (plasma, tenofovir detectable)
	iPrEx Grant 2010[137,159] Brazil, Ecuador, Peru, Thailand, South Africa, United States 1.2 years (median) Good	A. TDF-FTC 300/200 mg (n=1,251) B. Placebo (n=1,248)	Men who have sex with men: Anal sex with ≥4 male partners, a diagnosis of an STI, history of transactional sex activity, condomless anal sex with an HIV-infected partner or partner of unknown infection status in the previous 6 months	A vs. B Ages 18 to 24 years: 47% vs. 53% Ages 25 to 29 years: 22% vs. 19% Ages 30 to 39 years: 20% vs. 18% Age ≥40 years: 11% vs. 10% Born male: 100% vs. 100% Black: 9% vs. 8% White: 18% vs. 17% Mixed race or other: 68% vs. 70% Asian: 5% vs. 5% Hispanic: 72% vs. 73%	48% (plasma, tenofovir or FTC detectable)
	Partners PrEP Baeten 2012[51] Kenya, Uganda 2 years (median) Good	A. TDF 300 mg + placebo TDF-FTC (n=1,571) B. TDF-FTC 300/200 mg + placebo TDF (n=1,565) C. Placebo TDF + placebo TDF-FTC (n=1,570)	High-risk heterosexual men and women: ART-naive HIV-infected partner	A vs. B vs. C Ages 18 to 24 years: 12% vs. 11% vs. 11% Ages 25 to 34 years: 46% vs. 44% vs. 43% Ages 35 to 44 years: 30% vs. 32% vs. 32% Age ≥45 years: 13% vs. 14% vs. 13% Male: 62% vs. 64% vs. 61% Race: NR	82% (plasma, tenofovir detectable)
	PROUD McCormack 2016[118] England 1 year Fair	A. Immediate TDF-FTC 245/200 mg (n=275) B. TDF-FTC deferred for 1 year (n=269)	Men who have sex with men: Anal intercourse without a condom in the previous 90 days and likely to have anal intercourse without a condom in the next 90 days	A vs. B Age (mean): 35 vs. 35 years Male: 100% vs. 100% White: 81% vs. 83% Asian: 5% vs. 6% Black: 4% vs. 4% Other race: 10% vs. 8%	100% (plasma, tenofovir detectable)‡

Table 2. Study Characteristics of Placebo-Controlled RCTs of PrEP

Type of PrEP	Study name Author, year* Country Duration of followup Quality	Interventions†	HIV risk group(s) Risk-based inclusion criteria	Patient characteristics	Adherence (method for measuring adherence)
Oral PrEP Versus Placebo or No PrEP	Study of TDF Peterson 2007[55] Cameroon, Ghana, Nigeria 6 months (mean) Good	A. TDF 300 mg (n=469) B. Placebo (n=467)	High-risk women: Average of ≥3 coital acts per week and ≥4 sexual partners per month	A vs. B Age (mean): 24 vs. 24 years 100% female Race: NR	69% (pill count)
	TDF2 Thigpen 2012[170] Botswana 1 year (median) Good	A. TDF-FTC 300/200 mg, (n=611) B. Placebo (n=608)	High-risk heterosexual men and women: Sexually active in high-prevalence area	A vs. B Ages 18 to 20 years: 2% vs. 3% Ages 21 to 29 years: 90% vs. 87% Ages 30 to 39 years: 8% vs. 10% Female: 46% vs. 46% Race: NR	80% (plasma, tenofovir detectable)
	VOICE Marrazzo 2015[54] South Africa, Uganda, Zimbabwe 3 years (maximum) Good	A. TDF 300 mg + placebo (n=1,007) B. TDF-FTC 300/200 mg + placebo (n=1,003) C. Placebo only (n=1,009)	High-risk women: Sexually active in a high-prevalence area	A vs. B vs. C Age (mean): 26 vs. 25 vs. 25 years Female: 100% all groups Race: NR	30% (plasma, tenofovir detectable)
Dapivirine Vaginal Ring Versus Placebo Ring	ASPIRE Baeten, 2016[73] Malawi, South Africa, Uganda, Zimbabwe 2.6 years (maximum) 1.6 years (median) Fair	A. Dapivirine 25 mg vaginal ring (n=1,313) B. Placebo vaginal ring (n=1,316)	High-risk women: Sexually active in a high-prevalence area	A vs. B Age (mean): 27.2 vs. 27.3 Female: 100% Race: NR	82% (plasma, dapirivine level >95 pg/mL)
	Ring Study Nel, 2016[74] South Africa, Uganda 2 years Fair	A. Dapivirine 25 mg vaginal ring (1,307) B. Placebo vaginal ring (n=652)	High-risk women: Sexually active in a high-prevalance area	A vs. B Age (mean):25.9 vs. 26.1 Female: 100% Black: 99.4% vs. 98.5% Other: 0.6% vs. 1.5%	84% (plasma, dapivirine level ≥95 pg/mL)

*Primary publication.
†Daily, oral dose unless specified.
‡Sample of patients who reported that they were taking PrEP.
Abbreviations: ART=antiretroviral therapy; ASPIRE=Antiretroviral Strategy to Promote Improvement and Reduce Exposure; FTC=emtricitabine; iPrEx=Pre-Exposure Prophylaxis Initiative; MEMS=medication event monitoring system NR=not reported; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; RCTs=randomized, controlled trials; STI=sexually transmitted infection; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

Table 3. Risk of HIV Infection in Placebo-Controlled RCTs of Oral PrEP

Study characteristics	Subgroups	Number of trials	RR (95% CI)	I^2
All trials	-	11[51-55,66,67,118,137,170,172]	0.46 (0.33 to 0.66)	67%
Study quality	Restricted to good-quality trials	10[51-55,66,67,137,170,172]	0.48 (0.33 to 0.71)	71%
PrEP drug regimen *(p=0.79 for interaction)*	TDF	5[51-55]	0.49 (0.28 to 0.84)	58%
	TDF-FTC	8[51,54,55,66,67,118,137,172]	0.44 (0.27 to 0.72)	67%
Adherence *(p<0.00001 for interaction)*	Adherence ≥70%	6[51,52,66,67,118,170]	0.27 (0.19 to 0.39)	0%
	Adherence >40% to <70%	3[53,55,137]	0.51 (0.38 to 0.70)	0%
	Adherence ≤40%	2[54,172]	0.93 (0.72 to 1.20)	0%
HIV risk category *(p=0.43 for interaction)*	Heterosexual men and women	5[51,54,55,170,172]	0.54 (0.31 to 0.97)	82%
	Men who have sex with men	4[52,66,118,137]	0.23 (0.08 to 0.62)	64%
	Persons who inject drugs	1[53]	0.52 (0.29 to 0.92)	Not applicable
Dosing schedule *(p=0.13 for interaction)*	Daily dosing	9[51-55,67,118,137,170,172]	0.47 (0.32 to 0.71)	75%
	On-demand dosing	1[66]	0.14 (0.03 to 0.63)	Not applicable
Followup duration *(p=0.35 for interaction)*	Duration of followup <1 year	3[55,66,67]	0.21 (0.07 to 0.58)	0%
	Duration of followup ≥1 to 2 years	4[118,137,170,172]	0.48 (0.28 to 0.84)	70%
	Duration of followup ≥2 years	4[51-54]	0.47 (0.22 to 1.00)	86%
Industry support *(p=0.38 for interaction)*	Study reported industry support	3[67,170,172]	0.58 (0.27 to 1.22)	54%
	Study reported government or nonprofit funding only	8[51-55,66,118,137]	0.39 (0.23 to 0.64)	77%
Country setting *(p=0.004 for interaction)*	U.S. or other high-income countries	3[52,66,118]	0.13 (0.05 to 0.32)	0%
	Africa, Asia, or international trial	8[51,53-55,67,137,170,172]	0.54 (0.37 to 0.79)	72%

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; RCT=randomized, controlled trial; RR=relative risk; TDF=tenofovir disoproxil fumarate; U.S.=United States.

Table 4. Effect of PrEP vs. Placebo on HIV Infection in Population Subgroups

Type of PrEP	Study	Age	Sex and Gender	Race and Ethnicity	Risk behaviors
Oral PrEP Versus Placebo or No PrEP	Bangkok Tenofovir Study Choopanya, 2013[53]	Efficacy 20–29 years: 33.6% (95% CI, -40.1 to 69.8) 30–39 years: 29.2% (95% CI, -121.7 to 79.1) ≥40 years: 88.9% (95% CI, 41.1 to 99.4); p=NR	Efficacy Female: 78.6% (95% CI, 16.8 to 96.7) Male: 37.6% (95% CI, -17.8 to 67.9); p=NR	NR	Efficacy *Shared needles* Yes: 54.7% (95% CI, -44.0 to 87.9) No: 47.6% (95% CI, -2.5 to 74); p=NR *Injected during 12 weeks before enrollment* Yes: 44.3% (95% CI, -12.5 to 72.4) No: 57.4% (95% CI, -17.0 to 86.6); p=NR
	FEM-PrEP Van Damme 2012[172]	≥25 years: RR, 0.91 (95% CI, 0.41 to 2.05) <25 years: RR, 0.97 (95% CI, 0.55 to 1.72); p=0.91 for interaction	NA	NR	NR
	iPrEx Grant 2010[137]	<25 years: HR, 0.67 (95% CI, 0.40 to 1.14) ≥25 years: HR, 0.41 (95% CI, 0.24 to 0.87; p=0.36 for interaction	Transgender women: HR, 1.1 (95% CI, 0.5 to 2.7) Male (MSM): HR, 0.50 (95% CI, 0.34 to 0.75); **p=0.09 for interaction**	Non-Hispanic: HR, 0.48 (95% CI, 0.14 to 1.60) Hispanic: HR, 0.57 (95% CI, 0.37 to 0.89); p=0.79 for interaction	*Unprotected receptive anal intercourse* Yes: HR, 0.42 (95% CI, 0.26 to 0.68) No: HR, 1.59 (95% CI, 0.66 to 3.84); **p=0.01 for interaction**
	Partners PrEP Baeten 2012[51]	*TDF vs. placebo* <25 years: HR, 0.28 (95% CI, 0.01 to 1.01) ≥25 years: HR, 0.34 (95% CI, 0.18 to 0.61) p=0.79 for interaction *TDF-FTC vs. placebo* <25 years: HR, 0.59 (95% CI, 0.21 to 1.61) ≥25 years: HR, 0.17 (95% CI, 0.07 to 0.37) p=0.06 for interaction	*TDF vs. placebo* Female: HR, 0.29 (95% CI, 0.13 to 0.63) Male: HR, 0.37 (95% CI, 0.17 to 0.80); p=0.65 for interaction *TDF-FTC vs. placebo* Female: HR, 0.34 (95% CI, 0.16 to 0.72) Male: HR, 0.16 (95% CI, 0.06 to 0.46); p=0.24 for interaction	NR	*TDF vs. placebo, unprotected sex with study partner* Yes: HR, 0.47 (95% CI, 0.25 to 0.89) No: HR, 0.13 (95% CI, 0.04 to 0.44); **p=0.05 for interaction** *TDF-FTC vs. placebo, unprotected sex with study partner* Yes: HR, 0.27 (95% CI, 0.12 to 0.58) No: HR, 0.22 (95% CI, 0.08 to 0.58); p=0.77 for interaction
	TDF2 Thigpen 2012[170]	NR	Female: RR, 0.49 (95% CI, 0.02 to 1.21) Male: RR, 0.20 (95% CI, 0.4 to 0.91); p=0.31 for interaction	NR	NR

Table 4. Effect of PrEP vs. Placebo on HIV Infection in Population Subgroups

Type of PrEP	Study	Age	Sex and Gender	Race and Ethnicity	Risk behaviors
Dapivirine Vaginal Ring Versus Placebo Ring	ASPIRE Baeten, 2016[73] Peebles, 2020[163]	Efficacy: 18 to 21 years: -27% (95% CI, -133 to 31) 22 to 26 years: 56% (95% CI, 19 to 76%) 27 to 45 years: 51% (95% CI, 8 to 74) Over 21 years: 56% (95% CI, 31 to 71), p<0.001 <25 years: 8.1% vs. 8.8%, HR 0.90, 95% CI, 0.57 to 1.41 ≥25 years: 2.4% vs. 6.0%, HR 0.39, 95% CI, 0.23 to 0.68 HIV-1 incidence when also engaging in receptive anal intercourse (RAI): 5.2/100 woman-years (95% CI, 3.4 to 7.7) with dapivirine ring vs. 4.3/100 woman-years (95% CI, 3.4 to 5.3) with placebo ring	All female	NR	STIs at baseline: Yes: HR 0.78 (95% CI, 0.45 to 1.34) No: HR 0.53 (95% CI, 0.34 to 0.83) Number of sexual partners: 0-1: HR 0.63 (95% CI, 0.42 to 0.93) 2+: HR 0.62 (95% CI, 0.31 to 1.23) Receptive anal intercourse (RAI): aHR 0.93 (95% CI, 0.57 to 1.54, p=0.71) Reduction of HIV-1 risk with dapivirine ring no RAI vs. RAI: 27% (95% CI, -5% to 49%) vs. 18% (95% CI, -57% to 57%)
	Ring Study Nel, 2016[74]	Efficacy: ≤21 years: 9.0% vs. 10.9%; HR 0.85 (95% CI, 0.45 to 1.60) >21 years: 5.0% vs. 7.9%, HR 0.63 (95% CI, 0.41 to 0.97)	All female	NR	NR

Abbreviations: aHR=adjusted hazard ratio; ASPIRE= Antiretroviral Strategy to Promote Improvement and Reduce Exposure; CI=confidence interval; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; HR=hazard ratio; FTC=emtricitabine; HR=hazard ratio; iPrEx=Pre-Exposure Prophylaxis Initiative; MSM=men who have sex with men; NR=not reported; PrEP=pre-exposure prophylaxis; RAI=receptive anal intercourse; RR=relative risk; STI=sexually transmitted infection; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study.

Table 5. Study Characteristics of Head-to-Head Trials of PrEP

Type of PreP	Study name Author, year* Country Duration of followup Quality	Interventions	HIV risk group(s) Risk-based inclusion criteria	Patient characteristics	Adherence (method for measuring adherence)
Event Driven Versus Daily Oral PrEP†	*ADAPT/ HPTN 067* Bekker 2018[130] South Africa 34 weeks Fair Included in prior report	A. Daily TDF-FTC (n=59) B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex; n=59) C. Event-driven TDF-FTC (one tablet both before and after sex; n=60)	High-risk women or transgender men: History of an acute STI, transactional sex, intercourse without a condom with someone of unknown or HIV-infected status, or >1 sex partner in 6 months	A vs. B vs. C Age, mean: 25 vs. 26 vs. 25 years Female: 100% (no transgender men enrolled) Black: 98% vs. 100% vs. 100%	A vs. B vs. C (plasma level ≥2.5 ng/mL at week 30 [consistent with ≥2 doses/week [daily and time-driven] or when reporting sex in prior week [event-driven]): 54% vs. 36% vs. 31%
	ADAPT/ HPTN 067 Grant, 2018[136] Thailand, U.S. 34 weeks Fair Included in prior report	A. Daily TDF-FTC (n=119) B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex; n=119) C. Event-driven TDF-FTC (one tablet both before and after sex; n=119)	MSM: Reported anal or neovaginal sex with a man in the past 6 months, and have at least 1 of the following in the past 6 months: sex with >1 man or transgender woman; history of an acute STI; sex in exchange for money, goods, or favors; or intercourse without a condom with an HIV-infected partner or partner of unknown HIV infection status	A vs. B vs. C Bangkok site: Age 18 to 24 years: 13% vs. 20% vs. 14% Ages 25 to 29 years: 22% vs. 32% vs. 27% Age 30 to 39 years: 60% vs. 39% vs. 48% Age ≥40 years: 5% vs. 9% vs. 12% MSM: 98% vs. 98% vs. 100% Transgender: 2% vs. 2% vs. 0% Race NR Harlem site: Age 18 to 24 years: 32% vs. 28% vs. 28% Age 25 to 29 years: 22% vs. 18% vs. 13% Age 30 to 39 years:19% vs. 20% vs. 23% Age ≥40 years: 27% vs. 33% vs. 35% MSM: 97% vs. 98% vs. 97% Transgender: 3% vs. 0% vs. 2% Gender queer: 0% vs. 2% vs. 2% Black 70%, White 13%, Asian 3%, Native American 3%, Hispanic 25%, Other 21%	A vs. B vs. C Bangkok site: (peripheral blood mononuclear cell levels consistent with ≥2 tablets on visits when sex was reported in prior week) 97.6% vs. 98.7% vs. 95.7% Harlem site: (dried blood spot levels consistent with ≥2 tablets on visits when sex was reported in prior week) 48.5% vs. 30.9% vs. 16.7%
Event Driven Versus Daily Oral PrEP†	Kwan, 2021[144] Hong Kong 32 weeks Fair	A: Daily TDF-FTC (n=59) B: Event-driven TDF-FTC (n=60)	MSM: Had condomless anal intercourse in the preceding 6 months	A vs B Age, mean: 29 vs. 30 years	Median 100% vs. 93% (self-report, proportion of days with PrEP-covered condomless anal intercourse)

Table 5. Study Characteristics of Head-to-Head Trials of PrEP

Type of PreP	Study name Author, year* Country Duration of followup Quality	Interventions	HIV risk group(s) Risk-based inclusion criteria	Patient characteristics	Adherence (method for measuring adherence)
Oral TAF-FTC Versus TDF-FTC	*DISCOVER* Mayer, 2020[121] Ogbuagu, 2021[162] Europe and North America 96 weeks Good	A: TAF-FTC (n=2694) B: TDF-FTC (n=2693)	Cisgender MSM or transgender women who have sex with men: Condomless anal sex with at least two partners in the previous 12 weeks or syphilis, rectal gonorrhea, or rectal chlamydia in the prior 24 weeks	A vs. B Age (mean): 34 vs. 34 years Cisgender MSM: 98% vs. 99% Transgender women who have sex with men: 2% vs. 1% White: 84% vs. 84% Black: 9% vs. 9% Asian: 4% vs. 5% Hispanic or Latinx ethnicity: 24% vs. 25%	A vs. B 88%-96% vs. 84%-93% (dried blood spot, random sample consistent with ≥4 doses/week)
Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC	*HPTN 083* Landovitz, 2021[70] International Median 1.4 years Good	A: Cabotegravir long-acting injectable 600 mg at weeks 5, 9, 17, and every 8 weeks afterward and oral placebo (n=2,282) B: Oral tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg once daily and injectable placebo (n=2,284)	Cisgender MSM and transgender women who have sex with men	A vs. B Median age: 26 vs. 26 years MSM: 88% vs. 87% Transgender women who have sex with men: 12% vs. 13%	A vs. B 91.5% (received injection with no delay ≥2 weeks) vs. 74% (plasma, tenofovir level >40 ng/mL [consistent with ≥4 doses/week])
	HPTN 084 Delany-Moretwle, 2022[88] Sub-Sahara Africa Median 1.24 years Good	A: Cabotegravir 600 mg in a 3 mL IM injectable every 8 weeks (n=1,592) B: Daily TDF-FTC 300 mg + 200 mg (n=1,586)	High risk women: Reporting at least 2 episodes of vaginal intercourse in the previous 30 days at risk of HIV infection based on an HIV risk score	A vs. B Median age: 25 vs. 25 years Race/ethnicity: 97.2% vs. 96.5% Black Gender identity: 99.9% vs. 99.8% female, 0% vs 0.2% male, and 0.1% vs. 0% transgender male	A vs. B 93% (received injection with no delay ≥2 weeks) vs. 42% (plasma, tenofovir level ≥40 ng/mL)

*Primary publication.

†Additional study (IPERGAY, Molina 2015[66]) of event-driven PrEP, but versus placebo, in Table 2.

Abbreviations: ADAPT= Alternative Dosing to Augment PrEP pill Taking; FTC=emtricitabine; HPTN= HIV Prevention Trials Network; IM=intramuscular; MSM=men who have sex with men; NR=not reported; PrEP=pre-exposure prophylaxis; STI=sexually transmitted infection; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.

Table 6. Risk of HIV Infection and Adverse Events in Head-to-Head Trials of PrEP

Type of PrEP	Study name Author, year*	Interventions	Clinical health outcomes	Adverse events
Event Driven Versus Daily Oral PrEP†	*ADAPT/ HPTN 067* Bekker 2018[130]	A. Daily TDF-FTC (n=59) B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex; n=59) C. Event-driven TDF-FTC (one tablet both before and after sex; n=60)	A vs. B vs. C HIV infection: 0% (0/59) vs. 3% (2/59) vs. 3% (2/60); A vs. B: RR, 0.20 (95% CI, 0.01 to 4.08); A vs. C: RR, 0.20 (95% CI, 0.01 to 4.15)	A vs. B vs. C Any headache, dizziness, or lightheadedness: 12% (43/348) vs. 6% (20/331) vs. 8% (26/332); A vs. B: OR, 2.19 (95% CI, 1.13 to 4.27); A vs. C: OR, 1.66 (95% CI, 0.88 to 3.13) Any GI symptom: 11% (37/348) vs. 9% (29/331) vs. 5% (18/332); A vs. B: OR, 1.24 (95% CI, 0.61 to 2.51); A vs. C: OR, 2.08 (95% CI, 0.98 to 4.40)
	ADAPT/ HPTN 067 Grant, 2018[136]	A. Daily TDF-FTC (n=119) B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex; n=119) C. Event-driven TDF-FTC (one tablet both before and after sex; n=119)	A vs. B vs. C HIV infection: 0.8% (1/119) vs. 0% (0/119) vs. 0% (0/119); A vs. B; A vs. C: RR, 3.03 (95% CI, 0.12 to 75) South Africa (from Bekker 2017), Bangkok and Harlem sites combined: 0.6% (1/178) vs. 1.1% (2/178) vs. 1.1% (2/179); A vs. B: RR, 0.50 (95% CI, 0.04 to 5.53); A vs. C: RR, 1.01 (95% CI, 0.14 to 7.22)	A vs. B vs. C Bangkok Proportion of visits when patients reported neurologic events: 14.2% vs. 14.3% vs. 13.3% Proportion of visits when patients reported GI events: 13.1% vs. 8.5% vs. 10.5% Harlem Proportion of visits when patients reported neurologic events: 6.1% vs. 3.3% vs. 4.5% Proportion of visits when patients reported GI events: 8.0% vs. 5.8% vs. 7.1%
	Kwan, 2021[144]	A: Once-daily TDF-FTC (n=59) B: On-demand TDF-FTC (n=60)	NR	A vs. B Creatinine clearance: no difference between arms

Table 6. Risk of HIV Infection and Adverse Events in Head-to-Head Trials of PrEP

Oral TAF-FTC Versus TDF-FTC	*DISCOVER* Mayer, 2020[121] Ogbuagu, 2021[162]	A: TAF-FTC (n=2694) B: TDF-FTC (n=2693)	HIV infection, primary (interim) analysis (for which 100% of patients had completed 48 weeks and 50% had completed 96 weeks): 0.16 vs. 0.34 per 100 person-years, IRR 0.47 (95% CI 0.19 to 1.15); 0.3% (7/2670) vs. 0.6% (15/2665), RR 0.47 (95% CI, 0.19 to 1.14)‡ HIV infection at 96 weeks (all patients had completed 96 weeks): 0.16 vs. 0.30 per 100 person-years; IRR 0.54 (0.23 to 1.26); 0.3% (8/2694) vs. 0.6% (15/2693), RR 0.53 (95% CI 0.23 to 1.26)‡	A vs. B Mortality: 0.1% (3/2694) vs. 0.07% (2/2693), RR 1.50 (95% CI 0.25 to 8.97) Serious adverse event: 7.5% (202/2694) vs. 6.9% (186/2693), RR 1.09 (95% CI 0.90 to 1.32) Discontinuation of study drug due to adverse event: 1.5% (40/2694) vs. 1.9% (51/2693), RR 0.78 (95% CI 0.52 to 1.18) Any adverse event: 94% (2523/2694) vs. 94% (2521/2693), RR 1.00 (95% CI 0.99 to 1.01) Rectal chlamydia: 33% (890/2694) vs. 33% (902/2693), RR 0.99 (95% CI 0.91 to 1.06) Oropharyngeal gonorrhea: 32% (871/2694) vs. 31% (838/2693), RR 1.04 (95% CI 0.96 to 1.12) Rectal gonorrhea: 30% (805/2694) vs. 30% (797/2693), RR 0.99 (95 % CI 0.91 to 1.06) Syphilis: 15% (413/2694) vs. 15% (392/2693), RR 1.05 (95% CI 0.93 to 1.20) Urethral chlamydia: 13% (346/2694) vs. 12% (314/2693), RR 1.10 (95% CI 0.95 to 1.27) Any renal adverse event: 10% (263/2694) vs. 10% (266/2693), RR 0.99 (95% CI, 0.84 to 1.16), in primary (interim) analysis Grade ≥3 renal adverse event: 0.07% (2/2694) vs. 0.1% (3/2693), RR 0.67 (95% CI 0.11 to 3.99), in primary (interim) analysis Renal adverse event leading to discontinuation: 0.07% (2/2694) vs. 0.2% (6/2693), RR 0.33 (95% CI 0.07 to 1.65) Creatinine clearance, median percentage change from baseline: -2.3% vs. +1.8%, p<0.0001, in primary (interim) analysis Fracture: 2.2% (60/2694) vs. 2.2% (60/2693), RR 1.00 (95% CI 0.70 to 1.42) Diarrhea: 18% (480/2694) vs. 17% (453/2693), RR 1.06 (95% CI 0.94 to 1.19) Nausea: 4.2% (114/2694) vs. 4.6% (123/2693), RR 0.93 (95% CI 0.72 to 1.19), in primary (interim) analysis Hip bone mineral density, percent change from baseline: +0.6% vs. -1.0% in persons ≥25 years (p<0.001) and +1.2% vs. -1.7% in persons <25 years (p=0.04) Spine bone mineral density, percent change from baseline: +0.9% vs. -1.4% in persons ≥25 years (p<0.001) and +1.4% vs. -1.2% in persons <25 years (p=0.14) Body weight, change from baseline (kg): +1.7 vs. +0.5, p<0.0001

Table 6. Risk of HIV Infection and Adverse Events in Head-to-Head Trials of PrEP

Type of PrEP	Study name Author, year*	Interventions	Clinical health outcomes	Adverse events
				Note: outcomes at 96 weeks, except where noted as primary (interim) analysis, for which 100% of patients had completed 48 weeks and 50% had completed 96 weeks
Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC	*HPTN 083* Landovitz, 2021[70]	A: Cabotegravir 600 mg in a 3 mL IM injectable every 8 weeks (n=2,282) B: Daily TDF-FTC 300 mg + 200 mg (n=2,284)	A vs. B HIV infection: 0.57% (13/2,243) vs. 1.71% (39/2,247); RR 0.33 (95% CI, 0.18 to 0.62‡); incidence rate per 100 person-years, 0.41 vs. 1.22; HR 0.34 (95% CI 0.18 to 0.62)	A vs. B Serious adverse events: 5.3% (120/2,280) vs. 5.3% (121/2,282) Grade 3 or higher adverse events: 31.9% (727/2,280) vs. 33.6% (767/2,282) Hepatic-related discontinuations: 2.1% (47/2,280) vs. 2.1% (48/2,282) Decreased creatinine cleareance: 7.0% (159/2,280) vs. 8.3% (190/2,282) Increased aspartate aminotransferase: 2.3% (53/2,280) vs. 3.0% (69/2,282) Increased alanine aminotransferase: 1.0% (23/2,280) vs. 1.4% (32/2,282) Deaths: 0.18% (4/2,280) vs. 0
Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC	*HPTN 084* Delany-Moretwle, 2022[88]	A: Cabotegravir 600 mg in a 3 mL IM injectable every 8 weeks (n=1,592) B: Daily TDF-FTC 300 mg + 200 mg (n=1,586)	A vs. B HIV infection: 0.3% (4/1,592) vs. 2.3% (36/1,586); RR 0.11 (95% CI 0.04 to 0.31‡); incidence rate per 100 person-years, 0.20 (95% CI 0.06 to 0.52) vs. 1.85 (95% CI 1.30 to 2.57); HR 0.12 (95% C, 0.05 to 0.31)	A vs. B Serious adverse events: 2.0% (33/1,614) vs. 2.0% (33/1,610) Grade 3 or higher adverse events: 17.1% (276/1,614) vs. 17.4% (280/1,610) Hepatic-related discontinuation: 0.9% (15/1,614) vs. 1.1% (18/1,610) Deaths: 0.2% (3/1,614) vs. 0 Chlamydia: 16.2% (261/1,614) vs. 17.8% (287/1,610) Gonorrhea: 7.8% (126/1,614) vs. 7.8% (125/1,610) Trichomonas: 7.7% (124/1,614) vs. 6.8% (109/1,610) Grade 3 decreased creatinine clearance: 6.8% (110/1,614) vs. 7.8% (125/1,610)

*Primary publication.
†Additional study (IPERGAY, Molina 2015[66]) of event-driven PrEP, but versus placebo, in Table 2.
‡Relative risk calculated from data provided in the trial.
Abbreviations: ADAPT= Alternative Dosing to Augment PrEP pill Taking; CI=confidence interval; FTC=emtricitabine; GI=gastrointestinal; HPTN= HIV Prevention Trials Network; HR=hazard ratio; IM=intramuscular; IPERGAY=Intervention Préventive de l'Exposition aux Risques avec et pour les Gays; IRR=incidence rate ratio; NR=not reported; OR=odds ratio; PrEP=pre-exposure prophylaxis; RR=relative risk; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.

Table 7. Study Characteristics of Risk Assessment Tools

Study, Year Followup Target	Study design	Population characteristics	Sample size Acquired HIV	Screening instrument items
Beymer, 2017[131] Mean 1.8 years MSM	Cohort MSM who were negative at baseline and had at least one subsequent test; no formal testing protocol	Derivation cohort: Los Angeles LGBT center (2009 to 2014) Age <25 years: 26% Ages 25 to 29 years: 26% Ages 30 to 39 years: 28% Age ≥40 years: 21% White: 48% Hispanic: 32% Black: 7.8%	Derivation cohort: 9,481 Acquired HIV: Derivation cohort: 3.9% (370/9,481)	1) Race/ethnicity 2) History of any STI 3) Condom use during receptive anal sex, last partner 4) Race/ethnicity, last partner 5) Age difference, last partner 6) Number sex partners, last 3 months 7) Intimate partner violence 8) Ecstasy use, prior 12 months 9) Methamphetamine use, prior 12 months 10) Nitrates use, prior 12 months Scoring of items unclear, total
Hoenigl, 2015[140] SDET score Duration of followup not applicable due to cross-sectional design; utilized risk behavior data from prior 12 months MSM	Cross-sectional MSM who underwent HIV testing and classified as EAH or no EAH	San Diego "Early Test" (2008 to 2014) cohort Age (median, years): 30 in acute and early HIV infection, 33 in those who remained uninfected White: 67% Asian: 8% Black: 6% Hispanic ethnicity: 27%	Derivation cohort: 5,568 Validation cohort: 2,758 Acquired HIV: Entire cohort: 2.4% (200/8,326) for acute and early HIV infection	1) ≥10 male partners (0 or 2) 2) Condomless receptive anal intercourse and ≥5 male partners (0 or 3) 3) Condomless receptive anal intercourse with HIV-infected partner (0 or 3) 4) Bacterial STI (0 or 2)

Table 7. Study Characteristics of Risk Assessment Tools

Study, Year Followup Target	Study design	Population characteristics	Sample size Acquired HIV	Screening instrument items
Jones, 2017[142] 1) ARCH-MSM 2) Menza 3) SDET Up to 24 months (mean/ median NR) MSM	Cohort Non-Hispanic, Black and White MSM who were HIV-negative at baseline and had HIV testing every 6 months or until HIV-infected for 24 months	Involve[men]t study cohort Age (mean, years): 27 White: 54% Black: 46%	562 Acquired HIV: 5.7% (32/562); 6 were determined to be acutely infected at baseline (included in analysis)	1) ARCH-MSM: See Smith 2012 (drug use questions modified from last 6 to last 12 months) 2) SDET: See Hoenigl 2015 3) Menza: See Menza 2009 (drug use question modified from last 6 to last 12 months)

Table 7. Study Characteristics of Risk Assessment Tools

Study, Year Followup Target	Study design	Population characteristics	Sample size Acquired HIV	Screening instrument items
Krakower, 2019[143] Duration of followup NR General population (>15 years of age)	Cohort Development cohort, Atrius health years 2007 to 2015 Prospective validation cohort, Atrius health year 2016 External validation cohort, Fenway Health 2011 to 2016	Development cohort Age: 35.0 years Gender: Male 42.9%, female 57.0% Race/ethnicity: White 60.0%, Black 5.2%, American Indian/Alaskan Native 0.1%, Asian 5.8%, Native Hawaiian/Other Pacific Islander <0.1%, Other 3.3%, Hispanic or Latinx 2.9% Prospective validation cohort Age: 39.1 years Gender: Male 42.5%, female 57.5% Race/ethnicity: White 72.7%, Black 6.9%, American Indian/Alaskan Native 0.1%, Asian 6.4%, Native Hawaiian/Other Pacific Islander <0.1%, Other 4.0%, Hispanic or Latinx 3.2% External validation cohort Age: 34.5 years Gender: Male 62.3%, female 31.0%, transgender or gender nonconforming 6.7 Race/ethnicity: White 68.3%, Black 8.1%, American Indian/Alaskan Native 0.2%, Asian 7.1%, Native Hawaiian/Other Pacific Islander 0.4%, Other 10.2%, Hispanic or Latinx 5.6%	Develop-ment cohort: n= 1,155,966 Prospect-ive validation cohort: n=537,257 External validation cohort: n=33,404 Acquired HIV: Development cohort: <0.1% (n=150) Prospect-ive validation cohort: <0.1% (n=16) External validation cohort: 1.3% (n=423)	LASSO algorithm (coefficient), based on electronic health record data: Diagnosis codes: 1) Syphilis of any site or stage except late latent (1.00) 2) HIV counseling in previous 2 years (1.10) 3) Contact with or exposure to venereal disease (0.29) Lab tests and results 4) No. of positive gonorrhea tests in previous 2 years (3.07) 5) No. of chlamydia tests (-0.15) 6) No. of HIV tests (0.12) 7) No. of HIV ELISA tests (0.16) 8) No. of HIV tests in previous 2 years (0.23) 9) No. of HIV RNA tests in previous year (0.15) Testing for acute HIV (1.82) 10) Testing for acute HIV in previous 2 years (0.16) Prescriptions 11) Intramuscular penicillin G benzathine (1.80) 12) Intramuscular penicillin G benzathine in previous year (1.36) 13) Intermuscular penicillin G benzathine in previous 2 years (0.21) 14) Buprenorphine and naloxone in previous 2 years (0.20) Demographics and registration data 15) Years of previous HER data (-0.07) 16) At least 1 year of previous HER data (-0.63) 17) At least 2 years of previous HER data (-0.40) 18) Any data on primary language (-0.08) 19) English as primary language (-0.42) 20) Black race (1.06) 21) White race (-0.66) 22) Male gender (1.87)

Table 7. Study Characteristics of Risk Assessment Tools

Study, Year Followup Target	Study design	Population characteristics	Sample size Acquired HIV	Screening instrument items
Lancki, 2018[145] 1) ARCH-MSM 2) CDC criteria 3) Gilead indications Mean 0.77 years MSM	Cohort Self-identified as African American or Black, ages 16 to 29 years, oral or anal intercourse with a man within the past 24 months, located on South Side of Chicago, HIV-uninfected, testing at baseline and at 9-month intervals over 18 months	uConnect study cohort Age (mean, years): NR White: 0% Black: 100%	300 Acquired HIV: 11% (33/300)	1) ARCH-MSM: See Smith 2012 (drug use questions modified from last 6 to last 12 months) 2) CDC criteria: Any male sex partner in past 6 months, not in a monogramous partnership with a recently tested, HIV-uninfected man and one of the following: a) Any anal sex without condoms (receptive or insertive) b) Any STI diagnosed or reported in past 6 months c) In an ongoing sexual partnership with an HIV-positive male partner 3) Gilead indications: a) Inconsistent or no condom use b) Diagnosis of STI c) Exchange of sex for commodities d) Use of illicit drugs or alcohol dependence (excluding marijuana) e) Incarceration f) Partners of unknown HIV-1 status with above factors

Table 7. Study Characteristics of Risk Assessment Tools

Study, Year Followup Target	Study design	Population characteristics	Sample size Acquired HIV	Screening instrument items
Marcus, 2019[151] Up to 3 years (validation cohort), (mean/ median NR) General population (≥18 years of age)	Cohort Development cohort: Kaiser Permanente Northern California 2007-2014 Prospective validation cohort: Kaiser Permanente Northern California 2015-2017 data	Development cohort: Age, mean: 44.6 years Gender: Male 46.5% Race/ethnicity: White 51.9%, Hispanic 19.3%, Asian 17.2%, Black 7.4%, other 4.1%, unknown 6.8% Sexual orientation among known: heterosexual 96.4%, gay or lesbian 2.9%, bisexual 0.7% Unknown sexual orientation: 84.4% Validation cohort: Age, mean: 37.4 years Gender: Male 49.0% Race/ethnicity: White 44.0%, Hispanic 24.3%, Asian 23.0%, Black 6.4%, other 2.3%, unknown 5.8% Sexual orientation among known: heterosexual 95.5%, gay or lesbian 3.4%, bisexual 1.1% NR sexual orientation: 59.7%	3,750,664 Develop-ment cohort: 3,143,963 Validation cohort: 606,701 Acquired HIV: 0.02% (784/ 3,750,664) within 3 years	LASSO algorithm (coefficient), based on electronic health record data: 1) Male 2) MSM 3) Sexually active 4) Age 50-59 5) Age ≥60 6) Black 7) Hispanic 8) Asian 9) Other race/ethnicity 10) Neighborhood deprivation index (NDI), Quintile 2 11) NDI, Quintile 3 12) NDI, Quintile 4 13) Received care in one of three cities with high HIV incidence 14) Resided in one of eight urban ZIP codes with high HIV incidence 15) Positive urine test for methadone 16) Positive urine test for cocaine 17) No. of HIV testing episodes in previous 2 years 18) No. of HIV antibody or RNA tests in previous 2 years 19) No. of tests for rectal gonorrhea or chlamydia 20) No. of positive tests for rectal gonorrhea or chlamydia in previous 2 years 21) No. of positive tests for urethral chlamydia in previous 2 years 22) No. of positive tests for urethral gonorrhea in previous 2 years 23) No. of RPR or treponemal tests for syphilis in previous 2 years 24) No. of reactive RPR or positive treponemal tests for syphilis in previous 2 years 25) Medications for erectile dysfunction 26) No. of penicillin G benzathine injections with syphilis test within 90 days in previous 2 years 27) No. of anal wart diagnoses 28) Depression 29) Any psychiatric diagnosis 30) Transgender-related diagnosis 31) High-risk sexual behavior (homosexual) 32) High-risk sexual behavior (not specified) 33) Exposure to HIV 34) HIV counseling 35) HIV education

Table 7. Study Characteristics of Risk Assessment Tools

Study, Year Followup Target	Study design	Population characteristics	Sample size Acquired HIV	Screening instrument items
Menza, 2009[155] Median 3 years (validation cohort) MSM	Cohort Derivation cohort, MSM were HIV-negative at baseline and had at least one subsequent HIV test; no formal testing protocol Validation cohort, MSM were HIV-negative at baseline and underwent retesting every 6 months	Derivation cohort: Public Health-Seattle and King County STI Clinic (2001 to 2008) repeat testers cohort Age <40 years: 80% Age ≥40 years: 20% White, Asian, or Pacific Islander: 77% Other race: 23% Validation cohort: Project EXPLORE (1999 to 2001) RCT, control arm (behavioral intervention trial) Age <40 years: 76% Age ≥40 years: 24% White, Asian, or Pacific Islander: 75% Other race: 25%	Derivation cohort: 1,903 Validation cohort: 2,081 Acquired HIV: Derivation cohort: 5.3% (101/1,903) Validation cohort: 6.9% (144/2,081)	1) Gonorrhea, chlamydia, or syphilis, or a history of these infections (0 or 4 points) 2) Used methamphetamine or inhaled nitrites in the past 6 months (0 or 11 points) 3) Unprotected anal intercourse with an HIV-infected partner or unknown HIV status in the past year (0 or 1 point) 4) 10 or more male sexual partners in the prior year (0 or 3 points)
Ridgway, 2021[164] Duration of followup NR Cisgender women	Cohort Cohort was cisgender women with a new positive HIV test in the ED between January 1, 2011 and April 30, 2018	Age, median: 38 years (IQR 29-47) Black: 95.2% (20/21)	21 Acquired HIV: 21 (100%)	Calculated from data available in electronic medical record: 1) Male sex (7 points) 2) Chief complaint related to STI-associated symptoms (6 points) 3) Age ≤20 years (13 points) 4) Age 21-24 years (8 points) 5) Positive STI in previous 6 months (21 points) 6) MSM (21 points)

Table 7. Study Characteristics of Risk Assessment Tools

Study, Year Followup Target	Study design	Population characteristics	Sample size Acquired HIV	Screening instrument items
Scott, 2020[165] Sexual Health Promotion (SexPro) tool mysexpro.org Ranged from 1-3 years (validation cohorts) MSM, inclusive of Black MSM	Cohort Development cohort: EXPLORE trial 1991 to 2003 , US Validation cohorts: VAX0004 trial from 1998 to 2002, HPTN061 cohort study from 2009 to 2013, HVTN505 trial from 2009 to 2013	EXPLORE vs. VAX004 vs. HPTN061 vs. HVTN505 Age <35 years: 60.9%, 48.8%, 44.8%, 68.3% Race/ethnicity: Black 7.4%, 3.4%, 100%, 18.3%, Latino 14.8%, 0.7%, 7.7%, 8.5%	Development cohort: =4,069 Validation cohorts: Total 8,047 (VAX004 n=4,878 vs. HPTN061 n=973 vs. HVTN505 n=2,196) Acquired HIV: Development cohort: 217 Validation cohorts: Total 433 (VAX004 343 vs. HPTN061 25 vs. HVTN505 65)	Final model (score 1-20, with 20=lowest HIV risk): 1) Age ≤35 2) Black race 3) Latino ethnicity 4) No. of receptive anal intercourse episodes without a condom with HIV positive or unknown status partners 5) No. of receptive anal intercourse episodes with a condom with HIV positive or unknown status partners 6) No. of insertive anal intercourse episodes without a condom with HIV positive or unknown status partners 7) No. of HIV-negative anal sex partners 8) 1 HIV-negative sex partner only 9) Heavy alcohol use 10) Methamphetamine use 11) Popper use 12) Gonorrhea, syphilis, or chlamydia diagnosis

Table 7. Study Characteristics of Risk Assessment Tools

Study, Year Followup Target	Study design	Population characteristics	Sample size Acquired HIV	Screening instrument items
Smith, 2012[166] HIRI-MSM (now ARCH-MSM) Up to 4 years (mean/ median NR) MSM	Cohort In derivation and validation cohorts, MSM were HIV-negative at baseline and underwent retesting every 6 months	Derivation cohort: VAXGEN 004 (1998 to 1999) RCT (HIV vaccine trial) Ages 18 to 28 years: 19% Ages 29 to 49 years: 48% Ages 41 to 48 years: 22% Age ≥49 years: 11% Non-Hispanic White: 86% Validation cohort: Project EXPLORE (1999 to 2001) RCT (behavioral intervention trial) Age ≤25 years: 18% Ages 26 to 30 years: 22% Ages 31 to 35 years: 22% Age ≥36 years: 39% Non-Hispanic White: 75%	Derivation cohort: 4,386 Validation cohort: 3,368 Acquired HIV: Derivation cohort: 7.2% (318/4,386) Validation cohort: 4.3% (144/3,368)	1) Age (0 to 8 points) 2) Total number of male partners, prior 6 months (0 to 7 points) 3) Total number of infected male partners, prior 6 months (0 to 8 points) 4) Times had unprotected receptive anal intercourse with any HIV status partner, prior 6 months (0 or 10 points) 5) Used amphetamines, prior 6 months (0 or 5 points) 6) Used poppers, prior 6 months (0 or 3 points)
Smith, 2015[167] ARCH-IDUs Median 5.85 years PWID	Cohort Patients who reported drug use in the last 11 years and HIV-uninfected, underwent testing every 6 months	Derivation cohort: ALIVE (1988 to 2008) cohort Age <30 years: 17% Ages 30 to <40 years: 46% Ages 40 to <50 years: 27% Age ≥50 years: 7.9% MSM: 1.8%	Derivation cohort: 1,904 Acquired HIV: Derivation cohort 11% (205/1,904)	1) Age (0 to 38 points) 2) In the last 6 months, in methadone maintenance program (0 or 31 points) Next 5 items receive 0 or 1 points on injection subscore: 3) In the last 6 months, inject heroin 1 or more times 4) In the last 6 months, inject cocaine 1 or more times 5) In the last 6 months, share cooker 1 or more times 6) In the last 6 months, share needle 1 or more times 7) In the last 6 months, visit shooting gallery 1 or more times Add 5 injection subscores, 0=score 0, 1=score 7, 2=score 21, 3=score 24, 4=score 24, 5=score 31

Table 7. Study Characteristics of Risk Assessment Tools

Study, Year Followup Target	Study design	Population characteristics	Sample size Acquired HIV	Screening instrument items
Tordoff, 2020[171] A: Seattle PrEP Score B: Menza C: HIRI-MSM D: SDET E: CDC 2018 Mean 7.6 years MSM	Cohort Derivation and validation cohorts consisted of 2 STD clinic data sets	Derivation cohort (n=13,527; visits 37,814) Age, median: 33 years Race/ethnicity: White 65.3%, Black 11.0%, Asian 5.6%, Hispanic 5.0%, Native American/Alaskan Native 1.2%, Multiracial/other/unknown 11.8% Validation cohort data set (n=9,234; visits 18,908) Age, median: 33 years Race/ethnicity: White 65.6%, Black 10.6%, Asian 6.0%, Hispanic 4.9%, Native American/Alaskan Native 1.2%, Multiracial/other/unknown 11.9%	Derivation cohort: 13,527 Validation cohort: 9,234 Acquired HIV: Derivation cohort: 1.2% (440/13,527) Validation cohort: 1.1% (200/9,234)	Seattle PrEP Score model (all items based on prior 12 months) 1) Methamphetamine use* (1 point) 2) Condomless receptive anal intercourse* (1 point) 3) ≥10 sex partners* (1 point) 4) Composite: gonorrhea or syphilis diagnosis or self-reported STI history* (1 point) Menza score Smith's HIRI-MSM Hoenigl's SDET CDC 2018 1) Any condomless anal intercourse (1 point) 2) Any HIV-positive sex partner (1 point) 3) Self-reported history of bacterial STI (1 point) 4) Injection drug use in past 6 months (1 point)

Abbreviations: ARCH-IDUs=Assessing the Risk of Contracting HIV in Injection Drug Users; ARCH-MSM=Assessing the Risk of Contracting HIV in Men Who Have Sex With Men; CDC=Centers for Disease Control and Prevention; EAH=early or acute HIV infection; ED=emergency department; ELISA=enzyme-linked immunosorbent assay; EXPLORE=A Randomized Clinical Trial of the Efficacy of a Behavioral Intervention to Prevent Acquisition of HIV Among Men Who Have Sex With Men; HER=historic environment record; HIRI-MSM=HIV Incidence Risk Index for Men Who Have Sex With Men; HPTN= HIV Prevention Trials Network; HVTN=HIV Vaccine Trials Network; LASSO= Least Absolute Shrinkage and Selection Operators; LGBT=lesbian, gay, bisexual, and transgender; MSM=men who have sex with men; NDI=Neighborhood deprivation index; NR=not reported; PrEP= pre-exposure prophylaxis; PWID=persons who inject drugs; RCT=randomized, controlled trial; RNA=ribonucleic acid; RPR=rapid plasma regain;SDET=San Diego Early Test; STD=sexually transmitted disease; STI=sexually transmitted infection; U.S.=United States.

Table 8. Adverse Events in Placebo-Controlled RCTs of PrEP

Outcome	Number of trials*	RR (95% CI)	I^2
Serious adverse events *PrEP drug regimen (p=0.23 for interaction)*	12[51-55,66-68,118,137,170,172]	0.93 (0.77 to 1.12)	56%
TDF	5[51-55]	0.79 (0.56 to 1.12)	72%
TDF-FTC	9[51,54,66-68,118,137,170,172]	1.02 (0.81 to 1.30)	46%
Withdrawal due to adverse events *PrEP drug regimen (p=0.67 for interaction)*	4[51,66,137,172]	1.25 (0.99 to 1.59)	0%
TDF	1[51]	1.00 (0.34 to 2.92)	Not applicable
TDF-FTC	4[51,66,137,172]	1.27 (1.00 to 1.59)	0%
Fracture *PrEP drug regimen (p=0.50 for interaction)*	8[51-54,66,118,137,170]	1.23 (0.97 to 1.56)	0%
TDF	4[51-54]	1.29 (0.98 to 1.70)	0%
TDF-FTC	6[51,54,66,118,137,170]	1.06 (0.66 to 1.72)	0%
Renal adverse events *PrEP drug regimen (p=0.31 for interaction)*	12[51-55,66-68,118,137,170,172]	1.43 (1.18 to 1.75)	0%
TDF	5[51-55]	1.24 (0.87 to 1.76)	0%
TDF-FTC	9[51,54,66-68,118,137,170,172]	1.54 (1.21 to 1.96)	0%
Gastrointestinal adverse events *PrEP drug regimen (p=0.30 for interaction)*	12[51-55,66-68,118,137,170,172]	1.63 (1.26 to 2.11)	43%
TDF	5[51-55]	1.45 (1.13 to 1.85)	0%
TDF-FTC	9[51,54,66-68,118,137,170,172]	1.84 (1.26 to 2.70)	49%

*Two trials included both TDF and TDF-FTC arms and one trial included both TDF and TDF-FTC arms.
Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; RR=relative risk; TDF=tenofovir disoproxil fumarate.

Table 9. Risk of STI in Placebo-Controlled RCTs of PrEP

Outcome	Number of trials*	RR (95% CI)	I^2
Any bacterial sexually transmitted infection *PrEP drug regimen (p=0.60 for interaction)* *HIV risk category (p=0.38 for interaction)*	2[51,118]	1.14 (0.97 to 1.34)	16%
TDF	1[51]	1.21 (0.86 to 1.72)	Not applicable
TDF-FTC	2[51,118]	1.07 (0.80 to 1.44)	58%
Heterosexual men and women	1[51]	1.05 (0.82 to 1.35)	Not applicable
MSM	1[118]	1.20 (1.01 to 1.42)	Not applicable
Syphilis *PrEP drug regimen (p=0.86 for interaction)* *HIV risk category (p=0.90 for interaction)*	4[51,54,118,137]	1.08 (0.98 to 1.18)	0%
TDF	2[51,54]	1.13 (0.66 to 1.93)	0%
TDF-FTC	4[51,54,118,137]	1.07 (0.98 to 1.18)	0%
Heterosexual men and women	2[51,54]	1.05 (0.71 to 1.54)	0%
MSM	2[118,137]	1.08 (0.98 to 1.18)	0%
Gonorrhea *PrEP drug regimen (p=0.02 for interaction)* *HIV risk category (p=0.59 for interaction)*	5[54,118,137,170,172]	1.07 (0.82 to 1.39)	49%
TDF	1[54]	0.57 (0.33 to 0.98)	Not applicable
TDF-FTC	5[54,118,137,170,172]	1.15 (0.97 to 1.37)	2%
Heterosexual men and women	3[54,170,172]	1.20 (0.76 to 1.92)	69%
MSM	2[118,137]	1.05 (0.85 to 1.30)	0%
Chlamydia *PrEP drug regimen (p=0.004 for interaction)* *HIV risk category (p=0.46 for interaction)*	5[54,118,137,170,172]	0.97 (0.80 to 1.18)	59%
TDF	1[54]	0.68 (0.52 to 0.90)	Not applicable
TDF-FTC	5[54,118,137,170,172]	1.07 (0.94 to 1.22)	0%
Heterosexual men and women	3[54,170,172]	0.81 (0.47 to 1.41)	93%
MSM	2[118,137]	1.09 (0.62 to 1.92)	50%
Herpes simplex virus infection *PrEP drug regimen (p=0.67 for interaction)* *HIV risk category (p=0.06 for interaction)*	3[120,150,170]	0.85 (0.67 to 1.07)	19%
TDF	1[120]	0.76 (0.48 to 1.21)	Not applicable
TDF-FTC	3[120,150,170]	0.86 (0.62 to 1.18)	40%
Heterosexual men and women	2[120,170]	0.73 (0.56 to 0.96)	0%
MSM	1[150]	1.12 (0.80 to 1.56)	Not applicable
Hepatitis C virus infection†	2[66,118]	0.73 (0.25 to 2.10)	0%

*Two trials included both TDF and TDF-FTC arms.

†Both trials evaluated TDF-FTC in MSM.

Abbreviations: CI=confidence interval; FTC=emtricitabine; MSM=men who have sex with men; PrEP=pre-exposure prophylaxis; RR=relative risk; TDF=tenofovir disoproxil fumarate.

Table 10. Summary of Evidence

Key question	Number of studies (k) Number of participants* (n) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ1. Benefits of PrEP: Oral PrEP with TDF-FTC or TDF vs. placebo or no PrEP	HIV infection: k=12 RCTs (n=18,244) All RCTs in prior USPSTF review	11 trials; RR, 0.46 (95% CI, 0.33 to 0.66); I^2=67%; ARD, -2.0% (95% CI, -2.8% to -1.2%) after 4 months to 4 years Stratified by adherence (p=0.0002 for interaction) ≥70% adherence: 6 trials; RR, 0.27 (95% CI, 0.19 to 0.39); I^2=0% >40% to <70% adherence: 3 trials; RR, 0.51 (95% CI, 0.38 to 0.70); I^2=0% ≤40% adherence: 2 trials; RR, 0.93 (95% CI, 0.72 to 1.20); I^2=0%	Some inconsistency explained by level of adherence; precise Funnel plot asymmetry and Egger test statistically significant (p=0.03), but no unpublished studies identified	Good	Variability in duration of followup, although results consistent when trials stratified according to followup duration. Three trials reported some industry support, but no difference between studies that only reported industry support and those that only reported governmental or nonprofit funding on estimates.	High for benefit of oral PrEP	All trials evaluated daily oral PrEP with TDF or TDF-FTC, except for one trial of event-driven PrEP with TDF-FTC. Studies of women and men at increased risk via heterosexual contact conducted in Africa; the only study of PWID was conducted in Asia; several studies of MSM were conducted in the U.S., Europe, and Canada. PrEP was more effective in trials conducted in the U.S., Europe, and Canada (all of these trials reported high adherence and enrolled MSM).
	Mortality: k=9 RCTs (n=17,744) All RCTs in prior USPSTF review	RR, 0.81 (95% CI, 0.59 to 1.11); I^2=0%	Consistent; imprecise No reporting bias detected	Good	See Body of Evidence Limitations for KQ1, HIV infection. Trials were not designed to assess mortality and results were heavily weighted (73%) by a single trial of PrEP in PWID conducted in Thailand.	Low for benefit of oral PrEP	See Applicability for KQ1, HIV infection.
	Quality of life: k=0	--	--	--	--	--	--

Table 10. Summary of Evidence

Key question	Number of studies (k) Number of participants* (n) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ1. Benefits of PrEP: Dapivirine vaginal ring vs. placebo	HIV infection: k=2 RCTs (n=4,564) Both RCTs added for update	2 trials; RR, 0.71 (95% CI, 0.57 to 0.89); I^2=0%; ARD, -2.23% (95% CI, -3.75% to -0.74%) after 1.4 to 1.6 years	Consistent and precise No reporting bias detected	Good	Relatively short duration of follow-up	High for benefit of dapivirine vaginal ring	Dapivirine vaginal ring not FDA-approved and withdrawn from FDA review. Trials were conducted in women at increased risk of HIV infection in Africa.
KQ1a. Benefits of PrEP in populations of interest	HIV infection: k=12 RCTs (n=18,244) All RCTs in prior USPSTF review	Stratified by risk category (p=0.43 for interaction) MSM: 4 trials; RR, 0.23 (95% CI, 0.08 to 0.62); I^2=64% PWID: 1 trial; RR, 0.52 (95% CI, 0.29 to 0.92) Heterosexual contact: 5 trials; RR, 0.54 (95% CI, 0.31 to 0.97); I^2=82% No differences in within-study subgroup analyses on age (4 trials) or sex (3 trials)	Some inconsistency within risk category subgroups; precise No reporting bias detected	Good	See Body of Evidence Limitations for KQ1, HIV infection.	Moderate for benefit of oral PrEP in populations of interest	Studies of women and men at increased risk via heterosexual contact conducted in Africa; the only study of PWID conducted in Asia; several studies of MSM conducted in the U.S., Europe, and Canada.

Table 10. Summary of Evidence

Key question	Number of studies (k) Number of participants* (n) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ1b. Benefits of oral PrEP by dosing strategy or regimen	HIV infection: k=12 RCTs of PrEP vs. placebo or no PrEP (n=18,172), 1 RCT of daily vs. intermittent or event-driven PrEP (n=535), 1 RCT of daily vs. event-driven PrEP (n=119) 1 new study of daily vs. event-driven PrEP; otherwise, all other studies in prior USPSTF review	PrEP vs. placebo or no PrEP: Stratified by TDF or TDF-FTC (p=0.65 for interaction) TDF: 5 trials; RR, 0.49 (95% CI, 0.28 to 0.84); I^2=58% TDF-FTC: 8 trials; RR, 0.44 (95% CI, 0.27 to 0.72); I^2=74% Stratified by daily or on-demand dosing (p=0.13 for interaction) Daily dosing: 9 trials; RR, 0.47 (95% CI, 0.32 to 0.71); I^2=75% On-demand dosing: 1 trial; RR, 0.14 (95% CI, 0.03 to 0.63) One head-to-head trial found no difference between daily vs. intermittent or on-demand PrEP and one head-to-head trial of daily vs. event-drivien PrEP were not powered to assess effects on HIV infection and reported few cases.	Some inconsistency in stratified analyses (may be explained by level of adherence); precise for TDF vs. TDF-FTC; imprecise for daily vs. event-driven PrEP No reporting bias detected	Fair	See Body of Evidence Limitations for KQ1, HIV infection.	High for TDF vs. TDF-FTC, moderate for daily vs. event-driven PrEP	Five trials evaluated TDF alone, which is not approved for PrEP in the U.S. 1 trial evaluated event-driven PrEP vs. placebo and 2 trials evaluated daily vs. event-driven or intermittent PrEP in MSM; no studies on event-driven or intermittent dosing in women or PWID.
KQ2. Benefits of newer vs. older PrEP regimens: Oral TAF-FTC vs. TDF-FTC	HIV infection: k=1 new RCT (n=5,387)	TAF-FTC vs. TDF-FTC: 1 trial, 0.3% vs. 0.6%; RR, 0.53 (95% CI, 0.23 to 1.26); results within prespecified non-inferiority margin	Unable to assess consistency (1 trial); some imprecision. No reporting bias detected	Good	Single trial	Moderate for noninferiority of TAF-FTC (with potential benefit)	Trial was conducted in cisgender adult men and transgender women who have sex with men in Europe and North America

Table 10. Summary of Evidence

Key question	Number of studies (k) Number of participants* (n) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ2. Benefits of newer vs. older PrEP regimens: Long-acting injectable cabotegravir vs. daily oral TDF-FTC	HIV infection: k=2 new RCTs (n=7,668)	Cabotegravir vs. TDF-FTC: -1 trial in MSM and transgender women (n=4,490): 0.6% vs. 1.7%; RR, 0.33, 95% CI 0.18 to 0.62) -1 trial in women (n=3,178): 0.3% vs. 2.3%; RR, 0.11 (95% CI 0.04 to 0.31)	Consistent; precise No reporting bias detected	Good	Single trials conducted in different populations; both trials stopped early for meeting pre-specified efficacy threshold	High for reduced risk with cabotegravir	One trial conducted in MSM and transgender men in the United States, Latin America, Asia, and Africa and one trial conducted in women at increased risk of HIV infection in Africa. Cabotegravir has been FDA-approved for PrEP to prevent sexually acquired HIV infection
KQ3. Diagnostic accuracy of instruments for identifying persons at risk of incident HIV infection	k=12 studies of risk prediction or diagnostic accuracy (n=5,544,500) 7 studies in prior USPSTF review and 5 studies added	MSM: 5 studies (n=25,488 in validation cohorts); AUROC, 0.60 to 0.73 for different instruments in 5 studies; a sixth study reported better goodness of fit than with instruments evaluated in other studies (AUROC NR). AUROC, 0.49 to 0.75 for different instruments in 2 studies of Black MSM. PWID: AUROC, 0.72 in 1 study (n=1,904) Women: Sensitivity 95% (21 cases) General populations: AUROC, 0.77 and 0.84 in two studies (n=33,404 and 606,701 in validation cohorts)	Consistent; precise (for MSM and general populations of HIV-uninfected persons) No reporting bias detected	Fair	Retrospective design; some instruments validated in 1 study or not validated in a cohort independent from the one used to develop the instrument; cutoffs not predefined in some studies.	Moderate (for MSM and general populations); low (for PWID and women)	All studies conducted in the U.S.; some studies utilized cohorts that included persons who underwent HIV testing prior to the year 2000.

Table 10. Summary of Evidence

Key question	Number of studies (k) Number of participants* (n) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ4. Harms of PrEP: Oral PrEP vs. placebo	Serious adverse events: k=12 RCTs (n=18,282) All RCTs in prior USPSTF review	RR, 0.93 (95% CI, 0.77 to 1.12); I^2=56%	Some inconsistency; some imprecision No reporting bias detected	Good	Small number of serious adverse events in most trials. Composite outcome, some trials had limited details on serious adverse events.	Moderate for no difference	See Applicability for KQ1, Oral PrEP vs. Placebo
	Withdrawals due to adverse events: k=4 RCTs (n=10,563) All RCTs in prior USPSTF review	RR, 1.25 (95% CI, 0.99 to 1.59); I^2=0%	Consistent; some imprecision No reporting bias detected, but most trials did not report withdrawals due to adverse events	Good	Most trials did not report withdrawals due to adverse events. Composite outcome, with variability in cause of withdrawal (clinical or laboratory adverse event) and whether adverse event temporary or permanent.	Moderate for increased risk with oral PrEP	See Applicability for KQ1, Oral PrEP vs. Placebo
	Renal adverse events: k=12 RCTs (n=18,170) All RCTs in prior USPSTF review	RR, 1.43 (95% CI, 1.18 to 1.75); I^2=0%; ARD, 0.56% (95% CI, 0.09% to 1.04%)	Consistent; precise No reporting bias detected	Good	Variability in definition of adverse renal events (most trials defined as ≥1 grade 1 serum creatinine elevations).	High for increased risk with oral PrEP	See Applicability for KQ1, Oral PrEP vs. Placebo. Most events were mild and reversible
	Gastrointestinal adverse events: k=12 RCTs (n=18,300) All RCTs in prior USPSTF review	RR, 1.63 (95% CI, 1.26 to 2.11); I^2=43%; ARD, 1.95% (95% CI, 0.48% to 3.43%)	Some inconsistency; precise No reporting bias detected	Good	Composite outcome, with no difference for specific gastrointestinal adverse events.	High for increased risk with oral PrEP	See Applicability for KQ1, Oral PrEP vs. Placebo. Most events were mild and reversible.
	Fracture: k=7 RCTs (n=15,241) All RCTs in prior USPSTF review	RR, 1.23 (95% CI, 0.97 to 1.56); I^2=0%	Consistent; precise No reporting bias detected	Moderate	Limited details on fracture site; most fractures traumatic in studies that provided this information. Results heavily weighted by 1 trial.	Low for increased risk with oral PrEP	See Applicability for KQ1, Oral PrEP vs. Placebo

Table 10. Summary of Evidence

Key question	Number of studies (k) Number of participants* (n) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ4. Harms of PrEP: Oral PrEP vs. placebo	Syphilis: k=4 RCTs (n=10,775) All RCTs in prior USPSTF review	RR, 1.08 (95% CI, 0.98 to 1.18); I^2=0%	Consistent; precise No reporting bias detected, but NR in most trials	Good	Most trials were blinded, which might affect behaviors differently than when patients know they are on PrEP.	Moderate for no difference	See Applicability for KQ1, Oral PrEP vs. Placebo
	Gonorrhea: k=5 RCTs (n=9,296) All RCTs in prior USPSTF review	RR, 1.07 (95% CI, 0.82 to 1.39); I^2=49%	Some inconsistency; some imprecision No reporting bias detected, but NR in most trials	Good	Most trials were blinded, which might affect behaviors differently than when patients know they are on PrEP.	Moderate for no difference	See Applicability for KQ1, Oral PrEP vs. Placebo
	Chlamydia: k=5 RCTs (n=9,296) All RCTs in prior USPSTF review	RR, 0.97 (95% CI, 0.80 to 1.18); I^2=59%	Consistent; precise No reporting bias detected, but NR in most trials	Good	Most trials were blinded, which might affect behaviors differently than when patients know they are on PrEP.	Moderate for no difference	See Applicability for KQ1, Oral PrEP vs. Placebo
	Combined bacterial STIs: k=2 RCTs (n=5,291) All RCTs in prior USPSTF review	RR, 1.14 (95% CI, 0.97 to 1.34); I^2=0%	Consistent; some imprecision No reporting bias detected, but NR in most trials	Good	Most trials were blinded, which might affect behaviors differently than when patients know they are on PrEP.	Moderate for no difference	See Applicability for KQ1, Oral PrEP vs. Placebo

Table 10. Summary of Evidence

Key question	Number of studies (k) Number of participants* (n) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ4. Harms of PrEP: Oral PrEP vs. placebo	Herpes simplex virus infection: k=3 RCTs (n=4,088) All RCTs in prior USPSTF review	RR, 0.85 (95% CI, 0.67 to 1.07); I^2=19%	Some inconsistency; some imprecision No reporting bias detected, but NR in most trials	Good	Trials were blinded, which might affect behaviors differently than when patients know they are on PrEP.	Moderate for no difference	See Applicability for KQ1, Oral PrEP vs. Placebo
	Hepatitis C virus infection: k=2 RCTs (n=896) All RCTs in prior USPSTF review	RR, 0.73 (95% CI, 0.25 to 2.10); I^2=0%	Some inconsistency; imprecise No reporting bias detected, but NR in most trials	Good	One trial was blinded, which might affect behaviors differently than when patients know they are on PrEP.	Low for decreased risk with oral PrEP	See Applicability for KQ1, Oral PrEP vs. Placebo
	Spontaneous abortion†: k=3 RCTs (n=415) All RCTs in prior USPSTF review	RR, 1.09 (95% CI, 0.79 to 1.50); I^2=0%	Consistent; some imprecision No reporting bias detected	Good	Analysis restricted to women who became pregnant in trials of PrEP and were taken off PrEP.	Moderate for no difference	Analyses of women at high risk of HIV infection via heterosexual contact who were taken off PrEP at time of pregnancy
KQ4. Harms of PrEP: Dapivirine vaginal ring vs. placebo	Serious adverse events: k=2 RCTs (n=4,587) Both RCTs added for update	RR, 1.73 (95% CI, 0.60 to 4.94); I^2=80%	Inconsistent; very imprecise No reporting bias detected	Good	Substantial heterogeneity; events varied widely and did not appear related to PrEP	Insufficient	See Applicability to KQ 2, Dapivirine vs. Placebo
	Syphilis: k=1 RCT (n=1,959) Added for update	1.3% vs. 0.8%	Unable to assess consistency; some imprecision No reporting bias detected	Good	Trial was blinded, which might affect behaviors differently than when patients know they are on PrEP.	Low for similar risk	See Applicability for KQ1, Oral PrEP vs. Placebo

Table 10. Summary of Evidence

Key question	Number of studies (k) Number of participants* (n) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ4. Harms of PrEP: Dapivirine vaginal ring vs. placebo	Gonorrhea: k=2 RCTs (n=4,587) Both RCTs added for update	RR, 1.01 (95% CI, 0.80 to 1.27); I^2=63%	Some inconsistency; precise No reporting bias detected	Good	Trials were blinded, which might affect behaviors differently than when patients know they are on PrEP.	Moderate for no difference	See Applicability for KQ1, Oral PrEP vs. Placebo
	Chlamydia: k=2 RCTs (n=4,587) Both RCTs added for update	RR, 0.98 (95% CI, 0.89 to 1.07); I^2=0%	Consistent; precise No reporting bias detected	Good	Trials were blinded, which might affect behaviors differently than when patients know they are on PrEP.	High for no difference	See Applicability for KQ1, Oral PrEP vs. Placebo
	Any STI: k=1 RCT (n=1,959) Added for update	RR, 1.06 (95% CI, 0.96 to 1.16)	Unable to assess consistency; precise No reporting bias detected	Good	Trial was blinded, which might affect behaviors differently than when patients know they are on PrEP.	Moderate for no difference	See Applicability for KQ1, Oral PrEP vs. Placebo
	Pregnancy: k=2 RCTs (n=4,587) Both RCTs added for update	3.9 vs. 4.0 per 100 person-years and 1.6 vs. 2.0 per 100 person-years	Consistent, precise No reporting bias detected	Good	Trial was blinded, which might affect behaviors differently than when patients know they are on PrEP	High for no difference	See Applicability for KQ1, Oral PrEP vs. Placebo
KQ5: Harms of PrEP: TAF-FTC vs. TDF-FTC	Serious adverse events, discontinuation due to adverse events, or any adverse event: k=1 new RCT (n=5,387)	Serious adverse events: 7% vs. 7% Discontinuation due to adverse events: 1% vs. 2% Any adverse event: 94% vs. 94%	Unable to assess consistency; some imprecision No reporting bias detected	Good	Adverse events varied and most did not appear related to PrEP	Moderate for no difference	See Applicability for KQ2, TAF-FTC vs. TDF-FTC

Table 10. Summary of Evidence

Key question	Number of studies (k) Number of participants* (n) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ5: Harms of PrEP: TAF-FTC vs. TDF-FTC	Renal adverse events: k=1 new RCT (n=5,387)	Any renal adverse event: 10% vs. 10% Renal adverse event leading to discontinuation: 0.07% vs. 0.2%	Unable to assess consistency; some imprecision No reporting bias detected	Good	Adverse events leading to discontinuation rare	Moderate for no difference	See Applicability for KQ2, TAF-FTC vs. TDF-FTC
	Fracture, bone mineral density: k=1 new RCT (n=5,387)	Fracture: 2% vs. 2% Hip bone mineral density (change from baseline): +0.6% vs. -1.0%, p<0.001 Spine bone mineral density (change from baseline): +0.9% vs. -1.4%, p<0.001	Unable to assess consistency; precise No reporting bias detected	Good	Duration may be insufficient to evaluate fracture risk	Moderate for increased bone mineral density with TAF-FTC	See Applicability for KQ2, TAF-FTC vs. TDF-FTC
	Lipid parameters, weight gain: k=1 new RCT (n=5,387)	Low density lipoprotein cholesterol (change from baseline): median -0.05 vs. -0.18 mmol/L, p<0.0001 Weight gain (change from baseline): median +1.7 vs. +0.5 kg, p<0.0001	Unable to assess consistency; precise No reporting bias detected	Good	No additional limitations noted	Moderate for negative effects of lipids and weight gain with TAF-FTC	See Applicability for KQ2, TAF-FTC vs. TDF-FTC. Clinical significance of differences uncertain
KQ5: Harms of Injectable Cabotegravir vs. Oral TDF-FTC	Serious adverse events: k=2 new RCTs (n=7,786)	5.3% vs. 5.3% and 2.0% vs. 2.0%	Consistent; precise No reporting bias detected	Good	No additional limitations noted	High for no difference	See Applicability for KQ1, Cabotegravir vs. TDF-FTC.
	Renal events, liver events, STIs: k=2 new RCTs (n=7,786)	No differences in renal events, liver events, or STIs	Consistent; precise No reporting bias detected	Good	Trial was blinded, which might affect sexual risk behaviors differently than when patients know they are on PrEP.	High for no difference	See Applicability for KQ1, Cabotegravir vs. TDF-FTC.

Table 10. Summary of Evidence

Key question	Number of studies (k) Number of participants* (n) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ5: Harms of Injectable Cabotegravir vs. Oral TDF-FTC	Weight gain: k=2 new RCTs (n=7,786)	Mean differences 0.86 kg and 0.4 kg	Consistent; precise No reporting bias detected	Good	No additional limitations noted	High for increased weight gain with cabotegravir	See Applicability for KQ1, Cabotegravir vs. TDF-FTC.
	Injection site reactions: k=2 new RCTs (n=7,786)	81.4% vs. 31.3% and 38.0% vs. 10.8%	Consistent; precise No reporting bias detected	Good	No additional limitations noted	High for increased risk with cabotegravir	See Applicability for KQ1, Cabotegravir vs. TDF-FTC. Injection site reactions were usually mild and occurred most commonly with the first injection, with diminishing frequency over time
	Pregnancy: k=1 new RCT (n=3,178)	1.5 vs. 1.0 per 100 person-years	Unable to assess consistency; some imprecision No reporting bias detected	Good	No additional limitations noted	Moderate for similar risk	See Applicability for KQ1, Cabotegravir vs. TDF-FTC. One trial evaluated pregnancy incidence among women in Africa.

*For KQs 1 and 5, number of participants included in analysis.
†In women who became pregnant while on PrEP.
Abbreviations: ARD=adjusted risk difference; aRR=adjusted relative risk; AUROC=area under the receiver operating characteristics curve; CI=confidence interval; FDA=U.S. Food and Drug Administration; FTC=emtricitabine; KQ=key question; MSM=men who have sex with men; NR=not reported; OR=odds ratio; PrEP=pre-exposure prophylaxis; PWID=persons who inject drugs; RCT=randomized, controlled trial; RR=relative risk; STI=sexually transmitted infection; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; U.S.=United States; USPSTF=United States Preventive Services Task Force.

Database: Ovid MEDLINE(R) ALL

1 exp Pre-Exposure Prophylaxis/
2 ("preexposure prophylaxis" or prep or tenofovir or truvada or descovy or biktarvy or cabotegravir or dapivirine).ti,ab,kf.
3 Anti-HIV Agents/
4 (hiv or "human immunodeficiency virus").ti,ab,kf.
5 (1 or 2) and (3 or 4)
6 limit 5 to yr="2018 -Current"
7 limit 6 to english language
8 (random* or control* or trial).ti,ab,kf.
9 7 and 8
10 limit 7 to (clinical trial or comparative study or meta analysis or randomized controlled trial or "systematic review")
11 9 or 10
12 exp "Sensitivity and Specificity"/
13 (sensitivity or specificity or "AUROC" or "ROC").ti,ab,kf.
14 (risk adj2 (predict* or accura*)).ti,ab,kf.
15 (diagnos* adj2 accura*).ti,ab,kf.
16 12 or 13 or 14 or 15
17 7 and 16
18 11 or 17

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 "pre-exposure prophylaxis".ti,ab.
2 (prep or tenofovir or truvada or descovy or biktarvy or cabotegravir or dapivirine).ti,ab.
3 Anti-HIV Agents/
4 (hiv or "human immunodeficiency virus").ti,ab.
5 (1 or 2) and (3 or 4)
6 exp "Sensitivity and Specificity"/
7 (sensitivity or specificity or "AUROC" or "ROC").ti,ab.
8 (risk adj2 (predict* or accura*)).ti,ab.
9 (diagnos* adj2 accura*).ti,ab.
10 6 or 7 or 8 or 9
11 (random* or control* or trial).ti,ab.
12 limit 5 to (comparative study or meta analysis or randomized controlled trial)
13 5 and 11
14 12 or 13
15 5 and 10
16 13 or 14 or 15
17 limit 16 to english language
18 conference abstract.pt.
19 "journal: conference abstract".pt.
20 "journal: conference review".pt.
21 "http://.www.who.int/trialsearch*".so.
22 "https://clinicaltrials.gov*".so.
23 18 or 19 or 20 or 21 or 22

24 17 not 23
25 limit 24 to yr="2018 -Current"

Database: EBM Reviews - Cochrane Database of Systematic Reviews >
1 "pre-exposure prophylaxis".ti,ab.
2 (prep or tenofovir or truvada or descovy or biktarvy or cabotegravir or dapivirine).ti,ab.
3 (hiv or "human immunodeficiency virus").ti,ab.
4 (1 or 2) and 3
5 (2018$ or 2019$ or 2020$ or 2021$).up.
6 4 and 5

Database: Elsevier Embase
'pre-exposure prophylaxis'/exp OR 'pre-exposure prophylaxis' AND 'human immunodeficiency virus'/exp AND [embase]/lim NOT [medline]/lim AND ('article'/it OR 'article in press'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'review'/it OR 'short survey'/it)

Appendix A2. Inclusion and Exclusion Criteria

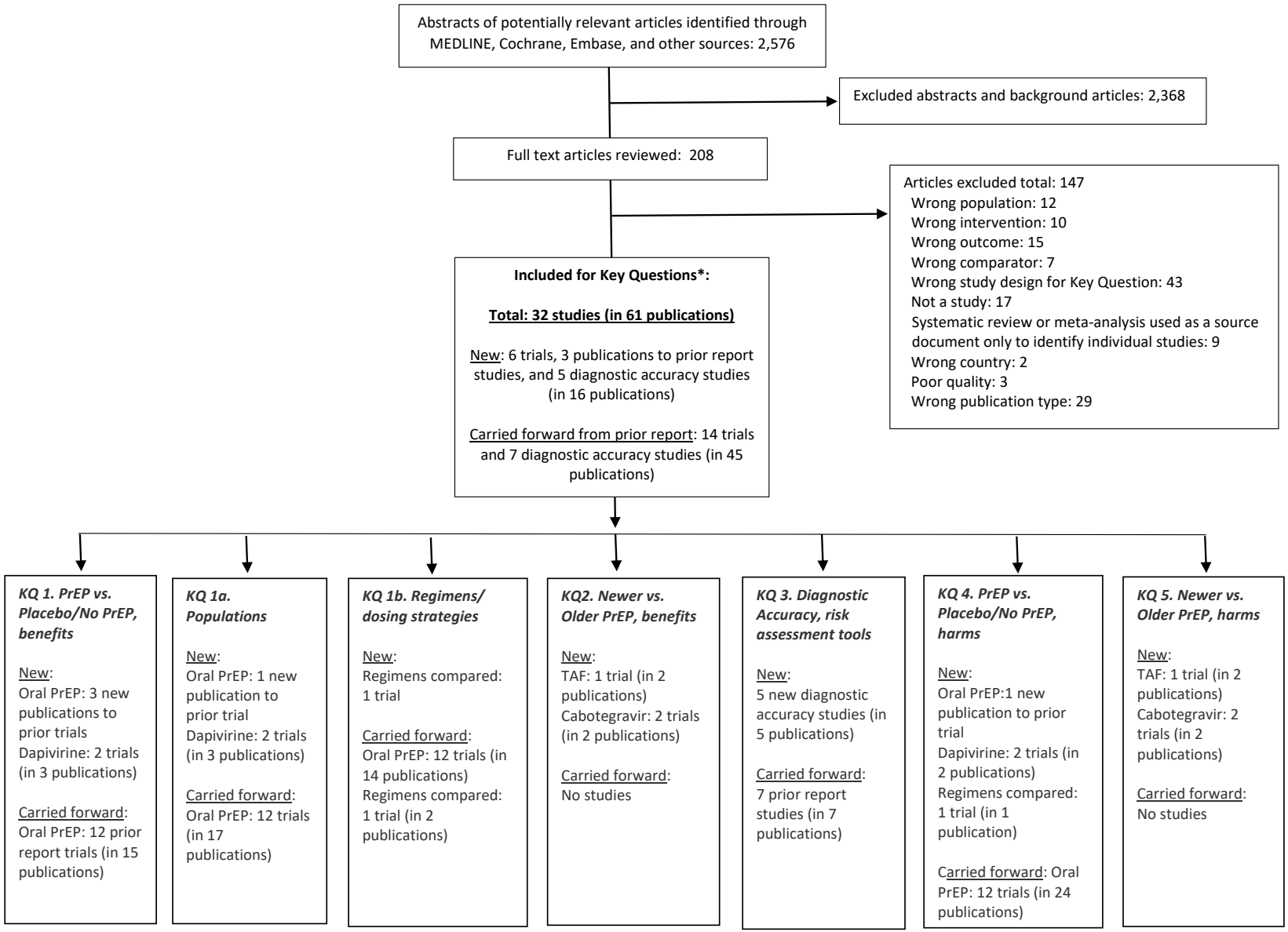
	Included	Excluded
Populations	Adolescents who weigh more than35 kg (ages 13 to <18 years) and adults (age ≥18 years) without pre-existing HIV infection at increased risk of HIV acquisition* Patient populations of interest defined by age, sex, gender identity, race/ethnicity, HIV risk category	Persons living with HIV, children
Interventions	**KQs 1, 2, 4, 5:** Daily oral TDF-FTC or TDF Daily oral TAF-FTC Alternate dosing regimens (event-driven or intermittent dosing) Injectable cabotegravir Dapivirine vaginal ring **KQ 3:** Provider or patient risk assessment tools	Other PrEP regimens
Comparisons	**KQs 1, 4:** Placebo or no PrEP (including deferred PrEP) **KQs 2, 5:** TDF-FTC (for TAF-FTC or cabotegravir) **KQ 3:** Reference standard for HIV infection	
Outcomes	**KQs 1, 2, 4, 5:** Risk of HIV acquisition, quality of life, risk of other sexually transmitted infections, risk of hepatitis B and C virus infections, renal insufficiency, fracture, and pregnancy-related outcomes; for KQ 2, lipid parameters and weight gain **KQ 3:** Diagnostic accuracy measures	Outcomes not listed, including condom use
Setting	Settings in which PrEP is delivered in ways applicable to U.S. primary care settings	Inpatient settings
Study design	**KQs 1, 2:** Randomized controlled trials for benefits and harms; controlled observational studies for harms† if randomized controlled trials are not available **KQ 3:** Diagnostic accuracy studies **KQs 4, 5:** Randomized, controlled trials; controlled observational studies for harms† if randomized controlled trials are not available	

* Including pregnant and breastfeeding women.

† Study must perform statistical adjustment for potential confounders to be included.

Abbreviations: FTC=emtricitabine; KQ=key question; PrEP=pre-exposure prophylaxis; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; U.S.=United States.

Appendix A3. Literature Flow Diagram



*The sum of the number of studies per key question (KQ) exceeds the total number of studies because some studies were applicable to multiple KQs.

Appendix A4. Included Studies List

1. Agot K, Taylor D, Corneli AL, et al. Accuracy of self-report and pill-count measures of adherence in the FEM-PrEP clinical trial: implications for future HIV-prevention trials. AIDS Behav. 2015 May;19(5):743-51. doi: 10.1007/s10461-014-0859-z. PMID: 25100053.
2*. Antoni G, Tremblay C, Delaugerre C, et al. On-demand pre-exposure prophylaxis with tenofovir disoproxil fumarate plus emtricitabine among men who have sex with men with less frequent sexual intercourse: a post-hoc analysis of the ANRS IPERGAY trial. Lancet HIV. 2020 02;7(2):e113-e20. doi: 10.1016/S2352-3018(19)30341-8. PMID: 31784343.
3. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV-1 prevention in heterosexual men and women. N Engl J Med. 2012 Aug 2;367(5):399-410. doi: 10.1056/NEJMoa1108524. PMID: 22784037.
4*. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med. 2016 Dec;375(22):2121-32. doi: 10.1056/NEJMoa1506110. PMID: 26900902.
5. Bekker LG, Roux S, Sebastien E, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town trial): a randomised, open-label, phase 2 trial. Lancet HIV. 2018 02;5(2):e68-e78. doi: 10.1016/S2352-3018(17)30156-X. PMID: 28986029.
6. Beymer MR, Weiss RE, Sugar CA, et al. Are Centers for Disease Control and Prevention guidelines for preexposure prophylaxis specific enough? Formulation of a personalized HIV risk score for pre-exposure prophylaxis initiation. Sex Transm Dis. 2017 Jan;44(1):48-56. doi: 10.1097/olq.0000000000000535. PMID: 27898570.
7. Celum C, Morrow RA, Donnell D, et al. Daily oral tenofovir and emtricitabine-tenofovir preexposure prophylaxis reduces herpes simplex virus type 2 acquisition among heterosexual HIV-1-uninfected men and women: a subgroup analysis of a randomized trial. Ann Intern Med. 2014 Jul 1;161(1):11-9. doi: 10.7326/M13-2471. PMID: 24979446.
8*. Chaix ML, Charreau I, Pintado C, et al. Effect of on-demand oral preexposure prophylaxis with tenofovir/emtricitabine on herpes simplex virus-1/2 incidence among men who have sex with men: A substudy of the ANRS IPERGAY trial. Open Forum Infect Dis. 2018;5(11)doi: 10.1093/ofid/ofy295. PMID: 30539039.
9. Chirwa LI, Johnson JA, Niska RW, et al. CD4(+) cell count, viral load, and drug resistance patterns among heterosexual breakthrough HIV infections in a study of oral preexposure prophylaxis. AIDS. 2014 Jan 14;28(2):223-6. doi: 10.1097/QAD.0000000000000102. PMID: 24361682.
10. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok tenofovir study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013 Jun 15;381(9883):2083-90. doi: 10.1016/S0140-6736(13)61127-7. PMID: 23769234.
11*. Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet. 2022 Apr 1doi: 10.1016/s0140-6736(22)00538-4. PMID: 35378077.
12. Deutsch MB, Glidden DV, Sevelius J, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. Lancet HIV. 2015 Dec;2(12):e512-9. doi: 10.1016/S2352-3018(15)00206-4. PMID: 26614965.
13. Donnell D, Baeten JM, Bumpus NN, et al. HIV protective efficacy and correlates of tenofovir blood concentrations in a clinical trial of PrEP for HIV prevention. J Acquir Immune Defic Syndr. 2014 Jul 1;66(3):340-8. doi: 10.1097/QAI.0000000000000172. PMID: 24784763.
14. Grant RM, Mannheimer S, Hughes JP, et al. Daily and nondaily oral preexposure prophylaxis in men and transgender women who have sex with men: The Human Immunodeficiency Virus Prevention Trials Network 067/ADAPT study. Clin Infect Dis. 2018 May 17;66(11):1712-21. doi: 10.1093/cid/cix1086. PMID: 29420695.
15. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010 Dec 30;363(27):2587-99. doi: 10.1056/NEJMoa1011205. PMID: 21091279.
16. Grohskopf LA, Chillag KL, Gvetadze R, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. J Acquir Immune Defic Syndr. 2013 Sep 1;64(1):79-86. doi: 10.1097/QAI.0b013e31828ece33. PMID: 23466649.
17. Haberer JE, Baeten JM, Campbell J, et al. Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa. PLoS Med. 2013;10(9):e1001511. doi: 10.1371/journal.pmed.1001511. PMID: 24058300.
18. Heffron R, Mugo N, Were E, et al. Preexposure prophylaxis is efficacious for HIV-1 prevention among women using depot medroxyprogesterone acetate for contraception. AIDS. 2014 Nov 28;28(18):2771-6. doi: 10.1097/QAD.0000000000000493. PMID: 25493602.
19. Hoenigl M, Weibel N, Mehta SR, et al. Development and validation of the San Diego early test score to predict acute and early HIV infection risk in men who have sex with men. Clin Infect Dis. 2015 Aug 1;61(3):468-75. doi: 10.1093/cid/civ335. PMID: 25904374.
20. Hosek SG, Siberry G, Bell M, et al. The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. J Acquir Immune Defic Syndr. 2013 Apr 01;62(4):447-56. doi: 10.1097/QAI.0b013e3182801081. PMID: 24135734.
21. Jones J, Hoenigl M, Siegler AJ, et al. Assessing the performance of 3 human immunodeficiency virus incidence risk scores in a cohort of black and white men who have sex with men in the South. Sex Transm Dis. 2017 May;44(5):297-302. doi: 10.1097/OLQ.0000000000000596. PMID: 28407646.
22. Kibengo FM, Ruzagira E, Katende D, et al. Safety, adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial. PLoS One. 2013;8(9):e74314. doi: 10.1371/journal.pone.0074314. PMID: 24086333.

Appendix A4. Included Studies List

23*. Krakower DS, Gruber S, Hsu K, et al. Development and validation of an automated HIV prediction algorithm to identify candidates for pre-exposure prophylaxis: a modelling study. Lancet HIV. 2019 10;6(10):e696-e704. doi: 10.1016/S2352-3018(19)30139-0. PMID: 31285182.

24*. Kwan TH, Lui GCY, Lam TTN, et al. Comparison between daily and on-demand PrEP (pre-exposure prophylaxis) regimen in covering condomless anal intercourse for men who have sex with men in Hong Kong: A randomized, controlled, open-label, crossover trial. J Int AIDS Soc. 2021 09;24(9):e25795. doi: 10.1002/jia2.25795. PMID: 34473402.

25. Lancki N, Almirol E, Alon L, et al. Preexposure prophylaxis guidelines have low sensitivity for identifying seroconverters in a sample of young Black MSM in Chicago. AIDS. 2018 Jan 28;32(3):383-92. doi: 10.1097/qad.0000000000001710. PMID: 29194116.

26*. Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med. 2021 08 12;385(7):595-608. doi: 10.1056/NEJMoa2101016. PMID: 34379922.

27. Lehman DA, Baeten JM, McCoy CO, et al. Risk of drug resistance among persons acquiring HIV within a randomized clinical trial of single- or dual-agent preexposure prophylaxis. J Infect Dis. 2015 Apr 15;211(8):1211-8. doi: 10.1093/infdis/jiu677. PMID: 25587020.

28. Liu A, Glidden DV, Anderson PL, et al. Patterns and correlates of PrEP drug detection among MSM and transgender women in the Global iPrEx Study. J Acquir Immune Defic Syndr. 2014 Dec 15;67(5):528-37. doi: 10.1097/QAI.0000000000000351. PMID: 25230290.

29. Liu AY, Vittinghoff E, Sellmeyer DE, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. PLoS One. 2011;6(8):e23688. doi: 10.1371/journal.pone.0023688. PMID: 21897852.

30. Mandala J, Nanda K, Wang M, et al. Liver and renal safety of tenofovir disoproxil fumarate in combination with emtricitabine among African women in a pre-exposure prophylaxis trial. BMC Pharmacol Toxicol. 2014;15:77. doi: 10.1186/2050-6511-15-77. PMID: 25539648.

31. Marcus JL, Glidden DV, McMahan V, et al. Daily oral emtricitabine/tenofovir preexposure prophylaxis and herpes simplex virus type 2 among men who have sex with men. PLoS One. 2014;9(3):e91513. doi: 10.1371/journal.pone.0091513. PMID: 24637511.

32*. Marcus JL, Hurley LB, Krakower DS, et al. Use of electronic health record data and machine learning to identify candidates for HIV pre-exposure prophylaxis: a modelling study. Lancet HIV. 2019 10;6(10):e688-e95. doi:10.1016/S2352-3018(19)30137-7. PMID: 31285183.

33. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2015 Feb 5;372(6):509-18. doi: 10.1056/NEJMoa1402269. PMID: 25651245.

34. Martin M, Vanichseni S, Suntharasamai P, et al. Renal function of participants in the Bangkok tenofovir study--Thailand, 2005-2012. Clin Infect Dis. 2014 Sep 1;59(5):716-24. doi: 10.1093/cid/ciu355. PMID: 24829212.

35. Martin M, Vanichseni S, Suntharasamai P, et al. The impact of adherence to preexposure prophylaxis on the risk of HIV infection among people who inject drugs. AIDS. 2015 Apr 24;29(7):819-24. doi: 10.1097/QAD.0000000000000613. PMID: 25985403.

36. Matthews LT, Heffron R, Mugo NR, et al. High medication adherence during periconception periods among HIV-1-uninfected women participating in a clinical trial of antiretroviral pre-exposure prophylaxis. J Acquir Immune Defic Syndr. 2014 Sep 1;67(1):91-7. doi: 10.1097/QAI.0000000000000246. PMID: 25118795.

37*. Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet. 2020 07 25;396(10246):239-54. doi: 10.1016/S0140-6736(20)31065-5. PMID: 32711800.

38. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet. 2016 Jan 2;387(10013):53-60. doi: 10.1016/S0140-6736(15)00056-2. PMID: 26364263.

39. Menza TW, Hughes JP, Celum CL, et al. Prediction of HIV acquisition among men who have sex with men. Sex Transm Dis. 2009 Sep;36(9):547-55. doi: 10.1097/OLQ.0b013e3181a9cc41. PMID: 19707108.

40. Mirembe BG, Kelly CW, Mgodi N, et al. Bone mineral density changes among young, healthy African women receiving oral tenofovir for HIV preexposure prophylaxis. J Acquir Immune Defic Syndr. 2016 Mar 1;71(3):287-94. doi: 10.1097/QAI.0000000000000858. PMID: 26866954.

41. Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 Infection. N Engl J Med. 2015 Dec 3;373(23):2237-46. doi: 10.1056/NEJMoa1506273. PMID: 26624850.

42. Mugo NR, Hong T, Celum C, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. JAMA. 2014 Jul 23-30;312(4):362-71. doi: 10.1001/jama.2014.8735. PMID: 25038355.

43. Mugwanya KK, Wyatt C, Celum C, et al. Changes in glomerular kidney function among HIV-1-uninfected men and women receiving emtricitabine-tenofovir disoproxil fumarate preexposure prophylaxis: a randomized clinical trial. JAMA Intern Med. 2015 Feb;175(2):246-54. doi: 10.1001/jamainternmed.2014.6786. PMID: 25531343.

Appendix A4. Included Studies List

44. Mulligan K, Glidden DV, Anderson PL, et al. Effects of emtricitabine/tenofovir on bone mineral density in HIV-negative persons in a randomized, double-blind, placebo-controlled trial. Clin Infect Dis. 2015 Aug 15;61(4):572-80. doi: 10.1093/cid/civ324. PMID: 25908682.
45. Murnane PM, Brown ER, Donnell D, et al. Estimating efficacy in a randomized trial with product nonadherence: application of multiple methods to a trial of preexposure prophylaxis for HIV prevention. Am J Epidemiol. 2015 Nov 15;182(10):848-56. doi: 10.1093/aje/kwv202. PMID: 26487343.
46. Murnane PM, Celum C, Mugo N, et al. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. AIDS. 2013 Aug 24;27(13):2155-60. doi: 10.1097/QAD.0b013e3283629037. PMID: 24384592.
47. Mutua G, Sanders E, Mugo P, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. PLoS One. 2012;7(4):e33103. doi: 10.1371/journal.pone.0033103. PMID: 22511916.
48*. Nel A, van Niekerk N, Kapiga S, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. N Engl J Med. 2016;375(22):2133-43. doi: 10.1056/NEJMoa1602046. PMID: 27959766.
49*. Ogbuagu O, Ruane PJ, Podzamczer D, et al. Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet HIV. 2021 07;8(7):e397-e407. doi: 10.1016/S2352-3018(21)00071-0. PMID: 34197772.
50*. Peebles K, van der Straten A, Palanee-Phillips T, et al. Brief report: anal intercourse, HIV-1 risk, and efficacy in a trial of a dapivirine vaginal ring for HIV-1 prevention. J Acquir Immune Defic Syndr. 2020 03 01;83(3):197-201. doi: 10.1097/QAI.0000000000002253. PMID: 31809308.
51. Peterson L, Taylor D, Roddy R, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials. 2007;2(5):e27. doi: 10.1371/journal.pctr.0020027. PMID: 17525796.
52*. Ridgway JP, Friedman EE, Bender A, et al. Evaluation of an electronic algorithm for identifying cisgender female pre-exposure prophylaxis candidates. AIDS Patient Care STDs. 2021 01;35(1):5-8. doi: 10.1089/apc.2020.0231. PMID: 33400588.
53*. Scott H, Vittinghoff E, Irvin R, et al. Development and validation of the personalized Sexual Health Promotion (SexPro) HIV risk prediction model for men who have sex with men in the United States. AIDS Behav. 2020 Jan;24(1):274-83. doi: 10.1007/s10461-019-02616-3. PMID: 31352633.
54. Smith DK, Pals SL, Herbst JH, et al. Development of a clinical screening index predictive of incident HIV infection among men who have sex with men in the United States. J Acquir Immune Defic Syndr. 2012 Aug 1;60(4):421-7. doi: 10.1097/QAI.0b013e318256b2f6. PMID: 22487585.
55. Smith DK, Pan Y, Rose CE, et al. A brief screening tool to assess the risk of contracting HIV infection among active injection drug users. J Addict Med. 2015 May-Jun;9(3):226-32. doi: 10.1097/ADM.0000000000000123. PMID: 25961495.
56. Solomon MM, Lama JR, Glidden DV, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. AIDS. 2014 Mar 27;28(6):851-9. doi: 10.1097/QAD.0000000000000156. PMID: 24499951.
57*. Solomon MM, Schechter M, Liu AY, et al. The safety of Tenofovir-Emtricitabine for HIV pre-exposure prophylaxis (PrEP) in individuals with active Hepatitis B. J Acquir Immune Defic Syndr. 2016 Mar 1;71(3):281-6. doi: 10.1097/qai.0000000000000857. PMID: 26413853.
58. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012 Aug 2;367(5):423-34. doi: 10.1056/NEJMoa1110711. PMID: 22784038.
59*. Tordoff DM, Barbee LA, Khosropour CM, et al. Derivation and validation of an HIV risk prediction score among gay, bisexual, and other men who have sex with men to inform PrEP initiation in an STD clinic setting. J Acquir Immune Defic Syndr. 2020 11 01;85(3):263-71. doi: 10.1097/QAI.0000000000002438. PMID: 32658131.
60. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012 Aug 2;367(5):411-22. doi: 10.1056/NEJMoa1202614. PMID: 22784040.
61. Were EO, Heffron R, Mugo NR, et al. Pre-exposure prophylaxis does not affect the fertility of HIV-1-uninfected men. AIDS. 2014 Aug 24;28(13):1977-82. doi: 10.1097/QAD.0000000000000313. PMID: 25259704.

*New studies/publications.

Appendix A5. Excluded Studies List

1. Apretude (cabotegravir extended-release injectable suspension). Highlights of Prescribing INformation. 2021. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Apretude/pdf/APRETUDE-PI-PIL-IFU.PDF. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
2. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010 Sep 03;329(5996):1168-74. doi: 10.1126/science.1193748. PMID: 20643915. Exclusion: Ineligible intervention
3. Anderson PL, Glidden DV, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med. 2012 Sep 12;4(151):1-8. PMID: 22972843. Exclusion: Ineligible outcome
4. Antoni G. On-demand PrEP with TDF/FTC remains highly effective among MSM with infrequent sexual intercourse: a sub-study of the ANRS IPERGAY trial. 2017. http://programme.ias2017.org/Abstract/Abstract/3629. Accessed January 3, 2018. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
5. Ascher SB, Scherzer R, Estrella MM, et al. HIV preexposure prophylaxis with tenofovir disoproxil fumarate/emtricitabine and changes in kidney function and tubular health. AIDS. 2020 04 01;34(5):699-706. doi: 10.1097/QAD.0000000000002456. PMID: 31794523. Exclusion: Ineligible study design for Key Question
6. Baeten J, Palanee-Phillips T, Mgodi N, et al. High uptake and reduced HIV-1 incidence in an open-label trial of the dapivirine ring. Top Antivir Med. 2018;26:61s. Exclusion: Wrong publication type (e.g., abstract only)
7. Baeten JM, Palanee-Phillips T, Mgodi N, et al. High adherence and sustained impact on HIV-1 incidence: Final results of an open-label extension trial of the dapivirine vaginal ring. Journal of the International AIDS Society. 2019;22doi: 10.1002/jia2.25327. Exclusion: Wrong publication type (e.g., abstract only)
8. Baeten JM, Palanee-Phillips T, Mgodi NM, et al. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. Lancet HIV. 2021 Feb;8(2):e87-e95. doi: 10.1016/s2352-3018(20)30304-0. PMID: 33539762. Exclusion: Ineligible study design for Key Question
9. Baker Z, Javanbakht M, Moore J, et al. Qualitative Study on the Acceptability of and Adherence to a Vaginal Ring for HIV Prophylaxis Among Adolescent Girls. J Acquir Immune Defic Syndr. 2021 07 01;87(3):944-50. doi: 10.1097/QAI.0000000000002674. PMID: 33675614. Exclusion: Ineligible outcome
10. Balkus JE, Brown E, Palanee T, et al. An empiric HIV risk scoring tool to predict HIV-1 acquisition in African women. J Acquir Immune Defic Syndr. 2016 Jul 1;72(3):333-43. doi: 10.1097/QAI.0000000000000974. PMID: 26918545. Exclusion: Poor quality
11. Balkus JE, Brown ER, Palanee-Phillips T, et al. Performance of a Validated Risk Score to Predict HIV-1 Acquisition Among African Women Participating in a Trial of the Dapivirine Vaginal Ring. J Acquir Immune Defic Syndr. 2018 01 01;77(1):e8-e10. doi: 10.1097/QAI.0000000000001556. PMID: 28961677. Exclusion: Ineligible population
12. Baranek B, Wang S, Cheung AM, et al. The effect of tenofovir disoproxil fumarate on bone mineral density: a systematic review and meta-analysis. Antivir Ther. 2020;25(1):21-32. doi: 10.3851/IMP3346. PMID: 32077867. Exclusion: Systematic review or meta-analysis used as source document only to identify individual studies
13. Bauer R, Netzer E, Pintado C, et al. Coverage of Sex Acts by Event-Driven Pre-exposure Prophylaxis: A Sub-Study of the ANRS IPERGAY Trial. AIDS Behav. 2020 Nov;24(11):3244-51. doi: 10.1007/s10461-020-02890-6. PMID: 32350771. Exclusion: Ineligible outcome
14. Baum MM, Butkyavichene I, Churchman SA, et al. An intravaginal ring for the sustained delivery of tenofovir disoproxil fumarate. Int J Pharm. 2015 Nov 10;495(1):579-87. doi: 10.1016/j.ijpharm.2015.09.028. PMID: 26386138. Exclusion: Ineligible intervention
15. Bertoni M, Kennard B, Murrell D, et al. The effect of tenofovir alafenamide or tenofovir disoproxil fumarate on renal function of HIV-infected patients. JACCP J Am Coll Clin Pharm.. 2020;3(8):1592-3. doi: 10.1002/jac5.1351. Exclusion: Wrong publication type (e.g., abstract only)
16. Blumenthal J, Jain S, He F, et al. Results from a prep demonstration project for at-risk cisgender women in the us. Top Antivir Med. 2020;28(1):391-2. Exclusion: Wrong publication type (e.g., abstract only)
17. Brown ER, Hendrix CW, van der Straten A, et al. Greater dapivirine release from the dapivirine vaginal ring is correlated with lower risk of HIV-1 acquisition: a secondary analysis from a randomized, placebo-controlled trial. J Int AIDS Soc.. 2020 11;23(11):e25634. doi: 10.1002/jia2.25634. PMID: 33206462. Exclusion: Ineligible intervention
18. Bunge KE, Levy L, Szydlo DW, et al. Brief Report: Phase IIa Safety Study of a Vaginal Ring Containing Dapivirine in Adolescent Young Women. J Acquir Immune Defic Syndr. 2020 02 01;83(2):135-9. doi: 10.1097/QAI.0000000000002244. PMID: 31929401. Exclusion: Ineligible population
19. Campbell T, Clarke A, Trottier B, et al. Safety and efficacy of F/TAF and F/TDF for prep in discover participants taking F/TDF for prep at baseline. Open Forum Infect. 2020;7(SUPPL 1):S526-S7. doi: 10.1093/ofid/ofaa439.1182. Exclusion: Wrong publication type (e.g., abstract only)
20. Castillo-Mancilla JR, Searls K, Caraway P, et al. Short communication: Tenofovir diphosphate in dried blood spots as an objective measure of adherence in HIV-infected women. AIDS Res Hum Retroviruses. 2015 Apr;31(4):428-32. doi: 10.1089/aid.2014.0229. PMID: 25328112. Exclusion: Ineligible population
21. Centers for Disease Control and Prevention. HIV Risk Reduction Tool. https://hivrisk.cdc.gov/. Accessed December 3, 2021. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
22. Centers for Disease Control and Prevention, US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 Update: a clinical practice

guideline.https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf. 2017 Published March 2018. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
23. Centers for Disease Control and Prevention, US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. 2021. Published December 2021. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
24. Centers for Disease Control and Prevention, US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: clinical provider's supplement. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-provider-supplement-2021.pdf.; 2021. Accessed May 9 2022. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
25. Chan PA, Mena L, Patel R, et al. Retention in care outcomes for HIV pre-exposure prophylaxis implementation programmes among men who have sex with men in three US cities. J Int AIDS Soc. 2016;19(1):20903. doi: 10.7448/IAS.19.1.20903. PMID: 27302837. Exclusion: Ineligible study design for Key Question
26. Chan PA, Patel RR, Mena L, et al. Long-term retention in pre-exposure prophylaxis care among men who have sex with men and transgender women in the United States. J Int AIDS Soc. 2019 08;22(8):e25385. doi: https://dx.doi.org/10.1002/jia2.25385. PMID: 31423756. Exclusion: Ineligible study design for Key Question
27. Chen BA, Zhang J, Gundacker HM, et al. Phase 2a Safety, Pharmacokinetics, and Acceptability of Dapivirine Vaginal Rings in US Postmenopausal Women. Clin Infect Dis. 2019 03 19;68(7):1144-51. doi: 10.1093/cid/ciy654. PMID: 30289485. Exclusion: Ineligible population
28. Clinical Trials. Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy. 2021. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
29. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011 Aug 11;365(6):493-505. doi: 10.1056/NEJMoa1105243. PMID: 21767103. Exclusion: Ineligible intervention
30. Cohen SE, Vittinghoff E, Bacon O, et al. High interest in preexposure prophylaxis among men who have sex with men at risk for HIV infection: baseline data from the US PrEP demonstration project. J Acquir Immune Defic Syndr. 2015 Apr 1;68(4):439-48. doi: 10.1097/QAI.0000000000000479. PMID: 25501614. Exclusion: Ineligible study design for Key Question
31. Costello C, Mobley T, Arnold S, et al. 244. Retrospective Review of High-Risk Adolescents Eligible for Pre-Exposure Prophylaxis (Prep) Therapy For HIV. J Adolesc Health. 2020;66(2):S123-S4. doi: 10.1016/j.jadohealth.2019.11.247. Exclusion: Wrong publication type (e.g., abstract only)
32. Cotte L, Veyer D, Charreau I, et al. Prevalence and Incidence of Human Papillomavirus Infection in Men Having Sex With Men Enrolled in a Pre-exposure Prophylaxis Study: A Sub-study of the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales "Intervention Preventive de l'Exposition aux Risques avec et pour les hommes Gays" Trial. Clin Infect Dis. 2021 01 23;72(1):41-9. doi: 10.1093/cid/ciaa002. PMID: 31907521. Exclusion: Ineligible study design for Key Question
33. Council OD, Ruone S, Mock PA, et al. HIV-1 genetic diversity to estimate time of infection and infer adherence to preexposure prophylaxis. AIDS. 2019 12 01;33(15):2299-307. doi: 10.1097/QAD.0000000000002390. PMID: 31764095. Exclusion: Ineligible outcome
34. Cox S, Parikh U, Heaps A, et al. Ultrasensitive HIV-1 drug-resistance analysis in the discover prep trial. Top Antivir Med. 2021;29(1):154. Exclusion: Wrong publication type (e.g., abstract only)
35. Coyer L, Prins M, Davidovich U, et al. Trends in Sexual Behavior and Sexually Transmitted Infections After Initiating Human Immunodeficiency Virus Pre-Exposure Prophylaxis in Men Who Have Sex with Men from Amsterdam, the Netherlands: A Longitudinal Exposure-Matched Study. AIDS Patient Care STDS. 2022 Jun;36(6):208-18. doi: 10.1089/apc.2021.0219. PMID: 35687814. Exclusion: Ineligible study design for Key Question
36. Cranston RD, Brown E, Bauermeister J, et al. A Randomized, Double Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults (MTN-026). AIDS Res Hum Retroviruses. 2021 Sep 09;09:09. doi: 10.1089/AID.2021.0071. PMID: 34498980. Exclusion: Ineligible intervention
37. Curley CM, Rosen AO, Mistler CB, et al. Pleasure and PrEP: A Systematic Review of Studies Examining Pleasure, Sexual Satisfaction, and PrEP. J Sex Res. 2022 Sep;59(7):848-61. doi: 10.1080/00224499.2021.2012638. PMID: 35089110. Exclusion: Ineligible study design for Key Question
38. De Baetselier I, Tsoumanis A, Florence E, et al. Did Pre-exposure Prophylaxis Roll-Out Influence the Epidemic of Rectal Lymphogranuloma Venereum in Belgium? Results From the National Surveillance System. J Acquir Immune Defic Syndr. 2021 01 01;86(1):e1-e5. doi: 10.1097/QAI.0000000000002524. PMID: 33044320. Exclusion: Ineligible study design for Key Question
39. Delany-Moretlwe S, Hughes J, Bock P, et al. Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women: Interim results from HPTN 084. J Int AIDS Soc. 2021;24(SUPPL 1):8. doi: 10.1002/jia2.25659. Exclusion: Wrong publication type (e.g., abstract only)
40. Delany-Moretlwe S, Lombard C, Baron D, et al. Tenofovir 1% vaginal gel for prevention of HIV-1 infection in women in South Africa (FACTS-001): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Infect Dis. 2018 11;18(11):1241-50. doi: 10.1016/S1473-3099(18)30428-6. PMID: 30507409. Exclusion: Ineligible intervention

Appendix A5. Excluded Studies List

41. Di Ciaccio M, Sagaon-Teyssier L, Mimi M, et al. Changes in Sexual Behaviors in Men Who Have Sex with Men: A Comparison Between the Double-Blind and Open-Label Extension Phases of the ANRS-IPERGAY Trial. AIDS Behav. 2020 Nov;24(11):3093-106. doi: 10.1007/s10461-020-02864-8. PMID: 32306213. Exclusion: Ineligible outcome
42. Djomand G, Bingham T, Benech I, et al. Expansion of HIV Preexposure Prophylaxis to 35 PEPFAR-Supported Early Program Adopters, October 2016-September 2018. MMWR. 2020 Feb 28;69(8):212-5. doi: 10.15585/mmwr.mm6908a3. PMID: 32107367. Exclusion: Wrong publication type (e.g., abstract only)
43. Doblecki-Lewis S, Dosekun O, Ramgopal M, et al. Drug levels, adherence, and risks for low adherence in the discover prep study. Top Antivir Med. 2020;28(1):388. Exclusion: Wrong publication type (e.g., abstract only)
44. Drak D, McManus H, Vickers T, et al. Renal impairment in a large-scale HIV preexposure prophylaxis implementation cohort. AIDS. 2021 Nov 15;35(14):2319-26. doi: 10.1097/QAD.0000000000003035. PMID: 34310371. Exclusion: Ineligible study design for Key Question
45. Duthe JC, Bouzille G, Sylvestre E, et al. How to Identify Potential Candidates for HIV Pre-Exposure Prophylaxis: An AI Algorithm Reusing Real-World Hospital Data. Stud Health Technol Inform. 2021 May 27;281:714-8. doi: 10.3233/SHTI210265. PMID: 34042669. Exclusion: Ineligible outcome
46. E OM, Marshall L, Teljeur C, et al. Oral pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations. BMJ Open. 2022 May 11;12(5):e048478. doi: https://dx.doi.org/10.1136/bmjopen-2020-048478. PMID: 35545381. Exclusion: Systematic review or meta-analysis used as source document only to identify individual studies
47. Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. AIDS. 2016 Jul 31;30(12):1973-83. doi: 10.1097/QAD.0000000000001145. PMID: 27149090. Exclusion: Ineligible country
48. Fredericksen RJ, Mayer KH, Gibbons LE, et al. Development and Content Validation of a Patient-Reported Sexual Risk Measure for Use in Primary Care. J Gen Intern Med. 2018 Oct;33(10):1661-8. doi: 10.1007/s11606-018-4496-5. PMID: 29845470. Exclusion: Ineligible study design for Key Question
49. Freeborn K, Portillo CJ. Does pre-exposure prophylaxis for HIV prevention in men who have sex with men change risk behaviour? A systematic review. J Clin Nurs. 2018 Sep;27(17-18):3254-65. doi: 10.1111/jocn.13990. PMID: 28771856. Exclusion: Ineligible outcome
50. Gamarel KE, Chakravarty D, Neilands TB, et al. Composite Risk for HIV: A New Approach Towards Integrating Biomedical and Behavioral Strategies in Couples-Based HIV Prevention Research. Aids Behav. 2019 Jan;23(1):283-8. doi: 10.1007/s10461-018-2229-8. PMID: 30003506. Exclusion: Ineligible study design for Key Question
51. Gati Mirembe B, Cabrera MV, Cobbing M, et al. Correlates of dapivirine vaginal ring uptake among women participating in an open label extension trial-MTN-025/ HOPE. J Int AIDS Soc. 2021;24(SUPPL 1):89. doi: 10.1002/jia2.25659. Exclusion: Wrong publication type (e.g., abstract only)
52. Gauthier TP, Toro M, Carrasquillo MZ, et al. A PrEP Model Incorporating Clinical Pharmacist Encounters and Antimicrobial Stewardship Program Oversight May Improve Retention in Care. Clin Infect Dis. 2019 Jan 7;68(2):347-9. doi: 10.1093/cid/ciy640. PMID: 30107390. Exclusion: Wrong publication type (e.g., abstract only)
53. Giguere K, Behanzin L, Guedou FA, et al. PrEP Use Among Female Sex Workers: No Evidence for Risk Compensation. J Acquir Immune Defic Syndr. 2019 11 01;82(3):257-64. doi: 10.1097/QAI.0000000000002134. PMID: 31356468. Exclusion: Ineligible study design for Key Question
54. Giler RM, Bush S, Hawkins T, et al. Impact of prep and TASP on incidence of HIV diagnoses in 48 highest-burden us areas. Top Antivir Med. 2020;28(1):429. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
55. Gill K, Johnson L, Dietrich J, et al. Acceptability, safety, and patterns of use of oral tenofovir disoproxil fumarate and emtricitabine for HIV pre-exposure prophylaxis in South African adolescents: an open-label single-arm phase 2 trial. Lancet Child Adolesc Health. 2020 12;4(12):875-83. doi: 10.1016/S2352-4642(20)30248-0. PMID: 33222803. Exclusion: Ineligible population
56. Giovenco D, Pettifor A, MacPhail C, et al. Assessing risk for HIV infection among adolescent girls in South Africa: an evaluation of the VOICE risk score (HPTN 068). J Int AIDS Soc. 2019 07;22(7):e25359. doi: 10.1002/jia2.25359. PMID: 31353814. Exclusion: Ineligible population
57. Glidden DV, Amico KR, Liu AY, et al. Symptoms, side effects and adherence in the iPrEx open-label extension. Clin Infect Dis. 2016 May 1;62(9):1172-7. doi: 10.1093/cid/ciw022. PMID: 26797207. Exclusion: Ineligible study design for Key Question
58. Glidden DV, Mulligan K, McMahan V, et al. Metabolic Effects of Preexposure Prophylaxis With Coformulated Tenofovir Disoproxil Fumarate and Emtricitabine. Clin Infect Dis. 2018 07 18;67(3):411-9. doi: 10.1093/cid/ciy083. PMID: 29415175. Exclusion: Ineligible outcome
59. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis. 2014 Sep;14(9):820-9. doi: 10.1016/S1473-3099(14)70847-3. PMID: 25065857. Exclusion: Ineligible study design for Key Question
60. Gruber S, Krakower D, Menchaca JT, et al. Using electronic health records to identify candidates for human immunodeficiency virus pre-exposure prophylaxis: An application of super learning to risk prediction when the

outcome is rare. Stat Med. 2020 10 15;39(23):3059-73. doi: 10.1002/sim.8591. PMID: 32578905. Exclusion: Ineligible study design for Key Question

61. Gulick RM, Wilkin TJ, Chen YQ, et al. Phase 2 study of the safety and tolerability of maraviroc-containing regimens to prevent HIV Infection in men who have sex with men (HPTN 069/ACTG A5305). J Infect Dis. 2017 Jan 15;215(2):238-46. doi: 10.1093/infdis/jiw525. PMID: 27811319. Exclusion: Ineligible intervention
62. H. I. V. Prevention Trials Network. Evaluating the Safety and Efficacy of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women. 2021. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
63. H. I. V. Prevention Trials Network. Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV Among Adolescent Males - A Sub-study of HPTN 083. 2021. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
64. Haberer JE, Mugo N, Baeten JM, et al. PrEP as a Lifestyle and Investment for Adolescent Girls and Young Women in Sub-Saharan Africa. J Int Assoc Provid AIDS Care. 2019 Jan-Dec;18:2325958219831011. doi: 10.1177/2325958219831011. PMID: 30776954. Exclusion: Wrong publication type (e.g., abstract only)
65. Haukoos JS, White DAE, Rowan SE, et al. Development of a 2-step algorithm to identify emergency department patients for HIV pre-exposure prophylaxis. Am J Emerg Med. 2021 Oct 06;51:6-12. doi: 10.1016/j.ajem.2021.09.084. PMID: 34649008. Exclusion: Ineligible comparator
66. Hebel S, Kahn-Woods E, Enghuus C, et al. Disparities in prep uptake and adherence among cisgender women using a pharmacologic measure. Open Forum Infect. 2020;7(SUPPL 1):S517-S8. doi: 10.1093/ofid/ofaa439.1166. Exclusion: Wrong publication type (e.g., abstract only)
67. Heffron R, Mugo N, Hong T, et al. Pregnancy outcomes and infant growth among babies with in-utero exposure to tenofovir-based preexposure prophylaxis for HIV prevention. AIDS. 2018 07;32(12):1707-13. doi: 10.1097/QAD.0000000000001867. PMID: 30001244. Exclusion: Ineligible study design for Key Question
68. Hill S, Clark J, Simpson T, et al. Identifying missed opportunities for HIV pre-exposure prophylaxis at an adolescent health center in the deep south. J Adolesc Health. 2018;62(2):S38. Exclusion: Wrong publication type (e.g., abstract only)
69. Hoornenborg E, Coyer L, Achterbergh RCA, et al. Sexual behaviour and incidence of HIV and sexually transmitted infections among men who have sex with men using daily and event-driven pre-exposure prophylaxis in AMPrEP: 2 year results from a demonstration study. Lancet HIV. 2019 Jul;6(7):e447-e55. doi: 10.1016/s2352-3018(19)30136-5. PMID: 31178284. Exclusion: Ineligible study design for Key Question
70. Hoornenborg E, Coyer L, Boyd A, et al. High incidence of HCV in HIV-negative men who have sex with men using pre-exposure prophylaxis. J Hepatol. 2020 05;72(5):855-64. doi: 10.1016/j.jhep.2019.11.022. PMID: 31862485. Exclusion: Ineligible study design for Key Question
71. Hosek SG, Landovitz RJ, Kapogiannis B, et al. Safety and feasibility of antiretroviral preexposure prophylaxis for adolescent men who have sex with men aged 15 to 17 years in the United States. JAMA Pediatr. 2017 Sep 05doi: 10.1001/jamapediatrics.2017.2007. PMID: 28873128. Exclusion: Ineligible study design for Key Question
72. Hosek SG, Rudy B, Landovitz R, et al. An HIV preexposure prophylaxis demonstration project and safety study for young MSM. J Acquir Immune Defic Syndr. 2017 Jan 01;74(1):21-9. doi: 10.1097/qai.0000000000001179. PMID: 27632233. Exclusion: Ineligible study design for Key Question
73. Hoth AB, Shafer C, Dillon DB, et al. Iowa TelePrEP: A Public-Health-Partnered Telehealth Model for Human Immunodeficiency Virus Preexposure Prophylaxis Delivery in a Rural State. Sex Transm Dis. 2019;46(8):507-12. PMID: 31295217. Exclusion: Ineligible comparator
74. Huang X, Hou J, Song A, et al. Efficacy and safety of oral TDF-based pre-exposure prophylaxis for men who have sex with men: a systematic review and meta-analysis. Front Pharmacol. 2018;9:799. doi: 10.3389/fphar.2018.00799. PMID: 30233355. Exclusion: Systematic review or meta-analysis used as source document only to identify individual studies
75. Huhn GD, Wilkin A, Mussini C, et al. Week 96 subgroup analyses of the phase 3, randomized AMBER and EMERALD trials evaluating the efficacy and safety of the once daily darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) single-tablet regimen in antiretroviral treatment (ART)-naive and -experienced, virologically-suppressed adults living with HIV-1. HIV Res Clin Pract. 2020 Dec;21(6):151-67. doi: 10.1080/25787489.2020.1844520. PMID: 33528318. Exclusion: Ineligible intervention
76. Irungu E, Mugwanya K, Mugo N, et al. Integrating oral pre-exposure prophylaxis services to public HIV care clinics in Kenya: Results from a pragmatic stepped-wedge randomized trial. J Int AIDS Soc. 2021;24(SUPPL 1):138-9. doi: 10.1002/jia2.25659. Exclusion: Wrong publication type (e.g., abstract only)
77. Joseph Davey DL, Pintye J, Baeten JM, et al. Emerging evidence from a systematic review of safety of pre-exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading? J Int AIDS Soc. 2020 01;23(1):e25426. doi: 10.1002/jia2.25426. PMID: 31912985. Exclusion: Systematic review or meta-analysis used as source document only to identify individual studies
78. Kahle EM, Hughes JP, Lingappa JR, et al. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1-serodiscordant couples for targeted HIV-1 prevention. J Acquir Immune Defic Syndr. 2013 Mar 1;62(3):339-47. doi: 10.1097/QAI.0b013e31827e622d. PMID: 23187945. Exclusion: Poor quality

79. Kamis K, Scott K, Gardner E, et al. Same-day HIV pre-exposure prophylaxis (PrEP) initiation during drop-in std clinic appointments is a safe, feasible, and effective method to engage patients at risk for HIV in PrEP care. Open Forum Infect. 2018;5:S20. doi: 10.1093/ofid/ofy209.044. Exclusion: Wrong publication type (e.g., abstract only)
80. Kapadia SN, Wu C, Mayer KH, et al. No change in health-related quality of life for at-risk U.S. women and men starting HIV pre-exposure prophylaxis (PrEP): Findings from HPTN 069/ACTG A5305. PLoS ONE [Electronic Resource]. 2018;13(12):e0206577. doi: 10.1371/journal.pone.0206577. PMID: 30586364. Exclusion: Ineligible comparator
81. Keen P, Hammoud MA, Bourne A, et al. Use of HIV Pre-exposure Prophylaxis (PrEP) Associated With Lower HIV Anxiety Among Gay and Bisexual Men in Australia Who Are at High Risk of HIV Infection: Results From the Flux Study. J Acquir Immune Defic Syndr. 2020 Feb 1;83(2):119-25. doi: 10.1097/qai.0000000000002232. PMID: 31935203. Exclusion: Ineligible study design for Key Question
82. Keller MJ, Wood L, Billingsley JM, et al. Tenofovir disoproxil fumarate intravaginal ring for HIV pre-exposure prophylaxis in sexually active women: a phase 1, single-blind, randomised, controlled trial. Lancet HIV. 2019 08;6(8):e498-e508. doi: 10.1016/S2352-3018(19)30145-6. PMID: 31320290. Exclusion: Ineligible intervention
83. Koester K, Amico RK, Gilmore H, et al. Risk, safety and sex among male PrEP users: time for a new understanding. Cult Health Sex. 2017 Dec;19(12):1301-13. doi: 10.1080/13691058.2017.1310927. PMID: 28415911. Exclusion: Ineligible study design for Key Question
84. Kuo I, Olsen H, Patrick R, et al. Willingness to use HIV pre-exposure prophylaxis among community-recruited, older people who inject drugs in Washington, DC. Drug Alcohol Depend. 2016 Jul 1;164:8-13. doi: 10.1016/j.drugalcdep.2016.02.044. PMID: 27177804. Exclusion: Ineligible outcome
85. Kusemererwa S, Abaasa A, Kabarambi A, et al. Assessment of risk compensation following use of the dapivirine vaginal ring in southwestern Uganda. Sex Transm Infect. 2021 Feb 04;04:04. doi: 10.1136/sextrans-2020-054718. PMID: 33542153. Exclusion: Ineligible study design for Key Question
86. Lambert DN, Swartzendruber A. 69. Knowledge, Attitudes, and Willingness to Use Pre-Exposure Hiv Prophylaxis (PrEP) Among an Online Recruited Sample of Sexually Active Adolescent Substance Users in Southern HIV Hotspots. J Adolesc Health. 2021;68(2):S37-S8. doi: 10.1016/j.jadohealth.2020.12.078. Exclusion: Wrong publication type (e.g., abstract only)
87. Landovitz RJ, Beymer M, Kofron R, et al. Plasma tenofovir levels to support adherence to TDF/FTC preexposure prophylaxis for HIV prevention in MSM in Los Angeles, California. J Acquir Immune Defic Syndr. 2017 Dec 15;76(5):501-11. doi: 10.1097/QAI.0000000000001538. PMID: 28902074. Exclusion: Ineligible study design for Key Question
88. Landovitz RJ, Li S, Eron JJ, Jr., et al. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. Lancet HIV. 2020 07;7(7):e472-e81. doi: 10.1016/S2352-3018(20)30106-5. PMID: 32497491. Exclusion: Ineligible population
89. Landovitz RJ, Li S, Grinsztejn B, et al. Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial. PLoS Med. 2018 11;15(11):e1002690. doi: 10.1371/journal.pmed.1002690. PMID: 30408115. Exclusion: Ineligible population
90. Landovitz RJ, Zangeneh SZ, Chau G, et al. Cabotegravir Is Not Associated With Weight Gain in Human Immunodeficiency Virus-uninfected Individuals in HPTN 077. Clin Infect Dis. 2020 01 02;70(2):319-22. doi: 10.1093/cid/ciz439. PMID: 31125395. Exclusion: Ineligible population
91. Lazarus G, Wangsaputra VK, Christianto, et al. Safety and pharmacokinetic profiles of long-acting injectable antiretroviral drugs for HIV-1 pre-exposure prophylaxis: a systematic review and meta-analysis of randomized trials. Front Pharmacol. 2021;12:664875. doi: 10.3389/fphar.2021.664875. PMID: 34305587. Exclusion: Systematic review or meta-analysis used as source document only to identify individual studies
92. Liegeon G, Antoni G, Pialoux G, et al. Changes in kidney function among men having sex with men starting on demand tenofovir disoproxil fumarate - emtricitabine for HIV pre-exposure prophylaxis. Journal of the International AIDS Soc. 2020 02;23(2):e25420. doi: 10.1002/jia2.25420. PMID: 32086878. Exclusion: Ineligible outcome
93. Liu AY, Cohen SE, Vittinghoff E, et al. Preexposure prophylaxis for HIV infection integrated with municipal- and community-based sexual health services. JAMA Intern Med. 2016 Jan;176(1):75-84. doi: 10.1001/jamainternmed.2015.4683. PMID: 26571482. Exclusion: Ineligible study design for Key Question
94. Liu AY, Dominguez Islas C, Gundacker H, et al. Phase 1 pharmacokinetics and safety study of extended duration dapivirine vaginal rings in the United States. J Int AIDS Soc. 2021 06;24(6):e25747. doi: 10.1002/jia2.25747. PMID: 34118115. Exclusion: Ineligible comparator
95. Marcus JL, Levine K, Grasso C, et al. HIV Preexposure Prophylaxis as a Gateway to Primary Care. Am J Public Health. 2018 Oct;108(10):1418-20. doi: 10.2105/ajph.2018.304561. PMID: 30024802. Exclusion: Ineligible study design for Key Question
96. Markowitz M, Frank I, Grant RM, et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial. Lancet HIV. 2017 Aug;4(8):e331-e40. doi: 10.1016/s2352-3018(17)30068-1. PMID: 28546090. Exclusion: Ineligible population
97. Martin M, Vanichseni S, Suntharasamai P, et al. Factors associated with the uptake of and adherence to HIV pre-exposure prophylaxis in people who have injected drugs: an observational, open-label extension of the Bangkok

Appendix A5. Excluded Studies List

Tenofovir Study. Lancet HIV. 2017 Feb;4(2):e59-e66. doi: 10.1016/s2352-3018(16)30207-7. PMID: 27866873. Exclusion: Ineligible study design for Key Question

98. Marzinke M, Grinsztejn B, Fogel J, et al. Laboratory analysis of HIV infections in HPTN 083: Injectable cab for prep. Top Antivir Med. 2021;29(1):45-6. Exclusion: Wrong publication type (e.g., abstract only)
99. McManus H, Grulich AE, Amin J, et al. Comparison of Trends in Rates of Sexually Transmitted Infections Before vs After Initiation of HIV Preexposure Prophylaxis Among Men Who Have Sex With Men. JAMA Netw Open. 2020 Dec 1;3(12):e2030806. doi: 10.1001/jamanetworkopen.2020.30806. PMID: 33355675. Exclusion: Ineligible study design for Key Question
100. Mizushima D, Takano M, Uemura H, et al. Prophylactic effect of PrEP against HBV infection among MSM. Top Antivir Med. 2020;28(1):386-7. Exclusion: Wrong publication type (e.g., abstract only)
101. Montaño MA, Dombrowski JC, Dasgupta S, et al. Changes in Sexual Behavior and STI Diagnoses Among MSM Initiating PrEP in a Clinic Setting. AIDS Behav. 2019 Feb;23(2):548-55. doi: 10.1007/s10461-018-2252-9. PMID: 30117076. Exclusion: Ineligible study design for Key Question
102. Montgomery MC, Oldenburg CE, Nunn AS, et al. Adherence to pre-exposure prophylaxis for HIV prevention in a clinical setting. PLoS One. 2016;11(6):e0157742. doi: 10.1371/journal.pone.0157742. PMID: 27333000. Exclusion: Ineligible study design for Key Question
103. Moyer VA, U. S. Preventive Services Task Force. Screening for HIV: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2013 Jul 2;159(1):51-60. PMID: 23698354. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
104. Murewanhema G, Malisheni M, Takah NF. The effectiveness of tenofovir-based pre-exposure prophylaxis for prevention of HIV acquisition among sub-Saharan African women at high risk: a systematic review. Pan Afr Med J. 2021;38:308. doi: 10.11604/pamj.2021.38.308.26014. PMID: 34178226. Exclusion: Systematic review or meta-analysis used as source document only to identify individual studies
105. Murray MI, Markowitz M, Frank I, et al. Satisfaction and acceptability of cabotegravir long-acting injectable suspension for prevention of HIV: Patient perspectives from the ECLAIR trial. HIV Clin Trial. 2018 08;19(4):129-38. doi: 10.1080/15284336.2018.1511346. PMID: 30445896. Exclusion: Ineligible population
106. Musekiwa A, Fernando NB, Abariga SA. Effectiveness of vaginal microbicides in preventing HIV transmission. Trop Med Int Health. 2020 07;25(7):790-802. doi: 10.1111/tmi.13401. PMID: 32306503. Exclusion: Systematic review or meta-analysis used as source document only to identify individual studies
107. National Institute of Allergy and Infectious Diseases. Evaluating the Safety and Efficacy of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women. clinicaltrials.gov; 2017. https://clinicaltrials.gov/ct2/show/NCT03164564. Accessed February 2, 2018. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
108. Nel A, van Niekerk N, Van Baelen B, et al. Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study. Lancet HIV. 2021 Feb;8(2):e77-e86. doi: 10.1016/s2352-3018(20)30300-3. PMID: 33539761. Exclusion: Ineligible study design for Key Question
109. Nel A, Van Niekerk N, Van Baelen B, et al. HIV incidence and adherence in dream: An open-label trial of dapivirine vaginal ring. Top Antivir Med. 2018;26:61s. Exclusion: Wrong publication type (e.g., abstract only)
110. Network HIVPT. A phase 3 double blind safety and efficacy study of long-acting injectable cabotegravir compared to daily oral TDF/FTC for pre-exposure prophylaxis in HIV-uninfected women. 2020. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
111. Ngure K, Thuo N, Ogello V, et al. Dynamic Perceived HIV Risk and Sexual Behaviors Among Young Women Enrolled in a PrEP Trial in Kenya: A Qualitative Study. Front Reprod Health. 2021;3:637869. doi: 10.3389/frph.2021.637869. PMID: 36304002. Exclusion: Ineligible outcome
112. Nguyen AC, Young LE, Beymer MR, et al. Developing targeted HIV risk predictors for young black men who have sex with men: a two-city comparative study. Int J STD AIDS. 2020 03;31(4):335-44. doi: 10.1177/0956462419886472. PMID: 32089091. Exclusion: Ineligible study design for Key Question
113. Nguyen VK, Greenwald ZR, Trottier H, et al. Incidence of sexually transmitted infections before and after preexposure prophylaxis for HIV. AIDS. 2018 02 20;32(4):523-30. doi: 10.1097/QAD.0000000000001718. PMID: 29239887. Exclusion: Ineligible comparator
114. Nickolas TL, Barasch J, Mugwanya KK, et al. Kidney injury biomarkers during exposure to tenofovir-based preexposure prophylaxis. AIDS. 2021 06 01;35(7):1147-9. doi: 10.1097/QAD.0000000000002865. PMID: 33710023. Exclusion: Wrong publication type (e.g., abstract only)
115. Nickolas TL, Yin MT, Hong T, et al. Impact of Tenofovir-Based Pre-exposure Prophylaxis on Biomarkers of Bone Formation, Bone Resorption, and Bone Mineral Metabolism in HIV-Negative Adults. Open Forum Infect. 2019 Oct;6(10):ofz338. doi: 10.1093/ofid/ofz338. PMID: 31660332. Exclusion: Ineligible outcome
116. Obiero J, Ogongo P, Mwethera PG, et al. Topical microbicides for preventing sexually transmitted infections. Cochrane Database Syst Rev. 2021 03 13;3:CD007961. doi: 10.1002/14651858.CD007961.pub3. PMID: 33719075. Exclusion: Systematic review or meta-analysis used as source document only to identify individual studies
117. Ogbuagu O, Podzamczer D, Salazar LC, et al. Longer-term safety of F/TAF and F/TDF for HIV PrEP: Discover trial week-96 results. Top Antivir Med. 2020;28(1):31-2. Exclusion: Wrong publication type (e.g., abstract only)

Appendix A5. Excluded Studies List

118. Ong JJ, Baggaley RC, Wi TE, et al. Global epidemiologic characteristics of sexually transmitted infections among individuals using preexposure prophylaxis for the prevention of HIV infection: a systematic review and meta-analysis. JAMA Netw Open. 2019 12 02;2(12):e1917134. doi: 10.1001/jamanetworkopen.2019.17134. PMID: 31825501. Exclusion: Ineligible outcome
119. Parsons JT, Rendina HJ, Lassiter JM, et al. Uptake of HIV pre-exposure prophylaxis (PrEP) in a national cohort of gay and bisexual men in the United States: The motivational PrEP cascade. J Acquir Immune Defic Syndr. 2017:285-92. doi: 10.1097/QAI.0000000000001251. PMID: 28187084. Exclusion: Ineligible outcome
120. Pilkington V, Hill A, Hughes S, et al. How safe is TDF/FTC as PrEP? A systematic review and meta-analysis of the risk of adverse events in 13 randomised trials of PrEP. J Virus Erad. 2018 Oct 01;4(4):215-24. PMID: 30515300. Exclusion: Systematic review or meta-analysis used as source document only to identify individual studies
121. Pilkington V, Hughes SL, Pepperrell T, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate: an updated meta-analysis of 14 894 patients across 14 trials. AIDS. 2020 12 01;34(15):2259-68. doi: 10.1097/QAD.0000000000002699. PMID: 33048869. Exclusion: Ineligible intervention
122. Pintye J, Drake AL, Kinuthia J, et al. A risk assessment tool for identifying pregnant and postpartum women who may benefit from preexposure prophylaxis. Clin Infect Dis. 2017 Mar 15;64(6):751-8. doi: 10.1093/cid/ciw850. PMID: 28034882. Exclusion: Poor quality
123. Post F, Spinner C, Coll P, et al. DISCOVER in Europe: A sub-analysis of the phase 3 randomized, controlled trial of daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV pre-exposure prophylaxis (PrEP). HIV Med. 2019;20:243-4. doi: 10.1111/hiv.12815. Exclusion: Wrong publication type (e.g., abstract only)
124. Quinn KG, Christenson E, Sawkin MT, et al. The Unanticipated Benefits of PrEP for Young Black Gay, Bisexual, and Other Men Who Have Sex with Men. AIDS Behav. 2020 May;24(5):1376-88. doi: 10.1007/s10461-019-02747-7. PMID: 31768688. Exclusion: Ineligible study design for Key Question
125. Reddy K, Kelly C, Brown ER, et al. Use of the dapivirine vaginal ring and effect on cervical cytology abnormalities. AIDS. 2020 03 15;34(4):559-67. doi: 10.1097/QAD.0000000000002451. PMID: 31764068. Exclusion: Ineligible outcome
126. Refugio ON, Kimble MM, Silva CL, et al. Brief Report: PrEPTECH: A Telehealth-Based Initiation Program for HIV Pre-exposure Prophylaxis in Young Men of Color Who Have Sex With Men. A Pilot Study of Feasibility. J Acquir Immune Defic Syndr. 2019 Jan 1;80(1):40-5. doi: 10.1097/qai.0000000000001873. PMID: 30272632. Exclusion: Ineligible comparator
127. Ridgway JP, Almirol EA, Bender A, et al. Which Patients in the Emergency Department Should Receive Preexposure Prophylaxis? Implementation of a Predictive Analytics Approach. AIDS Patient Care STDS. 2018 05;32(5):202-7. doi: 10.1089/apc.2018.0011. PMID: 29672136. Exclusion: Ineligible comparator
128. Roberts ST, Haberer J, Celum C, et al. Intimate partner violence and adherence to HIV pre-exposure prophylaxis (PrEP) in African women in HIV serodiscordant relationships: A prospective cohort study. J Acquir Immune Defic Syndr. 2016 Nov 01;73(3):313-22. doi: 10.1097/qai.0000000000001093. PMID: 27243900. Exclusion: Ineligible study design for Key Question
129. Roux P, Fressard L, Suzan-Monti M, et al. Is on-Demand HIV Pre-exposure Prophylaxis a Suitable Tool for Men Who Have Sex With Men Who Practice Chemsex? Results From a Substudy of the ANRS-IPERGAY Trial. J Acquir Immune Defic Syndr. 2018 10 01;79(2):e69-e75. doi: 10.1097/QAI.0000000000001781. PMID: 30212434. Exclusion: Ineligible population
130. Sewell WC, Powell VE, Ball-Burack M, et al. Brief Report: "I Didn't Really Have a Primary Care Provider Until I Got PrEP": Patients' Perspectives on HIV Preexposure Prophylaxis as a Gateway to Health Care. J Acquir Immune Defic Syndr. 2021 Sep 01;88(1):31-5. doi: https://dx.doi.org/10.1097/QAI.0000000000002719. PMID: 34397743. Exclusion: Ineligible study design for Key Question
131. Songtaweesin WN, Kawichai S, Phanuphak N, et al. Youth-focused strategies to promote adherence to pre-exposure prophylaxis among adolescent men who have sex with men and transgender women at-risk for HIV in Thailand. J Int AIDS Soc. 2020;23(SUPPL 4)doi: 10.1002/jia2.25547. Exclusion: Wrong publication type (e.g., abstract only)
132. Thurman A, Brache V, Ouattara AL, et al. Randomized, placebo controlled phase I trial of safety, pharmacokinetics, pharmacodynamics and acceptability of a multipurpose prevention vaginal ring containing tenofovir and levonorgestrel. J Int AIDS Soc. 2021;24(Suppl. 1):16-7. PMID: CN-02252156. Exclusion: Wrong publication type (e.g., abstract only)
133. Traeger MW, Cornelisse VJ, Asselin J, et al. Association of HIV Preexposure Prophylaxis With Incidence of Sexually Transmitted Infections Among Individuals at High Risk of HIV Infection. JAMA. 2019 Apr 9;321(14):1380-90. doi: 10.1001/jama.2019.2947. PMID: 30964528. Exclusion: Ineligible study design for Key Question
134. Traeger MW, Guy R, Asselin J, et al. Real-world trends in incidence of bacterial sexually transmissible infections among gay and bisexual men using HIV pre-exposure prophylaxis (PrEP) in Australia following nationwide PrEP implementation: an analysis of sentinel surveillance data. Lancet Infect Dis. 2022 Aug;22(8):1231-41. doi: 10.1016/s1473-3099(22)00175-x. PMID: 35643090. Exclusion: Ineligible study design for Key Question
135. Traeger MW, Schroeder SE, Wright EJ, et al. Effects of pre-exposure prophylaxis for the prevention of HIV infection on sexual risk behavior in men who have sex with men: a systematic review and meta-analysis. Clin Infect Dis. 2018 Mar 2;67(5):676-86. doi: 10.1093/cid/ciy182. PMID: 29509889. Exclusion: Ineligible study design for Key Question

Appendix A5. Excluded Studies List

136. U.S. Food & Drug Administration. FDA Approves First Injectable Treatment for HIV Pre-Exposure Prevention. December 20, 2021.; 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-first-injectable-treatment-hiv-pre-exposure-prevention. Accessed December 20 2021. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
137. van Epps P, Maier M, Lund B, et al. Medication adherence in a nationwide cohort of veterans initiating pre-exposure prophylaxis (PrEP) to prevent HIV infection. J Acquir Immune Defic Syndr. 2018 Mar 01;77(3):272-8. doi: 10.1097/QAI.0000000000001598. PMID: 29210835. Exclusion: Ineligible study design for Key Question
138. Veloso VG, Vega-Ramírez EH, Hoagland B, et al. Safety, early continuation and adherence of same day PrEP initiation among MSM and TGW in Brazil, Mexico and Peru: The ImPrEP Study. J Int AIDS Soc. 2019;22doi: 10.1002/jia2.25327. Exclusion: Wrong publication type (e.g., abstract only)
139. Volk JE, Marcus JL, Phengrasamy T, et al. Incident hepatitis C virus infections among users of HIV preexposure prophylaxis in a clinical practice setting. Clin Infect Dis. 2015 Jun 1;60(11):1728-9. doi: 10.1093/cid/civ129. PMID: 25694649. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
140. Ware C, Sparks A, Levy M, et al. Null effect of financial incentives or social media support on PrEP adherence in a randomized controlled trial of young men who have sex with men of colour. J Int AIDS Soc. 2021;24(SUPPL 1):131. doi: 10.1002/jia2.25659. Exclusion: Wrong publication type (e.g., abstract only)
141. Watson DL, Shaw PA, Petsis DT, et al. Hiv prep counseling among black youth diagnosed with bacterial sti, 2014-2019. Top Antivir Med. 2021;29(1):282. Exclusion: Wrong publication type (e.g., abstract only)
142. Werner RN, Gaskins M, Nast A, et al. Incidence of sexually transmitted infections in men who have sex with men and who are at substantial risk of HIV infection - A meta-analysis of data from trials and observational studies of HIV pre-exposure prophylaxis. PLoS ONE. 2018;13(12):e0208107. doi: 10.1371/journal.pone.0208107. PMID: 30507962. Exclusion: Ineligible study design for Key Question
143. Whitfield THF, Jones SS, Wachman M, et al. The Impact of Pre-Exposure Prophylaxis (PrEP) Use on Sexual Anxiety, Satisfaction, and Esteem Among Gay and Bisexual Men. J Sex Res. 2019 Nov-Dec;56(9):1128-35. doi: 10.1080/00224499.2019.1572064. PMID: 30777781. Exclusion: Ineligible study design for Key Question
144. Wirtz AL, Weir BW, Mon SHH, et al. Testing the Effectiveness and Cost-Effectiveness of a Combination HIV Prevention Intervention Among Young Cisgender Men Who Have Sex With Men and Transgender Women Who Sell or Exchange Sex in Thailand: Protocol for the Combination Prevention Effectiveness Study. JMIR Res Protoc. 2020 Jan 27;9(1):e15354. doi: 10.2196/15354. PMID: 32012113. Exclusion: Ineligible study design for Key Question
145. World Health Organization. WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. 2017. http://www.who.int/hiv/pub/prep/prep-implementation-tool-policy/en/. Accessed 12.11.18. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
146. World Health Organization. PrEP Implementation Tool. 2021. https://www.who.int/tools/prep-implementation-tool. Accessed September 14, 2021. Exclusion: Not a study (letter, editorial, non-systematic review article, no original data)
147. Yacoub R, Nadkarni GN, Weikum D, et al. Elevations in serum creatinine with tenofovir-based HIV pre-exposure prophylaxis: A meta-analysis of randomized placebo-controlled trials. J Acquir Immune Defic Syndr. 2016 Apr 1;71(4):e115-8. doi: 10.1097/QAI.0000000000000906. PMID: 26627105. Exclusion: Ineligible country

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of ratings based on above criteria:
Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions
Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies
Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies

Case-Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls, with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Definition of ratings based on above criteria:
Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; accurate diagnostic procedures and measurements applied equally to cases and controls; and appropriate attention to confounding variables
Fair: Recent, relevant, and without major apparent selection or diagnostic workup bias, but response rate less than
80 percent or attention to some but not all important confounding variables
Poor: Major selection or diagnostic workup bias, response rate less than 50 percent, or inattention to confounding variables

RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For cohort studies: Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts

- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to treat analysis for RCTs

Definition of ratings based on above criteria:
Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.
Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.
Poor: Studies are graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies

Criteria:
- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria:
Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease
Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients

Appendix A6. Criteria for Assessing Internal Validity of Individual Studies

Poor: Has a fatal flaw, such as: Uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients

Source: U.S. Preventive Services Task Force Procedure Manual. Accessed at https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual/procedure-manual-appendix-vi-criteria-assessing-internal-validity-individual-studies

Appendix A7. Expert Reviewers of the Draft Report

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Anonymous Reviewer

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Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
Bangkok Tenofovir Study Choopanya, 2013[53] and Martin, 2015[153] *Oral PrEP Versus Placebo or No PrEP*	Double-blind RCT	17 drug treatment clinics Thailand	9,665 person-years (mean, 4.0 years [SD, 2.1], maximum, 6.9 years)	A. Tenofovir 300 mg once daily (n=1,204) B. Placebo (n=1,209) Participants could choose directly observed therapy or monthly take-home prescriptions, and switch at monthly followup appointments	HIV-uninfected, ages 20 to 60 years, reporting PWID in past 12 months Excluded: HBsAg-infected, pregnant or breastfeeding	A vs. B: Ages 20 to 29 years: 43% vs. 43% Ages 30 to 39 years: 38% vs. 37% Ages 40 to 49 years: 15% vs. 15% Ages 50 to 60 years: 5% vs. 5% Male: 80% vs. 80% Education ≤6 years: 47% vs. 49% Education 7 to 12 years: 45% vs. 41% Education >12 years: 8% vs. 10% Current methadone treatment: 21% vs. 22% Injected in past 12 weeks: 62% vs. 64% Heroin use: 22% vs 22% Methamphetamine use: 35% vs. 32% Midazolam use: 23% vs. 24% Shared needles in past 12 weeks: 19% vs. 18% >1 Sexual partner in past 12 weeks: 21% vs. 23% Sex with casual partner in past 12 weeks: 36% vs. 40%	Screened: 4,094 Eligible: NR Enrolled: 2,413 Analyzed: 2,411 Withdrawals: 0/1,204 vs. 2/1,209 excluded due to newly HIV-infected at enrollment Loss to followup: 34% (409/1,204) vs. 34% (410/1,207)	Good	U.S. Centers for Disease Control and Prevention; Bangkok Metropolitan Administration
Bangkok Tenofovir Study Martin, 2014[152] *Oral PrEP Versus Placebo or No PrEP*	Same as Choopanya 2013	Same as Choopanya 2013	5 years	Same as Choopanya 2013	Same as Choopanya 2013 In addition, had a creatinine clearance rate ≥60 mL/min by the Cockcroft-Gault formula	Same as Choopanya 2013	Same as Choopanya 2013	Same as Choop-anya 2013	Same as Choopanya 2013

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
FEM-PrEP Van Damme, 2012[172] and Agot, 2015[128] *Oral PrEP Versus Placebo or No PrEP*	RCT	4 sites Kenya, South Africa, and Tanzania	1 year	A. Oral TDF-FTC 300/200 mg once daily (n=1,062) B. Placebo, once daily (n=1,058)	Ages 18 to 35 years; HIV-uninfected; not pregnant/breastfeeding; willing to use an effective nonbarrier contraceptive method; able to swallow a vitamin tablet similar to study tablet; able to give informed consent; high-risk for HIV (≥1 vaginal sex acts in previous 2 weeks; or >1 sex partner in previous month); women in good health Exclusion criteria: HBsAg-infected; evidence of abnormal hepatic/renal function	A vs. B Age (mean): 24 vs. 24 years Female: 100% Race: NR Education (mean): 10 vs. 10 years Married: 30% vs. 32% Ever pregnant: 71% vs. 74% Has primary partner: 99% vs. 99% Sex for money/gifts with nonprimary partner in previous 4 weeks: 13% vs. 12% Sex without condom in past week (mean): 1.9 vs. 1.9 Gonorrhea: 6% vs. 6% Chlamydia: 15% vs. 13% Trichomoniasis: 7% vs. 5% Syphilis: 2% vs. 1% Bacterial vaginosis: 43% vs. 41% HBsAb-infected: 21% vs. 21%	Screened: 4,163 Eligible: 2,120 Enrolled: 2,120 Analyzed: 2,056 Withdrawals: 6% (59/1,024) vs. 5% (118/1,032) Loss to followup: 14% (148/1,024) vs. 11% (118/1,032)	Good	U.S. Agency for International Development; Gates Foundation; Gilead Sciences provided study drugs
FEM-PrEP Mandala, 2014[149] *Oral PrEP Versus Placebo or No PrEP*	Same as Van Damme 2012	Same as Van Damme 2012	1 year	Same as Van Damme 2012	Same as Van Damme 2012	Same as Van Damme 2012	Analyzed: 2,058 Also analyzed random subcohort of 150 assigned TDF-FTC (50 from each site where HIV infections occurred)	Same as Van Damme 2012	Same as Van Damme 2012
Grohskopf, 2013[52] (CDC Safety Study) *Oral PrEP Versus Placebo or No PrEP*	RCT	3 sites U.S.	2 years	A. TDF, 300 mg orally daily, immediately or after a 9-month delay (n=201) B. Placebo, immediately or after a 9-month delay (n=199)	Healthy biological males, ages 18 to 60 years, who reported anal sex with another man in the preceding 12 months, HIV-1-uninfected, calculated Cockcroft-Gault creatinine clearance ≥70 mL/min, HBsAg-uninfected, normal hematologic, biochemistry, and urinalysis profiles	A vs. B Age (mean): 38 vs. 37 years Male: 100% vs. 100% White: 79.6% vs. 66.8% African American: 23% vs. 37% Asian/Pacific Islander: 10% vs. 4% Other race: 8% vs. 25% Male partners in last 3 months, median: 4 vs. 4 Unprotected receptive anal sex with man in last 3 months: 29.9% vs. 32.7%	Screened: 679 Eligible: NR Enrolled: 400 Analyzed: 331 Withdrawals: NR Loss to followup: NR	Good	U.S. Department of Health and Human Services, Centers for Disease Control and Prevention

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
Liu, 2011[148] (companion to Grohskopf, 2013) *Oral PrEP Versus Placebo or No PrEP*	Cohort from larger RCT	1 site San Francisco	Same as Grohskopf 2013	Same as Grohskopf 2013	Same as Grohskopf 2013	A vs. B Age (median): 40 vs. 42 years White: 81% vs. 74% Black: 5% vs. 4% Asian/Pacific Islander: 7% vs. 3%, p=0.10 Latinx/Hispanic: 5% vs. 10% Other race: 1% vs. 8% Heavy alcohol use in past 3 months: 4% vs. 6% Any recreational drug use in past 3 months: 44% vs. 52%	Screened: 359 Enrolled: 200 Analyzed: 184 (94 vs. 90; had at least 1 followup DEXA scan)	Same as Grohs-kopf 2013	Same as Grohskopf 2013
IAVI Kenya Study Mutua, 2012[67] *Oral PrEP Versus Placebo or No PrEP*	RCT	2 sites Kenya	4 months	A. Daily TDF-FTC 300/200 mg (n=24) B. Intermittent (Monday, Friday and within 2 hours postcoital, not to exceed 1 dose/day) TDF-FTC (n=24) C. Daily placebo (n=12) D. Intermittent placebo (n=12)	HIV-uninfected MSM and female sex workers ages 18 to 49 years who reported at least one of the following risk criteria in the past 3 months: current or previous STI, multiple episodes of unprotected vaginal or anal sex, or engaging in transactional sex Excluded: chronic HBV infection or with circulation <80 mL/min and pregnant or lactating mothers	A vs. B vs. C vs. D Age (mean): 26 vs. 26 vs. 27 vs. 28 years Female: 12% vs. 0% vs. 8% vs. 8% Race: NR Illicit drug use: 33% vs. 42% vs. 58% vs. 42% Drank alcohol prior to sex: 38% vs. 58% vs. 42% vs. 50% Genital sore or discharge: 4% vs. 0% vs. 0% vs. 8% Condom use with new male partner: 85% vs. 100% vs. 83% vs. 100% Condom use with new female partner: 100% vs. 100% vs. 100% vs. 100% Gave/received money/gifts for sex: 74% vs. 63% vs. 73% vs. 58% Engaged in group sex: 4% vs. 0% vs. 0% vs. 0% Receptive anal sex: 59% vs. 71% vs. 45% vs. 75% Insertive anal sex: 65% vs. 61% vs. 80% vs. 55% Number of sex partners in past month (median): 3 vs. 3 vs. 3 vs. 3	Screened: 107 Eligible: 78 Enrolled: 72 Withdrawals: 0 Lost to followup: 6% (4/72)	Good	IAVI, study medication provided by Gilead Science

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
IAVI Uganda Study Kibengo, 2013[68] *Oral PrEP Versus Placebo or No PrEP*	RCT	Single center Uganda	4 months	A. Daily TDF-FTC 300/200 mg (n=24) B. Intermittent (Monday, Friday and within 2 hours postcoital, not to exceed 1 dose/day) TDF-FTC 300/200 mg (n=24) C. Daily placebo (n=12) D. Intermittent placebo (n=12)	HIV-uninfected ages 18 to 49 years in serodiscordant relationships who had reported any episodes of unprotected vaginal sex with their partner in the past 3 months and the infected partner is not using ART Excluded: chronic HBV infection or with creatinine clearance <80 mL/min or pregnant or lactating mothers	A vs. B vs. C vs. D Age (mean): 33 vs. 33 vs. 33 vs. 33 years Female: 50% vs. 46% vs. 67% vs. 42% Race: NR Illicit drug use: 2% vs. 0% vs. 3% vs. 0% Alcohol use prior to sex: 8% vs. 8% vs. 17% vs. 0% Presence of genital sore or discharge: 8% vs. 4% vs. 25% vs. 17% Number of sex partners in previous month: 1: 96% vs. 71% vs. 100% vs. 67% 2: 4% vs. 25% vs. 0% vs. 33% 3: 0% vs. 4% vs. 0% vs. 0% Number of HIV- infected partners past month: 0: 0% vs. 0% vs. 0% vs. 8% 1: 100% vs. 96% vs. 100% vs. 92% 2: 0% vs. 4% vs. 0% vs. 0% Condom use with HIV-infected partner: Not applicable: 0% vs. 0% vs. 0% vs. 8% Never: 4% vs. 0% vs. 0% vs. 0% Sometimes: 13% vs. 8% vs. 8% vs. 8% Frequently: 4% vs. 17% vs. 8% vs. 0% Always: 79% vs. 75% vs. 83% vs. 83%	Screened: 133 Eligible: 72 Enrolled: 72 Analyzed: 72 No withdrawals or loss to followup	Good	IAVI, study medication provided by Gilead Science

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
IPERGAY Molina, 2015[66] Chaix, 2018[132] Antoni, 2020[129] *Oral PrEP Versus Placebo or No PrEP*	RCT	7 sites France and Canada	Median, 9 months (IQR, 5 to 21 months)	A. On demand TDF-FTC 300/200 mg (n=199) B. Placebo (n=201) On demand dosing schedule: 1. Two pills 2 to 24 hours before sex 2. Third pill 24 hours after first drug intake 3. Fourth pill 24 hours later In the case of multiple consecutive episodes of sexual intercourse, participants were instructed to take 1 pill per day until the last sexual intercourse, then take 2 postexposure pills When resuming pre-exposure prophylaxis, participants were instructed to take a loading dose of 2 pills unless the last drug intake was less than 1 week earlier, in which case they were instructed to take only 1 pill	HIV-uninfected, at least age 18 years, male or transgender female sex among participants who have sex with men and who are at high risk for HIV infection (defined as a history of unprotected anal sex with ≥2 partners during the past 6 months). Excluded: HBsAg-infected, chronic infection with HCV virus, a creatinine clearance of <60 mL/min, ALT level of >2.5 ULN, glycosuria or proteinuria of more than 1+ on urine dipstick testing	A vs. B Age (median): 35 vs. 34 years (IQR, 29 to 43) Female: 0% Race: White 94% vs. 89%; other NR Relationship status: Not in a couple: 72% vs. 74% In a couple with HIV-1 infected partner: 10% vs. 6% Other: 18% vs. 19% Postsecondary education: 73% vs. 70% >5 Alcoholic drinks per day in past month: 25% vs. 21% Use of recreational drugs:43% vs. 46% Sexual partners in past 2 months (median): 8 vs. 8 Episodes of sexual intercourse in past 4 weeks (median): 10 vs. 10 Circumcised: 19% vs. 20% STI diagnosed at screening: 25% vs. 31% HBsAg status: Susceptible: 23% vs. 19% Immune from natural infection: 9% vs. 15% Immune from vaccination: 68% vs. 66%	Screened: 445 Eligible: 433 Enrolled: 414 Analyzed: 97% (400/414) Withdrawals: 8% (31/414) Loss to followup: 3% (12/414)	Good	ANRS, Canadian HIV Trials Network, Fonds de Dotation Pierre Berge Pour la Prevention, Bill and Melinda Gates Foundation

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
iPrEx Grant, 2010[137] *Oral PrEP Versus Placebo or No PrEP*	RCT	11 centers Peru, Ecuador, Brazil, U.S., Thailand, and South Africa	Median 1.2 years	A. TDF-FTC 300/200 mg (n=1,251) B. Placebo (n=1,248)	Men or transgender women who have sex with men, age 18 years or older, HIV-uninfected status, and evidence of high risk for acquisition of HIV infection based on: anal sex with ≥4 male partners, a diagnosis of STI, history of transactional sex activity, condomless anal sex with an HIV-infected partner or partner of unknown infection status in the previous 6 months. Excluded: Serious and active illness, including diabetes requiring hypoglycemic agents, tuberculosis, cancer requiring therapy, substance use, use of nephrotoxic agents, history of pathological bone fracture, receipt of ART or anti-HIV vaccine, acute HBV infection (active HBV not enrolled in Brazilian sites)	A vs. B Ages 18 to 24 years: 47% vs. 53% Ages 25 to 29 years: 22% vs. 19% Ages 30 to 39 years: 20% vs. 18% Age ≥40 years: 11% vs. 10% Born male: 100% vs. 100% Black: 9% vs. 8% White: 18% vs. 17% Mixed race or other: 68% vs. 70% Asian: 5% vs. 5% Hispanic: 72% vs. 73% No. partners in past 12 weeks: 18±35 vs. 18±43 Unprotected receptive anal intercourse in past 12 weeks: 59% vs. 60% Transactional sex in past 6 months: 41% vs. 41% Known partner with HIV in past 6 months: 2% vs. 3% Circumcised: 13% vs. 14% Syphilis seroreactivity: 13% vs. 13% Serum HSV type 2: 37% vs. 35% Urine leukocyte esterase positive: 2% vs. 2%	Screened: 4,905 Eligible: 3,341 Enrolled: 2,499 (1,251 vs. 1,248) Analyzed: 3,678 (1,244 vs. 1,217) Withdrawals: 3% (41/1,251) vs. 4% (46/1,225) Loss to followup: 16% (199/1,251) vs. 15% (182/1,225)	Good	National Institutes of Health and Bill and Melinda Gates Foundation
iPrEx Deutsch, 2015[134] *Oral PrEP Versus Placebo or No PrEP*	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Transgender women only A. TDF-FTC 300/200 mg (n=170) B. Placebo (n=169)	Transgender women based on self-reported current gender identity	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name **Author, year** **Type of PrEP**	**Study design**	**Number of centers, Country**	**Study duration Mean followup**	**Interventions**	**Inclusion criteria**	**Patient characteristics**	**Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup**	**Quality rating**	**Funding source**
iPrEx Liu, 2014[147] *Oral PrEP Versus Placebo or No PrEP*	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010
iPrEx Marcus, 2014[150] *Oral PrEP Versus Placebo or No PrEP*	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	*HSV-2 negative substudy only* A. TDF-FTC 300/200 mg (n=692) B. Placebo (n=691)	iPrEx participants who were HSV type 2 negative at baseline	A vs. B Age <25 years: 60% vs. 65% 25 to 29 years: 21% vs. 18% 30 to 34 years: 9% vs. 8% 35 to 39 years: 4% vs. 5% ≥40 years: 7% vs. 5% Race NR Transgender: 6% vs. 7% Alcohol use, ≥5 drinks on drinking days: 52% vs. 57% Insertive anal intercourse without condom past 3 months: 61% vs. 59% Receptive anal intercourse without condom past 3 months: 48% vs. 52%	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010
iPrEx Mulligan, 2015[159] *Oral PrEP Versus Placebo or No PrEP*	Same as Grant 2010	Same as Grant 2010	Mean 61 weeks + 24 weeks poststop followup	*BMD substudy only* A. TDF-FTC 300/200 mg (n=247) B. Placebo (n=251)	iPrEx participants with DEXA scans performed	A vs. B Age (mean): 28 vs. 28 years Black/African American: 10% vs. 10% White: 18% vs. 17% Mixed/other: 47% vs. 53% Asian: 20% vs. 20% Hispanic: 50% vs. 54% Transgender women: 11% vs. 10% Alcohol use: 81% vs. 80% Marijuana use: 15% vs. 13% Cocaine use: 6% vs. 6% Amphetamine use: 3% vs. 3% Spine BMD: 1.04 vs. 1.04 gm/cm^2 Hip BMD: 1.02 vs. 1.02 gm/cm^2	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name **Author, year** **Type of PrEP**	**Study design**	**Number of centers, Country**	**Study duration Mean followup**	**Interventions**	**Inclusion criteria**	**Patient characteristics**	**Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup**	**Quality rating**	**Funding source**
iPrEx Solomon, 2014[168] *Oral PrEP Versus Placebo or No PrEP*	Same as Grant 2010	8 sites Brazil, Ecuador, Peru, Thailand, South Africa, U.S.	1.5 years	Renal substudy only A. TDF-FTC 300/200 mg (n=563) B. Placebo (n=574)	iPrEx participants with serum creatinine and urine dipstick testing available	A vs. B Age: 18 to 24 years: 47% vs. 52% 25 to 29 years: 22% vs. 19% 30 to 39 years: 21% vs. 19% >40 years: 10% vs. 10% Black/African American: 4% vs. 5% White: 12% vs. 12% Mixed/other: 75% vs. 76% Asian: 8% vs. 7% Hispanic/Latinx: 80% vs. 81% Non-Hispanic/Latinx: 20% vs. 19% Creatinine: 0.9 vs. 0.9 mg/dL Creatinine clearance: 118.4 vs. 119.5 mL/min Phosphorus: 3.7 vs. 3.7 mg/dL	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010
iPrEX Solomon, 2016[169] *Oral PrEP Versus Placebo or No PrEP*	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010 HBV substudy: Of the 2,499 total participants, 12 had chronic HBV	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
Partners PrEP Baeten, 2012[51] *Oral PrEP Versus Placebo or No PrEP*	RCT	9 sites in Kenya and Uganda	Study duration: 36 months Median followup: 23 months	A. Once-daily TDF 300 mg + placebo TDF-FTC (n=1,571) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=1,565) C. Placebo TDF + placebo TDF-FTC (n=1,570) All participants received a comprehensive package of HIV-1 prevention services and were offered HBV vaccination	HIV-1 uninfected with HIV-infected partner (heterosexual couples); age ≥18 and ≤65 years; sexually active; adequate renal, hepatic, and hematologic function; no evidence of chronic active HBV infection Excluded: Pregnant or planning to become pregnant, breastfeeding; repeated positive (≥1+) urine dipstick tests for glycosuria or proteinuria; active and serious infections; ongoing therapy with: ART; metformin; aminoglycoside antibiotics; amphotericin B; cidofovir; systemic chemotherapeutic agents; other agents with significant nephrotoxic potential; history of pathological bone fractures not related to trauma; enrolled in another HIV-1 vaccine or prevention trial	A vs. B vs. C Ages 18 to 24 years: 12% vs. 11% vs. 11% Ages 25 to 34 years: 46% vs. 44% vs. 43% Ages 35 to 44 years: 30% vs. 32% vs. 32% Age ≥45 years: 13% vs. 14% vs. 13% Male: 62% vs. 64% vs. 61% Married to study partner: 97% vs. 98% vs. 98% Number of sex acts in prior month (median): 4 vs. 4 vs. 4 Any unprotected sex acts in prior month: 28% vs. 26% vs. 26% Any sex with outside partner in prior month: 9% vs. 8% vs. 8% Circumcised (men only): 54% vs. 53% vs. 53% *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Trichomonas vaginalis*: 6% vs. 6% vs. 8% Syphilis: 4% vs. 4% vs. 4% HSV-2: 55% vs. 54% vs. 58%	Screened: 7,856 Eligible: 4,964 Enrolled: 4,758 (1,589 vs. 1,583 vs. 1,586) Analyzed: 4,708 (1,572 vs. 1,568 vs. 1,568) Withdrawals: 0.8% (12/1,584) vs. 0.7% (11/1,583) vs. 1.0% (16/1,586) Loss to followup: 0.4% (7/1,584) vs. 0.5% (8/1,583) vs. 0.6% (10/1,586)	Good	Bill & Melinda Gates Foundation (grant no. 47674)
Partners PrEP Celum 2014[120] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	A. Once-daily TDF 300 mg + placebo TDF-FTC (n=528) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=513) C. Placebo TDF + placebo TDF-FTC (n=481)	Partners PrEP enrolled, HSV type 2 seronegative at baseline and with HSV type 2 testing available from final study visit	A vs. B vs. C Median age 30 vs. 31 vs. 30 years Male: 80% vs. 80% vs. 81% Median number of sex acts in prior month: 4 vs. 4 vs. 4 % with unprotected sex act in prior month: 27% vs. 29% vs. 23%	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
Partners PrEP Donnell, 2014[135] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Haberer, 2013[138] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	*Adherence substudy only* A vs. B vs. C Mean age 34 vs. 35 vs. 34 years 55% vs. 53% vs. 52% male Race NR Unprotected sex in prior month 30% vs. 30% vs. 26%	*Adherence substudy only* Screened: 1,185 Eligible: NR Enrolled: 1,147 Analyzed: 1,147 Withdrawals: 0 Loss to followup: 0	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Heffron, 2014[139] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	A. TDF or FTC B. Placebo	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Lehman, 2015[146] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	*Seroconverters only* A. Once-daily TDF 300 mg + placebo TDF-FTC (n=39) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=25) C. Placebo TDF + placebo TDF-FTC (n=58)	Partners PrEP seroconverters only	18/122 determined to have acute seronegative HIV infection at baseline	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Matthews, 2014[154] *Oral PrEP Versus*	RCT	9 Kenya and Uganda	36 months; monthly followup	Oral TDF and TDF-FTC PrEP; placebo; risk reduction counseling, couples counseling, and condoms	HIV-1 uninfected members of HIV-1 serodiscordant couples. Sexually active couples planning to remain in the relationship for the	Mean age 33 years (IQR, 28 to 38) 100% female Race NR (study conducted in Africa) Risk behaviors 23% unprotected sex with study partner; 0.5% sex with additional	Same as Baeten 2012 Enrolled: 4,747 serodiscordant couples Analyzed: 1,785	Same as Baeten 2012	Same as Baeten 2012

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name **Author, year** **Type of PrEP**	**Study design**	**Number of centers, Country**	**Study duration Mean followup**	**Interventions**	**Inclusion criteria**	**Patient characteristics**	**Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup**	**Quality rating**	**Funding source**
Placebo or No PrEP					duration of the study.	partner; 53% no effective contraception; 8% STI			
Partners PrEP Mugo, 2014[157] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	*HIV-uninfected women only* A. Once daily TDF 300 mg (n=595) B. Once daily TDF-FTC 300/200 mg (n=565) C. Once daily placebo (n=621)	HIV uninfected women enrolled in Partners PrEP	A vs. B. vs. C Mean age 32 vs. 33 vs. 33 100% female Race NR Married 98% vs. 99% vs. 99% Contraception use 44% vs. 49% vs. 48%	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Mugwanya, 2015[158] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	A. Once daily TDF 300 mg (n=1,548) B. Once daily TDF-FTC 300/200 mg (n=1,545) C. Once daily placebo (n=1,547)	Same as Baeten 2012	See above	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Murnane, 2013[161] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name **Author, year** **Type of PrEP**	**Study design**	**Number of centers, Country**	**Study duration Mean followup**	**Interventions**	**Inclusion criteria**	**Patient characteristics**	**Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup**	**Quality rating**	**Funding source**
Partners PrEP Murnane, 2015[160] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Were, 2014[173] *Oral PrEP Versus Placebo or No PrEP*	See above	See above	See above	*HIV-uninfected men only* A. Once-daily TDF 300 mg + placebo TDF-FTC (n=986) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=1,013) C. Placebo TDF + placebo TDF-FTC (n=963)	HIV-uninfected males in a serodiscordant couple	A vs. B vs. C Ages 18 to 24 years: 10% vs. 11% vs. 10% Ages 25 to 29 years: 21% vs. 19% vs. 18% Ages 30 to 34 years: 24% vs. 24% vs. 23% Age ≥35 years: 45% vs. 46% vs. 49% Married: 98% vs. 98% vs. 98% Number of pregnancies: 192 vs. 193 vs. 198	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
Project PrEPare ATN 082 Hosek, 2013[141] *Oral PrEP Versus Placebo or No PrEP*	Double-blind medication pilot RCT with third nonmedication control group	2 clinics in Chicago, IL	24 weeks	A. PrEP with daily TDF-FTC (n=20) + 3MV B. Placebo (daily) + 3MV behavioral intervention (n=19) C. 3MV behavioral intervention, alone (n=19)	MSM, ages 18 to 22 years, at least 2 episodes of unprotected anal sex in past 12 months. Exclude: sickle cell disease, hypophosphatemia, creatinine clearance <75 mL/min, history of unexplained bone fractures, ≥2+ urine dipstick protein or urinary protein-creatinine ratio ≥3.5 g/g, normoglycemic glycosuria (≥1+ urine dipstick), serious psychiatric symptoms, active Hep B, use of nephrotoxic drugs, diuretics, NSAIDS, other antretroviral drugs, or drugs that interfere with TDF excretion	A vs. B vs. C Age (mean): 19.8 vs. 20.3 vs. 19.8 years Male: 100% vs. 100% vs. 100% White: 5% vs. 5.2% vs. 10.5% Native American/Alaskan Native: 5% vs 0% vs 0% Black: 50% vs 63% vs. 47% Other/mixed race: 40% vs. 32% vs 42%. Hispanic ethnicity: 35% vs. 32% vs. 53%. Some college: 40% vs. 74% vs. 42%. Unprotected anal sex with a man in past 30 days: 45% vs. 37% vs. 42% Unprotected anal sex with a woman in past 30 days: 0% vs. 11% vs. 5%	Screened: 753 Eligible: 241 Enrolled: 58 (20 vs. 19 vs. 19) Analyzed: 58 (20 vs. 19 vs. 19) Withdrawals: 2/20 vs. 4/19 vs. 1/19 Loss to followup: NR	Fair	Adolescent Medicine Trials Network for HIV/AIDS Interventions; National Institutes of Health (Eunice Kennedy Shriver National Institute on Child Health and Human Development; National Institute on Drug Abuse; National Institute of Mental Health)

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
PROUD McCormack, 2016[118] *Oral PrEP Versus Placebo or No PrEP*	Open-label RCT	13 sites England	1 year	A.Immediate PrEP with daily TDF-FTC 245/200 mg (n=275) B. Deferred PrEP for 1 year (n=269)	Age ≥18 years; male at birth; previously attended the enrolling clinic; screened for HIV and other STIs; HIV negative in the previous 4 weeks or on the day of enrollment; history of anal intercourse without a condom in the previous 90 days and likely to have anal intercourse without a condom in the next 90 days. Excluded: Participants with acute viral illness, contraindication to TDF or FTC; currently being treated for HBV infection	A vs. B Age (mean): 35 vs. 35 years Male: 100% vs. 100% White: 81% vs. 83% Asian: 5% vs. 6% Black: 4% vs. 4% Other race: 10% vs. 8% Partner, living together: 32% vs. 27% Partner, living separately: 15% vs. 17% No partner: 53% vs. 55% Circumcised: 28% vs. 30% STI in the past 12 months: 63% vs. 65% Use of postexposure prophylaxis in the past 12 months: 35% vs. 37%	Screened: NR Eligible: NR Enrolled: 544 Analyzed: 523 Withdrawals: 1% (3/275) vs. 2% (4/269) Loss to followup: 6% (17/275) vs. 6% (16/269)	Fair	Medical Research Council Clinical Trials Unit; Public Health England; Gilead Sciences
Study of TDF Peterson, 2007[55] *Oral PrEP Versus Placebo or No PrEP*	RCT	3 sites Ghana, Cameroon, and Nigeria	Duration: 33 months Mean followup: 5.5 months	A. TDF, 300 mg orally daily (n=469) B. Placebo (n=467) All participants received HIV posttest counseling, and received condoms and risk reduction counseling at every monthly visit	HIV-antibody-uninfected women ages 18 to 35 years who were at risk of HIV infection by virtue of having an average of ≥3 coital acts per week and ≥4 sexual partners per month. Willing to use the study drug as directed and participate for up to 12 months of followup. Adequate renal function (serum creatinine, 1.5 mg/dL), liver function (AST and ALT 43 U/L), and serum phosphorus (2.2 mg/dL) at their screening visit Excluded: Pregnant or breastfeeding, or wishing to become	A vs. B Age (mean): 23.6 vs. 23.5 years 100% female Not married, not living with a man: 92.7% vs. 89.1% Not married, living with a man; 5.4% vs. 7.2% Married, not living with a man: 1.4% vs. 3.7% Married, living with a man: 0.5% vs 0.0% Years of school completed (mean): 8.3 vs. 7.9 Ever been pregnant: 74.2% vs. 72.2% Number of pregnancies (mean): 2.4% vs. 2.4% Currently using condoms: 45.2% vs. 44.4% Any STI in past 6 months: 39.8% vs. 42.6%	Screened: 2,040 Eligible: 1,283 Enrolled: 936 Analyzed: 92% (859/936) Withdrawals: 45% (428/936) Lost to followup: 17% (162/936)	Good	Bill and Melinda Gates Foundation

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
					pregnant during the 12 months of study participation				
TDF2 Thigpen, 2012[170] *Oral PrEP Versus Placebo or No PrEP*	RCT	2 sites Botswana	2.5 years	A. Oral TDF-FTC 300/200 mg, once daily (n=611) B. Placebo, once daily (n=608)	Ages 18 to 39 years, HIV-uninfected, sexually active, normal serum and hematologic tests, HBsAg-uninfected, no long-term illness or medication use Excluded: Pregnant or breastfeeding	A vs. B Age: 18 to 20 years: 2% vs. 3% 21 to 29 years: 90% vs. 87% 30 to 39 years: 8% vs. 10% Female: 46% vs. 46% Race: NR Secondary education: 73% vs. 73% Single: 94% vs. 93% Male circumcised: 12% vs. 12% STI in the past 12 months: 63% vs. 65% Sex with HIV+ partner in past month: 3% vs. 3% Unknown history of sex with HIV+ partner in past month: 18% vs. 18% Any STI reported: 51% vs. 53%	Screened: 2,533 Eligible: 1,242 Enrolled: 1,219 Analyzed: 1,200 Withdrawals: 16% (100/601) vs. 13% (80/599) Loss to followup: 8% (52/601) vs. 10% (63/599)	Good	Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention and Division of AIDS, National Institutes of Health; one investigator reported royalties from Roche and one investigator reported funding from Gilead
TDF2 Chirwa, 2014[133] *Oral PrEP Versus Placebo or No PrEP*	Subset of participants from larger trial (those who serococonvert-ed)	Same as Thigpen 2012	Same as Thigpen 2012	Same as Thigpen 2012	Same as Thigpen 2012	Same as Thigpen 2012	Same as Thigpen 2012	Same as Thigpen 2012	Same as Thigpen 2012

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
VOICE Marrazzo, 2015[54] *Oral PrEP Versus Placebo or No PrEP*	RCT	15 sites South Africa, Uganda, Zimbabwe	Maximum 36 months (5,509 person-years)	A. Oral TDF 300 mg and TDF-FTC placebo (n=1,007) B. Oral TDF-FTC 300/200 mg and TDF placebo (n=1,003) C. Oral TDF placebo and oral TDF-FTC placebo (n=1,009) *Interventions outside the scope of this review:* D. Vaginal 1% TFV gel (n=1,007) E. Vaginal placebo gel (n=1,003) (all daily)	Women ages 18 to 45 years who were neither pregnant nor breastfeeding and who reported recent vaginal intercourse, were using effective contraception, and had normal renal, hematologic, and hepatic function	A vs. B vs. C vs. D vs. E Age (mean): 26 vs. 25 vs. 25 vs. 25 vs. 25 years Female: 100% all groups Race: NR Currently married: 21% all groups ≥2 male sex partners in past 3 months: 24% vs. 21% vs. 24% vs. 22% vs. 20% Episodes of vaginal intercourse in past 7 days: 2.5 vs. 2.5 vs. 2.5 vs. 2.6 vs. 2.6 Condom use during last vaginal sex: 87% vs. 86% vs. 86% vs. 86% vs. 83% Anal sex in the previous 3 months: 16% vs. 18% vs. 17% vs. 18% vs. 18% *Chlamydia trachomatis* present: 12% vs. 12% vs. 13% vs. 12% vs. 13% *Neisseria gonorrhoeae* present: 4% vs. 3% vs. 3% vs. 2% vs. 4% *Trichomonas vaginalis* present: 7% vs. 5% vs. 7% vs. 6% vs. 5% Syphilis present: 1% vs. 1% vs. 2% vs. 1% vs. 1% HSV-2 present: 48% vs. 45% vs. 45% vs. 44% vs. 47% Bacterial vaginosis present: 42% vs. 41% vs. 40% vs. 40% vs. 39%	Screened: 12,320 Eligible: NR Enrolled: 5,029 Analyzed: 4,969 Withdrawals: NR Loss to followup: 0.1% (38/5,029)	Good	National Institute of Allergy and Infectious Diseases (NIAID) Study product donated from Gilead Sciences
VOICE Mirembe, 2016[156] *Oral PrEP Versus Placebo or No PrEP*	Subset of participants randomized to oral arms of larger RCT (Marrazzo 2015)	Sites in Zimbabwe and Uganda	48 weeks and additional 48 weeks after active treatment period	A. TDF (n=172) B. TDF-FTC (n=174) C. Placebo (n=172)	Same as Marrazzo 2015 In addition, women were excluded if they reported any condition known to affect bone or were taking any medication known to affect bone	A vs. B vs. C Ages 18 to 24 years: 24% vs. 25% vs. 22% Ages 25 to 34 years: 65% vs. 67% vs. 65% Ages 35 to 39 years: 12% vs. 9% vs. 13% Married: 76% vs. 82% vs. 80% Alcohol use, past 3 months, never: 76% vs. 75% vs. 70%	Enrolled: 518 Analyzed: 432 (had DEXA at baseline at followup)	Same as Marrazzo 2015	Same as Marrazzo 2015

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
ADAPT/HPTN 067 Bekker 2018[130] *Event Driven Versus Daily Oral PrEP*	Open-label RCT	Single center South Africa	34 weeks	A. Daily TDF-FTC (n=59) B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex; n=59) C. Event-driven TDF-FTC (one tablet both before and after sex; n=60)	Age >18 years, HIV-uninfected women or transgender men, immune to HBV virus, history of an acute STI, transactional sex, intercourse without a condom with someone of unknown or HIV-infected status, or self-report of >1 sex partner in 6 months preceding study entry	A vs. B vs. C Mean age 25 vs. 26 vs. 25 years 100% vs. 100% vs. 100% female (no transgender men enrolled) 98% vs. 100% vs. 100% Black Mean number of sex partners in past 3 months: 1 vs. 1 vs. 1 Median number of sex events in the past 3 months: 4 vs. 4 vs. 4 Median number of condomless sex events in the past 3 months: 2 vs. 2 vs. 1	Screened: 294 Eligible: 269 Enrolled: 191 Analyzed: 178 Withdrawal: 0 (post-randomization) Loss to followup: 0	Fair	HIV Prevention Trials Network Study product donated from Gilead Sciences

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name **Author, year** **Type of PrEP**	**Study design**	**Number of centers, Country**	**Study duration Mean followup**	**Interventions**	**Inclusion criteria**	**Patient characteristics**	**Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup**	**Quality rating**	**Funding source**
ADAPT/ HPTN 067 Grant, 2018[136] *Event Driven Versus Daily Oral PrEP*	Same as Bekker 2018	Two centers Thailand (Bangkok), U.S. (NY, Harlem)	34 weeks	A. Daily TDF-FTC (n=119) B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex; n=119) C. Event-driven TDF-FTC (one tablet both before and after sex; n=119)	Age >18 years, male sex assigned at birth, normal renal function, HBV negative, reported anal or neovaginal sex with a man in the past 6 months, and have at least 1 of the following self-reported risk factors for HIV acquisition in the past 6 months: sex with >1 man or transgender woman; history of an acute STI; sex in exchange for money, goods, or favors; or intercourse without a condom with an HIV-infected partner or partner of unknown HIV infection status	A vs. B vs. C Bangkok site (n=178) Mean age NR; 13% vs. 20% vs. 14% Ages 18 to 24 years; 22% vs. 32% vs. 27% Ages 25 to 29 years; 60% vs. 39% vs. 48% Ages 30 to 39 years; 5% vs. 9% vs. 12% Age ≥40 years 98% vs. 98% vs. 100% MSM; 2% vs. 2% vs. 0% transgender Race NR Mean number of sex partners in past 3 months: 28% vs. 27% vs. 17% 0–1; 32% vs. 41% vs. 49% 2–4; 27% vs. 10% vs. 19% 5–9; 13% vs. 22% vs. 15% ≥10 Condomless anal intercourse in past 6 months: 37% vs. 44% vs. 29% Harlem site (n=179) Mean age NR; 32% vs. 28% vs. 28% Ages 18 to 24 years; 22% vs. 18% vs. 13% Ages 25 to 29 years; 19% vs. 20% vs. 23% Ages 30 to 39 years; 27% vs. 33% vs. 35% Age ≥40 years 97% vs. 98% vs. 97% MSM; 3% vs. 0% vs. 2% transgender; 0% vs. 2% vs. 2% gender queer 70% Black; 13% White; 3% Asian; 3% Native American; 21% other; 25% Hispanic (participants could self-identify in more than one category) Mean number of sex partners in past 3 months: 5% vs. 7% vs. 7% 0–1; 51% vs. 35% vs. 43% 2–4; 14% vs. 30% vs. 30% 5–9; 29% vs. 25% vs. 20% ≥10 Condomless anal intercourse in past 6 months: 80% vs. 67% vs. 83%	Screened: 608 Eligible: Unclear Enrolled: 431 Analyzed: 357 Withdrawal: 0 (post-randomization) Loss to followup: 19% (81/431)	Same as Bekker 2018	Same as Bekker 2018

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name **Author, year** **Type of PrEP**	**Study design**	**Number of centers, Country**	**Study duration Mean followup**	**Interventions**	**Inclusion criteria**	**Patient characteristics**	**Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup**	**Quality rating**	**Funding source**
Kwan, 2021[144] *Event Driven Versus Daily Oral PrEP*	Open-label crossover trial	Single center Hong Kong	32 weeks (mean NR)	A: Once-daily TDF-FTC (n=59) B: On-demand TDF-FTC (n=60)	HIV-negative MSM age 18 and older who had condomless anal intercourse in the preceding 6 months	A vs B Mean age: 29 vs. 30 years Ever had STI: 46% vs. 43% Ever had sex with HIV-positive individuals: 31% vs. 20% Ever had group sex: 78% vs. 80% Ever had chemsex: 59% vs. 47%	Screened: 120 Eligible: 119 Enrolled: 119 Analyzed: 119 Withdrawal: 14% (8/59) vs. 13% (8/60)	Fair	Gilead Sciences, AIDS Trust Fund
ASPIRE Baeten, 2016[73] Peebles, 2020[163] *Dapirivine Vaginal Ring Versus Placebo Ring*	RCT	15 centers Malawi, South Africa, Uganda, Zimbabwe	Median: 1.6 years Maximum: 2.6 years	A. Dapivirine Ring (n=1313) B. Placebo (1316)	Healthy, sexually active, nonpregnant, HIV-1 seronegative women aged 18 to 45 years	A vs. B Age: 27.2 vs. 27.3 Female: 100% Race: NR Two or more male sex partners in past 3 months: 16% vs. 17% Condom use during last vaginal sex: 59% vs. 56% Transactional sex in past year: 6% vs. 7%	Screened: 5519 Eligible: 2632 Enrolled: 2629 Analyzed: 2614 Withdrawal: 272 (including 7 deaths) Loss to followup: 12	Fair	Government, International Partnership for Microbicides, Inc.
Ring Study Nel, 2016[74] *Dapirivine Vaginal Ring Versus Placebo Ring*	RCT	7 research centers, South Africa, Uganda	2 years	A. Dapivirine Ring (n=1307) B. Placebo (652)	Healthy, sexually active, nonpregnant, HIV-1 seronegative women aged 18 to 45 years	A vs. B Age: 25.9 vs. 26.1 Female: 100% Black: 99.4% vs. 98.5% Main Sex Partner: 98.2% vs. 98.2% Usual number of vaginal sex acts each month: 8.1 vs. 8.4 Sexually transmitted infections identified: 27.4%	Screened: 3425 Eligible: 1959 Enrolled: 1959 Analyzed: 1950 Withdrawal: 92 (including 3 deaths) Loss to followup: 61	Fair	Nonprofit, government, industry provided rings

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
DISCOVER Mayer, 2020[121]; Ogbuagu, 2021[162] *Oral TAF-FTC Versus TDF-FTC*	RCT	94 sites Europe and North America	96 weeks (interim analysis also reported when all patients had at least 48 weeks of followup and >50% had completed 96 weeks[121])	A: TAF-FTC (n=2694) B: TDF-FTC (n=2693)	Cisgender MSM or transgender women who have sex with men, HIV-uninfected, and condomless anal sex with at least two partners in the previous 12 weeks or having syphilis, rectal gonorrhea, or rectal chlamydia in the prior 24 weeks (prior or current PrEP with TDF-FTC permitted)	A vs. B Age (mean): 34 vs. 34 years Cisgender MSM: 98% vs. 99% Transgender women who have sex with men: 2% vs. 1% White: 84% vs. 84% Black: 9% vs. 9% Asian: 4% vs. 5% Hispanic or Latinx ethnicity: 24% vs. 25% Two or more of receptive condomless anal sex partners in last 12 weeks: 62% vs. 60% Rectal gonorrhea in last 24 weeks: 10% vs. 10% Rectal chlamydia in last 24 weeks: 13% vs. 12% Syphilis in the last 24 weeks: 9% vs. 10% Recreational drug use in 12 weeks: 67% Vs. 67% TDF-FTC PrEP at baseline: 17% vs. 16%	Screened: 5857 Eligible/enrolled: 5399 Randomized: 5387 Analyzed: 5387 Withdrawals (excluding loss to followup): 633 Loss to followup: 497	Good	Gilead Sciences

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name **Author, year** **Type of PrEP**	**Study design**	**Number of centers, Country**	**Study duration Mean followup**	**Interventions**	**Inclusion criteria**	**Patient characteristics**	**Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup**	**Quality rating**	**Funding source**
HPTN 083 Landovitz, 2021[70] *Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC*	Double-blind RCT	43 centers International	Median, 1.4 (IQR, 0.8-1.9) years	A: Cabotegravir long-acting injectable 600 mg at weeks 5, 9, 17, and every 8 weeks afterward and oral placebo (n=2,282) B: Oral tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg oral once daily and injectable placebo (n=2,284)	Adult (≥18 years of age) cis-gender MSM and transgender women who have sex with men who were in general good health as determined by clinical and laboratory assessments and who had a negative HIV serologic test at enrollment, had an undetectable blood HIV RNA viral load within 14 days before trial entry, and had a creatinine clearance of 60 mL or more per minute Excluded: use of illicit intravenous drugs within 90 days before enrollment, coagulopathy, buttock implants or fillers, a seizure disorder, or a corrected QT interval of greater than 500 msec	A vs. B Median age: 26 vs. 26 years MSM: 88% vs. 87% Transgender women who have sex with men: 12% vs. 13%	Screened: 6,333 Eligible: 4,980 Enrolled: 4,570 Analyzed: 4,490 Withdrawals: 13.5% at 1 year	Good	National Institute of Allergy and Infectious Diseases, National Institutes of Health, National Institute of Mental Health, National Insitute on Drug Abuse, others ViiV Healthcare and Gilead Sciences donated trial medications and matching placebos, and ViiV Healthcare provided additional funding

Appendix B Table 1. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Study Characteristics

Study name Author, year Type of PrEP	Study design	Number of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
HPTN 084 Delany-Moretwle, 2022[88] *Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC*	Double-blind RCT	20 sites in 7 countries in Sub-Sahara Africa	Median 1.24 (IQR, 0.92-1.56) years	A: Cabotegravir 600 mg in a 3 mL IM injectable every 8 weeks (n=1,592) B: Daily TDF-FTC 300 mg + 200 mg (n=1,586)	Assigned female at birth, aged 18-45 years reporting at least 2 episodes of vaginal intercourse in the previous 30 days at risk of HIV infection based on an HIV risk score Excluded: pregnant or breastfeeding; renal, hepatic, or cardiovascular disease; history of seizures, coagulopathy, or allergy to an investigated product	A vs B Median age: 25 vs. 25 years Race/ethnicity: 97.2% vs. 96.5% Black Gender identity: 99.9% vs. 99.8% female, 0% vs 0.2% male, and 0.1% vs. 0% transgender male	Screened: 4,878 Eligible: 3,759 Enrolled: 3,224 Analyzed: 3,178	Good	National Institute of Allergy and Infectious Diseases, National Institutes of Health, National Institute of Mental Health, National Insitute on Drug Abuse, others including the Bill & Melinda Gates Foundation (OPP1154174) and ViiV Healthcare; Pharmaceutical support was provided by ViiV Healthcare and Gilead Sciences

Abbreviations: 3MV=Many Men, Many Voices; ALT=alanine aminotransferase; ANRS= France Recherche Nord et Sud SIDA-HIV et Hépatites; ART=antiretroviral therapy; AST=aspartate aminotransferase; BMD=bone mineral density; CDC=Centers for Disease Control and Prevention; DEXA=dual energy X-ray absorptiometry; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; HBsAg=surface antigen of hepatitis B; HBV=hepatitis B virus; HCV=hepatitis C virus; HSV=herpes simplex virus; IAVI=International AIDS Vaccine Initiative; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; IQR=interquartile range; MSM=men who have sex with men; NR=not reported; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; PWID=persons who inject drugs; RCT=randomized, controlled trial; SD=standard deviation; STI=sexually transmitted infection; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; TDF-FTC=emtricitabine/tenofovir disoproxil fumarate; TFV= tenofovir; ULN=upper limit of normal; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Bangkok Tenofovir Study Choopanya, 2013[53] and Martin, 2015[153] *Oral PrEP Versus Placebo or No PrEP*	A. Tenofovir 300mg once daily (n=1,204) B. Placebo (n=1,209) Participants could choose directly observed therapy or monthly take-home prescriptions, and switch at monthly followup appointments	A vs. B HIV infection: 1.4% (17/1,204) vs. 2.6% (33/1,207); RR, 0.52 (95% CI, 0.29 to 0.92)	A vs. B Deaths: 4.1% (49/1,204) vs. 4.8% (58/1,209); RR, 0.85 (95% CI, 0.58 to 1.23) Serious adverse events: 19% (227/1,204) vs. 20% (246/1,209); RR, 0.93 (95% CI, 0.79 to 1.09) Grade 4 adverse events: 2% (28/1,204) vs. 3% (31/1,209) Grade 3 adverse events: 12% (147/1,204) vs. 12% (142/1,209) Fracture/broken bone: 7.8% (94/1,204) vs. 6.0% (73/1,209); RR, 1.29 (95% CI, 0.96 to 1.74) Nausea and vomiting: 7.8% (96/1,204) vs. 4.9% (59/1,209); RR, 1.63 (95% CI, 1.19 to 2.24) Renal disease: 1% (13/1,204) vs. 1% (11/1,209); RR, 1.19 (95% CI, 0.53 to 2.64)	No tenofovir resistance mutations (K65R, K70E) in either group
Bangkok Tenofovir Study Martin, 2014[152] *Oral PrEP Versus Placebo or No PrEP*	Same as Choopanya 2013	Same as Choopanya 2013	A vs. B Creatinine, grade 1 (increase ≥0.5 mg/dL from baseline): 3.1% (37/1,204) vs. 2.3% (28/1,209); p=0.27 Creatinine, grade 2 (2.1 to 3.0 mg/dL): 0.2% (2/1,204) vs. 0% (0/1,209); p=0.25 Creatinine, grade 3 to 4 (≥3.1 mg/dL): 0.3% (3/1,204) vs. 0.3% (3/1,209); p=0.99 Creatinine clearance (Cockcroft-Gault) rate <50 mL/min: 3.7% (45/1,204) vs. 2.2% (26/1,209); p=0.01 Acute renal failure: 0.08% (1/1,204) vs. 0.08% (1/1,209) All 7 participants with grade 2, 3, and 4 creatinine results permanently stopped taking the study drug and serum creatinine levels returned to normal in all except 1 in the tenofovir group who was diagnosed with diabetes and hypertension during the study A (n=524) vs. B (n=511) Mean creatinine clearance, month 60 Cockcroft-Gault method: 91.8 vs. 97.0 mL/min; p=0.002 GFR (Modification of Diet in Renal Disease method): 88.5 vs. 91.9 mL/min/1.73 m^2; p=0.003 GFR (Chronic Kidney Disease Epidemiology Collaboration method): 97.4 vs. 100.7 mL/min/1.73 m^2; p=0.002 A vs. B Longitudinal analysis through month 60 Cockcroft-Gault method: slope -0.04, p<0.001 vs. slope 0.02, p=0.08; between-group p<0.001 GFR (Modification of Diet in Renal Disease method): slope -0.04, p<0.001 vs. slope -0.02, p=0.004; between-group p=0.12 GFR (Chronic Kidney Disease Epidemiology Collaboration method): slope -0.06, p<0.01 vs. slope -0.04, p<0.001; between-group p=0.07	Same as Choopanya 2013

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
FEM-PrEP Van Damme, 2012[172]* and Agot, 2015[128] *Oral PrEP Versus Placebo or No PrEP*	A. Oral TDF-FTC 300/200 mg once daily (n=1,062) B. Placebo, once daily (n=1,058)	A vs. B HIV infection: 5% (31/1,024) vs. 5% (35/1,032); HR, 0.94 (95% CI, 0.59 to 1.52); NNT, 275 Risk behaviors: Narratively described reduction in number of partners, vaginal sex acts, and sex without a condom from baseline, no between-group data reported	A vs. B Mortality: 0.1% (1/1,024) vs. 0.1% (1/1,032); RR, 1.01 (95% CI, 0.06 to 16) Any serious adverse event: 3.2% (33/1,025) vs. 2.2% (23/1,033); RR, 1.43 (95% CI, 0.84 to 2.42) Any adverse event: 74.1% (760/1,025) vs. 72.3% (747/1,033); RR, 1.01 (95% CI, 0.93 to 1.09) Withdrawals due to adverse event: 5.3% (55/1,025) vs. 3.2% (33/1,033) Withdrawals due to hepatic or renal lab abnormalities (temporary or permanent): 4.7% (48/1,024) vs. 3.0% (31/1,032) Elevated ALT (>Grade 3): 0.6% (6/1,025) vs. 0.8% (8/1,033); RR, 0.75 (95% CI, 0.26 to 2.17) Elevated AST (>Grade 3): 0.3% (3/1,025) vs. 0.1% (1/1,033); RR, 3.01 (95% CI, 0.31 to 28.9) Elevated creatinine (>Grade 2): 0.4% (4/1,025) vs. 0.2% (2/1,033); RR, 2.01 (95% CI, 0.36 to 10.95) Withdrawals due to renal events: 0.1% (1/1,025) vs. 0% (0/1,033) Trichomoniasis: 3.5% (36/1,024) vs. 5.8% (60/1,032); RR, 0.60 (95% CI, 0.40 to 0.91) Candidiasis: 15.2% (156/1,024) vs. 15.2% (157/1,032); RR, 1.00 (95% CI, 0.82 to 1.23) Gonorrhea: 4.9% (50/1,024) vs. 3.2% (33/1,032); RR, 1.53 (95% CI, 0.99 to 2.35) Chlamydia: 13.3% (136/1,024) vs. 12.0% (124/1,032); RR, 1.11 (95% CI, 0.88 to 1.39) Nausea: 4.9% (50/1,024) vs. 3.1% (32/1,032); RR, 1.57 (95% CI, 1.02 to 2.43) Vomiting: 3.6% (37/1,024) vs. 1.2% (12/1,032); RR, 3.11 (95% CI, 1.63 to 5.92) Diarrhea: 1.7% (17/1,024) vs. 0.8% (8/1,032); RR, 2.14 (95% CI, 0.93 to 4.94) Serious GI events: 0.4% (4/1,025) vs. 0.1% (1/1,033) Withdrawals due to GI adverse events: 0.1% (1/1,025) vs. 0% (0/1,033) Any adverse pregnancy-related outcomes, among women who became pregnant: 32.4% (24/74) vs. 23.5% (12/51); RR, 1.38 (95% CI, 0.76 to 2.50) Spontaneous abortion, among women who became pregnant: 14.9% (11/74) vs. 13.7% (7/51); RR, 1.08 (95% CI, 0.45 to 2.61)	A vs. B <u>HIV-uninfected at time of enrollment</u> K65R mutation: 0% vs. 0% K70E mutation: 0% vs. 0% M184V mutation: 75% (3/4) vs. 100% (1/1) M184I mutation: 25% (1/4) vs. 0%
FEM-PrEP Mandala, 2014[149] *Oral PrEP Versus Placebo or No PrEP*	Same as Van Damme 2012	NR	Elevated creatinine (Grade 1+): 0.08 vs. 0.67 (estimated from figure), cumulative probability p=0.128 Elevated creatininemia (Grade 2+): 0.4% (4/1,025) vs. 0.2% (2/1,033); all cases resolved or decreased to grade 1 by 28 weeks following drug withdrawal Elevated phosphatemia (Grade 2+): 0.23 vs. 0.22 (estimated from figure), cumulative probability p=0.621 Elevated ALT (Grade 1+): higher in TDF-FTC group, cumulative probability p=0.025 Elevated AST (Grade 1+): higher in TDF-FTC group, cumulative probability p=0.025 Elevated ALT and/or AST (Grade 3+): 0.78% (8/1,025) vs. 0.77% (8/1,033)	Same as Van Damme 2012
Grohskopf, 2013[52]	A. TDF, 300 mg orally daily,	A vs. B HIV infection: 0% (0/201)	A vs. B Death: 0.5% (1/201) vs. 0% (0/199); RR, 2.97 (95% CI, 0.12 to 72.5)	No K65R mutations were noted among any seroconverting

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
(CDC Safety Study) *Oral PrEP Versus Placebo or No PrEP*	immediately or after a 9-month delay (n=201) B. Placebo, immediately or after a 9 month delay (n=199)	vs. 3.5% (7/199); RR 0.07 (95% CI, 0.004 to 1.15); NNT 29	Serious adverse events: 5% (10/201) vs. 4% (8/199); RR, 1.24 (95% CI, 0.50 to 3.07) Fracture: 5.5% (15/201) vs. 1.9% (5/199); RR, 1.92 (95% CI, 0.49 to 7.5) Loss of bone density: 6.3% (9/201) vs. 3.7% (5/199); RR, 1.72 (95% CI, 0.6 to 4.98) Grade 3 or 4 adverse events: 17.9% (36/201) vs. 13.1% (26/199) Nausea: 13.4% (27/201) vs. 6.5% (13/199); RR, 2.06 (95% CI, 1.09 to 3.87) Diarrhea: 20.9% (42/201) vs. 28.6% (57/199); RR, 0.73 (95% CI, 0.52 to 1.03) Elevated serum creatinine: 1% (2/201) vs. 3% (6/199); RR, 0.33 (95% CI, 0.07 to 1.62) Withdrawal due to creatinine abnormality: 0% (0/201) vs. 1% (2/199) Fracture data from Food and Drug Administration: 9 vs. 5	participants (n=7; 3 TDF, 4 placebo)
Liu, 2011[148] (companion to Grohskopf, 2013) *Oral PrEP Versus Placebo or No PrEP*	Same as Grohskopf 2013	NR	A vs. B Fracture: 6.4% (6/94) vs. 4.4% (4/90); p=0.75 BMD femoral neck: 1.1% mean net decrease in TDF group vs. placebo (95% CI, 0.4 to 1.9; p=0.004) BMD total hip: 0.8% mean net decrease in TDF group vs. placebo (95% CI, 0.3 to 1.3; p=0.003) BMD L2-L4 spine: 0.7% mean net decrease in TDF group vs. placebo (95% CI, -0.1 to 1.5; p=0.11) After adjustment for those taken off study drug due to >5% drop in BMD or low BMD: BMD femoral neck: 1.2% mean net decrease in TDF group vs. placebo (p=0.002) BMD total hip: 0.8% mean net decrease in TDF group vs. placebo (p=0.003) BMD L2-L4 spine: 0.9% mean net decrease in TDF group vs. placebo (p=0.039) A vs. B, % change >3% loss in BMD from baseline at: Femoral neck: 36% vs. 20%; p=0.02 Total hip: 14% vs. 3%; p=0.02 L2-L4 spine: 17% vs. 15%; p=0.69	Same as Grohskoph 2013
IAVI Kenya Study Mutua, 2012[67] *Oral PrEP Versus Placebo or No PrEP*	A. Daily TDF-FTC 300/200 mg (n=24) B. Intermittent (Monday, Friday and within 2 hours postcoital, not to exceed 1 dose/day) TDF-FTC (n=24) C. Daily placebo (n=12) D. Intermittent placebo (n=12)	A vs. B vs. C vs. D HIV infection: Narrative report of one HIV infection in a placebo group participant (daily or intermittent NR) HIV immune response: Positive IFN-y, week 16: 0 vs. 1 vs. 0 vs. 0 Positive Env peptide: 0 vs. 2 vs. 0 vs. 0 Positive RT peptide: 0 vs. 0 vs. 0 vs. 1 Risk behavior, number of sexual partners: No between- group data	A vs. B vs. C vs. D Severe or very severe adverse event: 13% (3/24) vs. 4% (1/24) vs. 0% vs. 0% Any GI adverse event, A + B vs. C + D: 20/48 (42%) vs. 21% (5/24) Elevated serum creatinine, A + B vs. C + D: 6% (3/48) vs. 0% (0/24) Abnormal creatinine clearance: 2% (1/48) vs. 4% (1/24)	NR

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
		reported; narrative report of increase from median 3 to 4 partners at month 4		
IAVI Uganda Study Kibengo, 2013[68] *Oral PrEP Versus Placebo or No PrEP*	A. Daily TDF-FTC 300/200 mg (n=24) B. Intermittent (Monday, Friday and within 2 hours postcoital, not to exceed 1 dose/day) TDF-FTC 300/200 mg (n=24) C. Daily placebo (n=12) D. Intermittent placebo (n=12)	A vs. B vs. C vs. D HIV infection: Narrative report of no infections in any group A + B vs. C + D Pregnancy outcomes: 1 spontaneous abortion and 1 molar pregnancy vs. 1 term pregnancy HIV immune response: Positive Env response, week 16: 1 vs. 0 vs. 1 vs. 0 (no other data reported) Positive IFN-y ELISPOT, week 16: 0 vs. 1 vs. 0 vs. 0 (no other data reported) Risk behavior, number of sexual partners: Reported to be 1 (IQR, 1 to 1) for all groups	A vs. B vs. C vs. D Severe or very severe adverse event: 0% (0/24) vs. 0% (0/24) vs. 0% (0/12) vs. 8% (1/12) Severe neutropenia, A + B vs. C + D: 0% (0/48) vs. 4.1% (1/24) GI complaint, A + B vs. C + D: 33% (16/48) vs. 29% (7/24) Elevated serum creatinine, A + B vs. C + D: 4% (2/48) vs. 0% (0/24) Spontaneous abortion, among women who became pregnant, A + B vs. C + D: 100% (1/1) vs. 0% (0/1)	NR

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
IPERGAY Molina, 2015[66] Chaix 2018[132]; Antoni, 2020[129] *Oral PrEP Versus Placebo or No PrEP*	A. On demand TDF-FTC 300/200 mg (n=199) B. Placebo (n=201) On demand dosing schedule: 1. Two pills 2 to 24 hours before sex; third pill 24 hours after first drug intake; fourth pill 24 hours later In the case of multiple consecutive episodes of sexual intercourse, participants were instructed to take one pill per day until the last sexual intercourse, then take two postexposure pills. When resuming pre-exposure prophylaxis, participants were instructed to take a loading dose of two pills unless the last drug intake was less than 1 week earlier, in which case they were instructed to take only one pill.	A vs. B HIV infection: 2 (0.91/100 person-years) vs. 14 (6.6/100 person years); RR, 0.14 (95% CI, 0.03 to 0.63); NNT, 17; no resistance or mutations reported Number of sexual partners within past 2 months: 7.5 vs. 8; p=0.001 Any newly acquired STI: 41% vs. 33% No difference in total number of sexual episodes in previous 4 weeks (p=0.07), or proportion of receptive anal intercourse episodes without condoms (p=0.07) or any anal intercourse without condoms (p=0.90) Chaix 2018: HSV-1 incidence per 100 person-years (n=108 MSM): 16.2 (95% Ci 7.4 to 30.8) vs. 7.8 (95% CI 2.5 to 18.2); HR 2.08 (95% CI 0.63 to 7.92)	A vs. B Mortality: No deaths in either group Serious adverse events: 10% (20/199) vs. 8% (17/201); RR, 1.19 (95% CI, 0.64 to 2.20) Any grade 3 or 4 event: 10% (19/199) vs. 7.5% (15/201); RR, 1.28 (95% CI, 0.67 to 2.45) Withdrawals due to adverse event: 0.5% (1/199) vs. 0% (0/201); RR, 3.03 (95% CI, 0.12 to 74) Fracture: 1.5% (3/199) vs. 3.0% (6/201); RR, 0.51 (95% CI, 0.44 to 2.47) Any plasma creatinine elevation: 18% (35/199) vs. 10% (20/201) Grade 2 plasma creatinine elevation: 0% (0/199) vs. 0.5% (1/201); RR, 0.34 (95% CI, 0.01 to 8.22) Proteinuria ≥2+: 5.5% (11/199) vs. 4.5% (9/201); RR, 1.23 (95% CI, 0.52 to 2.91) Glycosuria ≥2+: 0.5% (1/199) vs. 0% (0/201); RR, 3.03 (95% CI, 0.12 to 74) Grade 4 ALT elevation: 0.5% (1/199) vs. 1.5% (3/201); RR, 1.08 (95% CI, 0.38 to 3.01) Any GI adverse event: 14% (28/199) vs. 5.0% (10/201); RR 2.83 (95% CI,1.41 to 5.67) Nausea: 8.0% (16/199) vs. 1.0% (2/201); RR, 8.08 (95% CI, 1.88 to 35) Diarrhea: 4.0% (8/199) vs. 3.0% (6/201); RR, 1.35 (95% CI, 0.48 to 3.81) No serious renal or GI adverse events in either group HCV infection: 1.5% (3/199) vs. 2.5% (5/201)	None of the participants who acquired HIV infection after enrollment (n=16) had resistance mutations; mutations in 3 participants with HIV infection at time of enrollment NR

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
iPrEx Grant, 2010[137] *Oral PrEP Versus Placebo or No PrEP*	A. TDF-FTC 300/200 mg (n=1,251) B. Placebo (n=1,248)	A vs. B HIV infection: 3.0% (38/1,251) vs 5.8% (72/1,248); HR, 0.53 (95% CI, 0.36 to 0.78); NNT, 37	A vs. B Death: 0.1% (1/1,251) vs. 0.3% (4/1,248); RR, 0.25 (95% CI, 0.03 to 2.23) Serious adverse events: 5% (60/1,251) vs. 5% (67/1,248); RR, 0.89 (95% CI, 0.64 to 1.25) Withdrawal due to adverse event: 6.3% (79/1,251) vs 5.8% (72/1,248) Acute HBV infection: 0.1% (2/1,244) vs. 0.0% (1/1,217); RR, 1.96 (95% CI, 0.18 to 21.6) Syphilis: 4.2% (527/1,244) vs. 4.0% (491/1,217); OR, 0.54 (95% CI, 0.35 to 0.81) Warts: 9.8% (122/1,244) vs. 9.0% (110/1,217); OR, 1.09 (95% CI, 0.83 to 1.43) Urethral gonorrhea: 1.1% (14/1,244) vs. 1.4% (17/1,217); OR, 0.80 (95% CI, 0.39 to 1.64) Urethral chlamydia: 0.8% (10/1,244) vs. 1.2% (14/1,217); OR, 0.70 (95% CI, 0.31 to 1.57) Bone fracture: 1% (15/1,251) vs. 1% (11/1,248); RR, 1.36 (95% CI, 0.63 to 2.95) Diarrhea: 3.7% (46/1,251) vs. 4.5% (56/1,248); RR, 0.82 (95% CI, 0.56 to 1.20) Grade 3 or 4 diarrhea: (3/1,251) vs. (2/1,248) Nausea: 1.6% (20/1,251) vs. 0.7% (9/1,248); RR, 2.21 (95% CI, 1.01 to 4.85) Grade 3 or 4 nausea: No cases in either group Permanent discontinuation of study drug: 2% (25/1,251) vs. 2% (27/1,248); RR, 0.92 (95% CI, 0.54 to 1.58) Permanent or temporary discontinuation of study drug: 6% (79/1,251) vs. 6% (72/1,248); RR, 1.09 (95% CI, 0.80 to 1.49) HSV-2: 9.7% (65/671) vs 8.9% (60/676); RR, 1.12 (95% CI, 0.80 to 1.56) Fracture data from Food and Drug Administration: 21 vs. 17	3 cases of resistance (2 TDF-FTC, 1 placebo); all had detectable plasma HIV RNA at time of enrollment: TDF-FTC case 1: M184V mutation (timing of resistance: secondary) TDF-FTC case 2: M184I mutation (timing of resistance: indeterminate) Placebo case 1: M184V, T215Y, and K103N mutations (timing of resistance: primary)
iPrEx Deutsch, 2015[134] *Oral PrEP Versus Placebo or No PrEP*	Transgender women only A. TDF-FTC 300/200 mg (n=170) B. Placebo (n=169)	Same as Grant 2010	A vs. B Death: 0.6% (1/170) vs. 0.6% (1/169); OR, 0.99 (95% CI, 0.06 to 16) Moderate/severe adverse events: 18% (31/170) vs. 17% (28/169); OR, 1.12 (95% CI, 0.64 to 2.97) Liver function abnormalities: 4% (6/170) vs. 3% (5/169); OR, 1.20 (95% CI, 0.36 to 4.01)	Same as Grant 2010
iPrEx Liu, 2014[147] *Oral PrEP Versus Placebo or No PrEP*	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010
iPrEx Marcus, 2014[150] *Oral PrEP Versus Placebo or No PrEP*	*HSV-2 negative substudy only* A. TDF-FTC 300/200 mg (n=692) B. Placebo (n=691)	Same as Grant 2010	A vs. B HSV infection: 9.7% (65/671) vs. 8.9% (60/676); OR, 1.09 (95% CI, 0.75 to 1.58) HSV ulcer adverse event grade ≥2: 2.9% vs. 65.9%; p<0.05 Perianal ulcer on STI exam: 4% vs. 5%; p=NS Groin ulcer on STI exam: 3% vs. 2%; p=NS	Same as Grant 2010

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
iPrEx Mulligan, 2015[159] *Oral PrEP Versus Placebo or No PrEP*	*BMD substudy only* A. TDF-FTC 300/200 mg (n=247) B. Placebo (n=251)	Same as Grant 2010	A vs. B Spine BMD, mean difference at treatment discontinuation: -0.84 (95% CI, -1.51 to -0.16) Hip BMD, mean difference at treatment discontinuation: -0.74 (95% CI, -1.19 to -0.29) Spine BMD, mean difference at poststop: -0.45 (95% CI, -1.30 to 0.30) Hip BMD, mean difference at poststop: -0.76 (95% CI, -1.39 to -0.13) Fracture, DEXA substudy only (see also Grant 2010, above): No participants who had fractures had BMD levels that met either ISCD criteria for low BMD or WHO criteria for osteoporosis at baseline or during the study	Same as Grant 2010
iPrEx Solomon, 2014[168] *Oral PrEP Versus Placebo or No PrEP*	Renal substudy only A. TDF-FTC 300/200 mg (n=563) B. Placebo (n=574)	Same as Grant 2010	A vs. B Persistent creatinine elevation: 1% (7/563) vs. 0.2% (1/574); OR, 7.21 (95% CI, 0.88 to 59); all resolved by 20 weeks after PrEP withdrawal Proximal tubulopathy, one indicator: 6% (34/563) vs. 5% (25/574); OR, 1.41 (95% CI, 0.83 to 2.40) Proximal tubulopathy, two indicators: 0% (0/563) vs. 0.3% (2/574); OR, 0.20 (95% CI, 0.01 to 4.24)	Same as Grant 2010
iPrEX Solomon 2016[169] *Oral PrEP Versus Placebo or No PrEP*	Active hepatitis B substudy only A. TDF-FTC (n=6 with hepatitis) B. Placebo (n=6 with hepatitis)	NA	A. No cases of hepatitis flare occurred following discontinuation of TDF-FTC in five patients of 6 tested	No evidence of resistance

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Partners PrEP Baeten, 2012[51] *Oral PrEP Versus Placebo or No PrEP*	A. Once-daily TDF 300 mg + placebo TDF-FTC (n=1,571) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=1,565) C. Placebo TDF + placebo TDF-FTC (n=1,570) All participants received a comprehensive package of HIV-1 prevention services and were offered HBV vaccination	A vs. B vs. C HIV infection: 1.1% (17/1,572) vs. 0.8% (13/1,568) vs. 3.3% (52/1,586); A vs. B: RR, 1.30 (95% CI, 0.64 to 2.68) NNT, 397; A vs. C: RR, 0.33 (95% CI, 0.19 to 0.56) NNT, 46; B vs. C: RR, 0.25 (95% CI, 0.14 to 0.46) NNT, 41 HIV infection among patients whose partner had not yet initiated ART: 14/17 vs. 13/13 vs. 50/52	A vs. B. vs. C Serious adverse events: 7.4% (118/1,584) vs. 7.3% (115/1,579) vs. 7.4% (118/1,584) Death: 0.5% (8/1,584) vs. 0.5% (8/1,579) vs. 0.6% (9/1,584) Withdrawal due to adverse events: 0.6% vs. 0.7% vs. 0.6% Grade 4 adverse events: 2.1% (34/1,584) vs. 2.8% (44/1,579) vs. 2.5% (39/1,584) Grade 3 adverse events: 18.2% (289/1,584) vs. 18.6% (293/1,579) vs. 16.9% (268/1,584) Bone fracture: <1% (11/1,584) vs. 0.6% (9/1,579) vs. 0.8% (12/1,584) Elevated creatinine grade 1: 1.0% (16/1,584) vs. 1.1% (18/1,579) vs. 0.8%% (12/1,584) Elevated creatinine grade 2 or 3: 0.2% (3/1,584) vs. 0.1% (2/1,579) vs. 0.1% (1/1,584) Nausea: 0.2% (3/1,584) vs. 0.1% (1/1,579) vs. 0% (0/1,584); A vs. C: RR, 3.50 (95% CI, 0.18 to 68); B vs. C: RR, 1.51 (95% CI, 0.06 to 37) Diarrhea: 3.0% (48/1,584) vs. 2.4% (38/1,579) vs. 2.5% (39/1,584); A vs. C: RR, 1.23 (95% CI, 0.81 to 1.87); B vs. C: RR, 0.98 (95% CI, 0.63 to 1.52) STI (*N. gonorrhoeae, C. trachomatis,* or *T. vaginalis*): 5.8% (102/1,584) vs. 4.2% (76/1,579) vs. 4.8% (85/1,584) Syphilis: 2% (28/1,584) vs. 2% (27/1,579) vs. 1% (23/1,584) Fracture data from Food and Drug Administration: 19 (PrEP) vs. 13 (placebo)	<u>Total population</u> A vs. B vs. C K65R mutation (TDF resistance): 5.0% (1/20) vs. 0% (0/15) vs. 0% (0/57) K70E mutation (TDF resistance): 0% (0/20) vs. 0% (0/15) vs. 0% (0/57) M184I mutation (FTC resistance): 0% (0/20) vs. 0% (0/15) vs. 0% (0/57) M184V mutation (FTC resistance): 0% (0/20) vs. 6.7% (1/15) vs. 0% (0/57) K65N mutation (TDF resistance): 5.0% (1/20) vs. 0% (0/15) vs. 0% (0/57) K70R mutation (TDF resistance): 5.0% (1/20) vs. 0% (0/15) vs. 0% (0/57) K103N or V106A mutations (NNRTI resistance): 10% (2/20) vs. 6.7% (1/15) vs. 1.8% (1/57) T215C mutation: 0% (0/20) vs. 0% (0/15) vs. 1.8% (1/57) <u>HIV infected at time of enrollment</u> A vs. B vs. C K65R mutation: 20% (1/5) vs. 0% (0/3) vs. 0% (0/6) K70E mutation: 0% (0/5) vs. 0% (0/3) vs. 0% (0/6) M184I mutation: 0% (0/5) vs. 0% (0/3) vs. 0% (0/6) M184V mutation: 0% (0/5) vs. 33.3% (1/3) vs. 0% (0/6) K70R mutation: 20% (1/5) vs. 0% (0/3) vs. 0% (0/6) K103N or V106A mutation: 0% (0/5) vs. 0% (0/3) vs. 0% (0/6) 25% (2/8) found to be infected at time of enrollment and randomized to PrEP developed resistance mutation (1 each K65R and M184V)

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
				HIV uninfected at time of enrollment A vs. B vs. C K65R mutation: 0% (0/15) vs. 0% (0/12) vs. 0% (0/51) K70E mutation: 0% (0/15) vs. 0% (0/12) vs. 0% (0/51) M184I mutation: 0% (0/15) vs. 0% (0/12) vs. 0% (0/51) M184V mutation: 0% (0/15) vs. 0% (0/12) vs. 0% (0/51) K70R mutation: 0% (0/15) vs. 0% (0/12) vs. 0% (0/51) K103N or V106A mutation: 13.3% (2/15) vs. 8.3% (1/12) vs. 2.0% (1/51)
Partners PrEP Celum 2014[120] *Oral PrEP Versus Placebo or No PrEP*	A. Once-daily TDF 300 mg + placebo TDF-FTC (n=528) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=513)	Same as Baeten 2012	A vs. B vs. C HSV-2 infection: 37/528 vs. 42/513 vs. 52/481; A vs. C: HR, 0.64 (95% CI, 0.42 to 0.98); RR, 0.65 (95% CI, 0.40 to 1.04); B vs. C: HR, 0.76 (95% CI, 0.51 to 1.14); RR, 0.76 (95% CI, 0.48 to 1.21) (A + B) vs. C HSV-2 infection: 79/1,041 vs. 52/481; HR, 0.70 (95% CI, 0.49 to 0.99); RR, 0.70 (95% CI, 0.50 to 0.98)	Same as Baeten 2012
Partners PrEP Donnell, 2014[135] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Haberer, 2013[138] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	NA	NA	NA
Partners PrEP Heffron, 2014[139]	A. TDF or FTC B. Placebo	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Oral PrEP Versus Placebo or No PrEP				
Partners PrEP Lehman, 2015[146] *Oral PrEP Versus Placebo or No PrEP*	*Seroconverters only* A. Once-daily TDF 300 mg + placebo TDF-FTC (n=39) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=25) C. Placebo TDF + placebo TDF-FTC (n=58)	Same as Baeten 2012	Same as Baeten 2012	A vs. B vs. C Total population Resistance frequencies >1%: 5.3% (2/38) vs. 20% (5/25) vs. 3.5% (2/58) HIV infected at time of enrollment Resistance frequencies >1%: 12.5% (1/8) vs. 50% (2/4) vs. 0% (0/6) HIV uninfected at time of enrollment Resistance frequencies >1%: 3.3% (1/30) vs. 14.3% (3/21) vs. 3.8% (2/52)
Partners PrEP Matthews, 2014[154] *Oral PrEP Versus Placebo or No PrEP*	Oral TDF and TDF-FTC PrEP; placebo; risk reduction counseling, couples counseling, and condoms	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Partners PrEP Mugo, 2014[157] *Oral PrEP Versus Placebo or No PrEP*	*HIV-uninfected women only* A. Once daily TDF 300 mg (n=595) B. Once daily TDF-FTC 300/200 mg (n=565) C. Once daily placebo (n=621)	A vs. B vs. C Pregnancy: 18.9% (112/595) vs. 14.1% (80/565) vs. 15.5% (96/621) Pregnancy loss: 27.7% (31/112) vs. 42.5% (34/80) vs. 32.3% (31/96); absolute difference for A vs. C, -4.6% (95% CI, -18.1% to 8.9%) and for B vs. C, 10.2% (95% CI, -5.3% to 25.7%) Preterm birth among live births: 2.5% (2/81) vs. 8.7% (4/46) vs. 7.7% (5/65); absolute difference for A vs. C, -5.2% (95% CI, -13.9% to 3.5%) and for B vs. C, 1.0% (95% CI, -11.3% to 13.3%) Any anomaly (among live births): 4.9% (4/81) vs. 8.5% (4/46) vs. 7.6% (5/65); absolute difference for A vs. C, -2.6% (95% CI, -12.0% to 6.7%) and for B vs. C, 0.9% (95% CI, -11.1% to 13.0%) Postpartum infant mortality: 1.2% (1/81) vs. 10.9% (5/46) vs. 6.1% (4/66); RR for A vs. C, 0.20 (95% CI, 0.02 to 1.8) and for B vs. C, 1.4 (95% CI, 0.38 to 5.4) Infant growth: No statistically significant differences in head circumference, length, or weight; some estimates indicated slightly faster growth in some measures for PrEP vs. placebo	Same as Baeten 2012	Same as Baeten 2012

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Partners PrEP Mugwanya, 2015[158] *Oral PrEP Versus Placebo or No PrEP*	A. Once daily TDF 300 mg (n=1,548) B. Once daily TDF-FTC 300/200 mg (n=1,545) C. Once daily placebo (n=1,547)	Same as Baeten 2012	A vs. B vs. C eGFR mean difference (mL/min/1.73 m^2): +0.14 vs. -0.22 vs. +1.37; difference for A vs. C, -1.23 (95% CI, -2.06 to -0.40) and for B vs. C, -1.59 (95% CI, -2.44 to -0.74) Serum GFR decline ≥25% from baseline (incidence/100 person-years): 1.8% vs. 2.5% vs. 2.2% by 36 months; adjusted HR for A vs. C, 1.33 (95% CI, 0.71 to 2.48) and for B vs. C, 1.45 (95% CI, 0.79 to 2.64) Elevated serum creatinine leading to study withdrawal: 0.1% (2/1,548) vs. 0.1% (2/1,545) vs. 0.1% (1/1,547)	Same as Baeten 2012
Partners PrEP Murnane, 2013[161] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Murnane, 2015[160] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Were, 2014[173] *Oral PrEP Versus Placebo or No PrEP*	*HIV-uninfected men only* A. Once-daily TDF 300 mg + placebo TDF-FTC (n=986) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=1,013) C. Placebo TDF + placebo TDF-FTC (n=963)	A vs. B vs. C Live births: 152/192 vs. 162/193 vs. 146/198 -Term birth: 142/192 vs. 148/193 vs. 135/198 -Premature birth: 7/192 vs. 9/193 vs. 6/198 Pregnancy loss: 32/192 vs. 23/193 vs. 35/198 -Loss at <20 weeks: 20/32 vs. 15/23 vs. 25/35 -Loss at 20 to 36 weeks: 10/32 vs. 7/23 vs. 6/35 -Loss at ≥37 weeks: 2/32 vs. 1/23 vs. 3/35	NR	Same as Baeten 2012
Project PrEPare ATN 082 Hosek, 2013[141]	A. PrEP with daily TDF-FTC (n=20) + 3MV behavioral HIV	NR	A vs. B vs. C Serious adverse events: None Nausea at 8 weeks: 24% vs 0% vs 6% ART resistance: NR	NR

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Oral PrEP Versus Placebo or No PrEP	prevention intervention B. Placebo (daily) + 3MV behavioral intervention (n=19) C. 3MV behavioral intervention, alone (n=19)			
PROUD McCormack, 2016[118] *Oral PrEP Versus Placebo or No PrEP*	A. Immediate PrEP with daily TDF-FTC 245/200 mg (n=275) B. Deferred PrEP for 1 year (n=269)	A vs. B HIV infection: 1.1% (3/268) vs. 7.5% (20/255); RR, 0.14 (95% CI, 0.04 to 0.47); 1.2 cases/100 person-years (90% CI, 0.4 to 2.9) vs. 9.0/100 person-years (90% CI, 6.1 to 12.8); NNT, 13	A vs. B Mortality: 0.4% (1/275) vs. 0% (0/269) Serious adverse events: 8% (21/275) vs. 2% (6/269); RR, 3.42 (95% CI, 1.40 to 8.35) Fracture/broken bone: 1% (3/275) vs. 0.4% (1/269); RR, 2.93 (95% CI, 0.31 to 28) Diarrhea (serious): 1.5% (4/275) vs. 0% (0/269); RR, 8.80 (95% CI, 0.48 to 163) Vomiting (serious): 0.7% (2/275) vs. 0% (0/269); RR, 4.89 (95% CI, 0.24 to 101) Any STI: 57% (152/265) vs 50% (124/247); OR, 1.33 (95% CI, 0.94 to 1.89); aOR (adjusted for number of screenings for specific infection), 1.07 (95% CI, 0.78 to 1.46) Gonorrhea: 39% (103/261) vs. 37% (89/242); OR, 1.12 (95% CI, 0.78 to 1.61); aOR, 0.86 (95% CI, 0.62 to 1.20) Chlamydia: 30% (77/261) vs. 22% (54/242); OR, 1.46 (95% CI, 0.97 to 2.18); aOR, 1.27 (95% CI, 0.89 to 1.80) Syphilis: 11% (30/263) vs. 9% (22/247); OR, 1.32 (95% CI, 0.74 to 2.35); aOR, 1.29 (95% CI, 0.79 to 2.10) Rectal gonorrhoea or chlamydia: 36% (93/258) vs. 32% (77/238); OR, 1.18 (95% CI, 0.81 to 1.71); aOR, 1.00 (95% CI, 0.72 to 1.38) HCV infection: 1.2% (3/258) vs. 1.3% (3/238)	A vs. B <u>Any HIV infection</u> M184I or M184V mutation: 40% (2/5) vs. not assessed K65R or K65E mutation: 0% (0/5) vs. not assessed <u>HIV infected at time of enrollment</u> M184I or M184V mutation: 66.7% (2/3) vs. not assessed <u>HIV uninfected at time of enrollment</u> M184I or M184V mutation: 0% (0/2) vs. not assessed

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Study of TDF Peterson, 2007[55] *Oral PrEP Versus Placebo or No PrEP*	A. TDF, 300 mg orally daily (n=469) B. Placebo (n=467) All participants received HIV posttest counseling, and received condoms and risk reduction counseling at every monthly visit	A vs. B HIV infection: 0.5% (2/427) vs. 1.4% (6/432); RR, 0.34 (95% CI, 0.07 to 1.66); NNT, 109 Condom use: increased from 52% to 95% at 1 year, no between-group data reported	A vs. B Mortality: 0.2% (1/427) vs. 0.2% (1/432); RR, 1.01 (95% CI, 0.06 to 16) Serious adverse events: 2% (9/427) vs. 3% (13/432); RR, 0.70 (95% CI, 0.30 to 1.62) Abdominal pain: 5.6% (24/427) vs. 5.1% (22/432); RR, 1.10 (95% CI, 0.63 to 1.84) Malaria: 29.7% (127/427) vs. 31.0% (134/432); RR, 0.96 (95% CI, 0.78 to 1.17) Urinary tract infection: 5.4% (23/427) vs. 3.5% (15/432); RR, 1.55 (95% CI, 0.82 to 2.93) Vaginal candidiasis: 22.5% (96/427) vs. 22.0% (95/432); RR, 1.02 (95% CI, 0.80 to 1.31) No withdrawals due to AEs	Standard genotypic analysis revealed no evidence of drug resistance mutations
TDF2 Thigpen, 2012[170] *Oral PrEP Versus Placebo or No PrEP*	A. Oral TDF-FTC 300/200 mg, once daily (n=611) B. Placebo, once daily (n=608)	A vs. B HIV infection: 1.6% (10/601) vs. 4.2% (26/606); RR, 0.39 (95% CI, 0.19 to 0.81); 1.2 cases/100 person-years (90% CI, 0.4 to 2.9) vs. 3.1 cases/100 person- years (90% CI, 0.03 to 3.2); NNT, 52	A vs. B Mortality: 0.3% (2/611) vs. 0.7% (4/608); RR, 0.50 (95% CI, 0.09 to 2.71) Serious adverse events: 10% (68/611) vs. 11% (79/608); RR, 0.85 (95% CI, 0.63 to 1.16) No Grade 3 or 4 creatinine elevation or GI events Fracture/broken bone: 1% (7/611) vs. 1% (6/608) Elevated creatinine: 0.2 (1/611) vs. 0% (0/608); RR, 2.98 (95% CI, 0.12 to 73.14) Diarrhea: 12.4% (76/611) vs. 10.7% (65/608) Nausea: 18.5% (113/611) vs. 7.1% (43/608) *Neisseria gonorrheae* infection: 4.6% (28/611) vs. 3.0% (18/608) *Chlamydia trachomatis* infection: 12.4% (76/611) vs. 12.3% (75/608) Trichomoniasis: 3.3% (20/611) vs. 3.0% (18/608) Genital herpes: 4.6% (28/611) vs. 5.8% (35/608) BMD changes, A (n=109) vs. B (n=112): There was a decline in T-scores and z-scores at the forearm, hip, and lumbar spine in participants who received TDF-FTC, compared with those who received placebo (p=0.004 for both T-scores and z- scores at the forearm and p<0.001 for both scores at the hip and lumbar spine) HSV-2: 4.6% (28/611) vs 5.8% (35/608); RR, 0.80 (95% CI, 0.49 to 1.29)	A vs. B 0.2% (1/611; HIV RNA >750,000 copies/ML at enrollment. M184V, K65R, and A62V mutations) vs. 0.2% (1/608; HIV RNA <400 copies/mL at enrollment. K65R mutation)

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
TDF2 Chirwa, 2014[133] *Oral PrEP Versus Placebo or No PrEP*	Same as Thigpen 2012	Of 36 HIV infections, 33 occurred during the course of the study and 3 were retrospectively found to be acutely HIV infected at study entry; 9 occurred among those receiving TDF-FTC and 24 receiving placebo	Same as Thigpen 2012	Of the 33 who acquired HIV during the course of the study, no resistance mutations were identified in their first RNA-positive samples or in any of their samples from subsequent study visits; 1 participant in the placebo group had low levels (<1%) of the K65R mutation, a level of expression attributable to replication error at and around codon 65 that has been observed with ART-naive HIV subtype C infections; 1 of the 3 participants who screened falsely negative at study entry and received TDF-FTC until HIV was diagnosed at month 7 developed the M184V mutation—this was retrospectively found to have occurred 1 month after study entry, and the A62V and K65R mutations occurred between 4 and 7 months after study entry; all mutations were at high levels

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
VOICE Marrazzo, 2015[54] *Oral PrEP Versus Placebo or No PrEP*	A. Oral TDF 300 mg and TDF-FTC placebo (n=1,007) B. Oral TDF-FTC 300/200 mg and TDF placebo (n=1,003) C. Oral TDF placebo and oral TDF-FTC placebo (n=1,009) *Interventions outside the scope of this review:* D. Vaginal 1% TFV gel (n=1,007) E. Vaginal placebo gel (n=1,003) (all daily)	A vs. B vs. C Number of HIV-1 infections: 5% (52/1,007) vs. 6% (61/1,003) vs. 6% (60/1,009); A vs. C: RR, 0.87 (95% CI, 0.61 to 1.25); B vs. C: RR, 1.02 (95% CI, 0.72 to 1.44) Effectiveness: TDF (group A): -49%; HR for infection, 1.49 (95% CI, 0.97 to 2.29) TDF-FTC (group B): -4.4%; HR for infection 1.04, (95% CI, 0.73 to 1.49) TFV gel (group D): 14.5%; HR for infection, 0.85 (95% CI, 0.61 to 1.21) HIV-1 incidence (cases per 100 person-years): 6.3 (95% CI, 4.7 to 8.3) vs. 4.7 (95% CI, 3.6 to 6.1) vs. 4.6 (95% CI, 3.5 to 5.9) vs. 6.0 (95% CI, 4.6 to 7.6) vs. 6.8 (95% CI, 5.3 to 8.6)	A vs. B vs. C Mortality: 0% (0/1,007) vs. 0% (0/1,003) vs. 0.3% (3/1,009) Serious adverse events: 8.6% (87/1,007) vs. 12.2% (123/1,003) vs. 11.3% (114/1,009) Grade 4 events: 0.4% (4/1,007) vs. 1.4% (14/1,003) vs. 1.7% (17/1,009) Lower limb fracture: 0.2% (2/1,007) vs. 0.1% (1/1,003) vs. 0% (0/1,009) Creatinine event: 0.4% (4/1,007) vs. 1.3% (13/1,003) vs. 0.2% (2/1,009) Nausea grade 2 or higher: 1.3% (13/1,007) vs. 0.8% (8/1,003) vs. 1.5% (15/1,009) Vomiting grade 2 or higher: 0.1% (6/1,007) vs. 0.1% (6/1,003) vs. 0.1% (9/1,009) Diarrhea grade 2 or higher: 1.2% (12/1,007) vs. 1.8% (18/1,003) vs. 2.1% (21/1,009) Any Grade 3 or 4 GI event: 0% (0/1,007 vs. 0.3% (3/1,003) vs. 0.7% (7/1,009) Chlamydia infection: 10.4% (105/1,007) vs. 14.4% (144/1,003) vs. 15.2% (153/1,009) Gonococccal infection: 2.6% (26/1,007) vs. 4.6% (46/1,003) vs. 4.5% (45/1,009) Syphilis infection: 1.5% (15/1,007) vs. 1.0% (10/1,003) vs. 1.5% (15/1,009)	A vs. B vs. C <u>Total population</u> K65R mutation (TDF resistance): 0% (0/70) vs. 0% (0/71) vs. 0% (0/69) K70E mutation (TDF resistance): 0% (0/70) vs. 0% (0/71) vs. 0% (0/69) M184V mutation (FTC resistance): 0% (0/70) vs. 4.2% (3/71) vs. 0% (0/69) M184I mutation (FTC resistance): 0% (0/70) vs. 1.4% (1/71) vs. 0% (0/69) <u>HIV infected at time of enrollment</u> K65R mutation: 0% (0/5) vs. 0% (0/9) vs. 0% (0/1) K70E mutation: 0% (0/5) vs. 0% (0/9) vs. 0% (0/1) M184V mutation: 0% (0/5) vs. 22% (2/9) vs. 0% (0/1) M184I mutation: 0% (0.5) vs. 11% (1/9) vs. 0% (0/1) <u>HIV uninfected at time of enrollment</u> K65R mutation: 0% (0/65) vs. 0% (0/62) vs. 0% (0/68) K70E mutation: 0% (0/65) vs. 0% (0/62) vs. 0% (0/68) M184V mutation: 0% (0/65) vs. 1.6% (1/62) vs. 0% (0/68) M184I mutation: 0% (0/65) vs. 0% (0/62) vs. 0% (0/68)

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
VOICE Mirembe, 2016[156] *Oral PrEP Versus Placebo or No PrEP*	A. TDF (n=172) B. TDF-FTC (n=174) C. Placebo (n=172)	Same as Marrazzo 2015	No significant differences were observed in the primary analysis comparing the mean percent changed in BMD TH and BMD LS from baseline to week 48 between the TDF or TDF-FTC arms compared with placebo; there was also no difference when the active arms were pooled A 3% decrease in BMD was observed in 24% and 17% participants for spine and hip, respectively, and did not differ significantly between active arms and placebo Outcomes after discontinuing active treatment for 68% (354/518) of participants: BMD increases at the spine and hip were observed after stopping study medication and were significantly greater in the active arm participants than placebo: 0.9% at the LS (p=0.007) and 0.7% at the TH (p=0.003); BMD at 48 weeks after active treatment discontinuation was at least as high as the mean BMD level at baseline	Same as Marrazzo 2015
ADAPT/ HPTN 067 Bekker 2018[130] *Event Driven Versus Daily Oral PrEP*	A. Daily TDF-FTC (n=59) B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex; n=59) C. Event-driven TDF-FTC (one tablet both before and after sex; n=60)	A vs. B vs. C HIV infection: 0% (0/59) vs. 3% (2/59) vs. 3% (2/60); A vs. B: RR, 0.20 (95% CI, 0.01 to 4.08); A vs. C: RR, 0.20 (95% CI, 0.01 to 4.15)	A vs. B vs. C Any headache, dizziness, or lightheadedness: 12% (43/348) vs. 6% (20/331) vs. 8% (26/332); A vs. B: OR, 2.19 (95% CI, 1.13 to 4.27); A vs. C: OR, 1.66 (95% CI, 0.88 to 3.13) Any GI symptom: 11% (37/348) vs. 9% (29/331) vs. 5% (18/332); A vs. B: OR, 1.24 (95% CI, 0.61 to 2.51); A vs. C: OR, 2.08 (95% CI, 0.98 to 4.40)	One participant in the time-driven group who seroconverted had M184Ile and L65Arg resistance
ADAPT/ HPTN 067 Grant, 2018[136] *Event Driven Versus Daily Oral PrEP*	A. Daily TDF-FTC (n=119) B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex e; n=119) C. Event-driven TDF-FTC (one tablet both before and after sex; n=119)	A vs. B vs. C HIV infection: 0.8% (1/119) vs. 0% (0/119) vs. 0% (0/119); A vs. B; A vs. C: RR, 3.03 (95% CI, 0.12 to 75) South Africa (from Bekker 2017), Bangkok and Harlem sites combined: 0.6% (1/178) vs. 1.1% (2/178) vs. 1.1% (2/179); A vs. B: RR, 0.50 (95% CI, 0.04 to 5.53); A vs. C: RR, 1.01 (95% CI, 0.14 to 7.22)	A vs. B vs. C Bangkok Proportion of visits when patients reported neurologic events: 14.2% vs. 14.3% vs. 13.3% Proportion of visits when patients reported GI events: 13.1% vs. 8.5% vs. 10.5% Harlem Proportion of visits when patients reported neurologic events: 6.1% vs. 3.3% vs. 4.5% Proportion of visits when patients reported GI events: 8.0% vs. 5.8% vs. 7.1%	No resistance in the Bangkok or Harlem cohorts

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Kwan, 2021[144] *Event Driven Versus Daily Oral PrEP*	A: Once-daily TDF-FTC (n=59) B: On-demand TDF-FTC (n=60)	NR	A vs. B Creatinine clearance: no difference between arms	NR
ASPIRE Baeten, 2016[73] *Dapivirine Vaginal Ring Versus Placebo Ring*	A. Dapivirine Ring (n=1313) B. Placebo (1316)	A vs. B Risk of HIV infection: 5.4% (71/1308) vs. 7.4% (97/1306); RR 0.73 (95% CI, 0.54 to 0.98) Efficacy based on age: 18 to 21 years: -27% (95% CI, -133 to 31) 22 to 26 years: 56% (95% CI, 19 to 76%) 27 to 45 years: 51% (95% CI, 8 to 74) Over 21 years: 56% (95% CI, 31 to 71), p<0.001 Efficacy based on risk behaviors: STIs at baseline: Yes: 9.6% (24/251) vs. 12.0% (29/241); HR 0.78 (95% CI, 0.45 to 1.34); RR 0.80, 95% CI 0.48 to 1.33 No: 3.2% (30/952) vs. 5.8% (56/962); HR 0.53 (95% CI, 0.34 to 0.83); RR 0.54, 95% CI 0.35 to 0.84; HR p-value for interaction 0.30 Number of sexual partners: 0-1: 4.1% (41/1008) vs. 6.5% (64/991); HR 0.63 (95% CI, 0.42 to 0.93); rR 0.63, 95% CI 0.43 to 0.92 2+: 6.7% (13/195) vs. 10.0% (21/211); HR 0.62 (95% CI, 0.31 to 1.23); RR 0.67, 95% CI 0.35 to 1.30; HR p-value for interaction 0.96	A vs. B Any serious adverse event, any grade 3 or 4 adverse event, any grade 2 adverse event assessed as related to study product: 14% vs. 14% Any SAE: 4% (52/1313) vs. 4% (48/1316) Death: <1% (4/1313) vs. <1% (3/1316) Any grade 4 event: 2% (22/1313) vs. 2% (23/1316) Any grade 3 event: 12% (151/1313) vs. 12% (162/1316) Any grade 2 event assessed as related: 1% (7/1313)vs. 1% (9/1316) Incident sexually transmitted infections during followup: Chlamydia: 27.3% vs. 28.0%, Incidence per 100 Person-Years: 17.4, 95% CI 15.7 to 19.3 vs. 17.7, 95% CI 15.9 to 19.6 Gonorrhoeae: 12.9% vs. 14.4%, Incidence per 100 Person-Years: 8.2, 95% CI 7.0 to 9.6 vs. 9.1, 95% CI 7.9 to 10.5 Trichomonas: 14.5% vs. 13.9%, Incidence per 100 Person-Years: 9.3, 95% CI 8.0 to 10.7 vs. 8.8, 95% CI 7.6 to 10.2	A vs. B NNRTI resistance mutation, among those with a newly diagnosed infection: 11.8% (8/68) vs. 10.4% (10/96), p=0.80 Dapivirine ring arm, among those with newly diagnosed HIV infection: K103N: 2.9% (2/69) V90I: 2.9% (2/69) K101E: 1.5% (1/68) K103S: 1.5% (1/68) V106M: 1.5% (1/68) V108I 1.5% (1/68) E138A: 4.4% (3/68) E138G: 1.5% (1/68) V179D: 1.5% (1/68) H221Y: 1.5% (1/68)

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name **Author, year** **Type of PrEP**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Ring Study Nel, 2016[74] *Dapivirine Vaginal Ring Versus Placebo Ring*	A. Dapivirine Ring (n=1307) B. Placebo (652)	A vs. B Risk of HIV infection: 5.9% (77/1300) vs. 8.6% (56/650); HR 0.69 (95% CI, 0.49 to 0.99); RR 0.69, 95% CI 0.49 to 0.96 Efficacy based on age: 18 to 21 years: 9.0% (28/312) vs. 10.9% (17/156); HR 0.85 (p5% CI, 0.45 to 1.60) > 21 years: 5.0% (49/988) vs. 7.9% (39/494)	A vs. B Any adverse event: 87.4 (1142/1306) vs. 85.7% (559/652) WAE: 0% (0/1306) vs. 0.2% (1/652) Any SAE: 2.9% (38/1306) vs. 0.9% (6/652) Death: 0.2% (2/1306) vs. 0.2% (1/652) Grade 3 or 4 AE: 4.8% (63/1306) vs. 2.9% (19/652) Any sexually transmitted infection: 49.8% (651/1306) vs. 47.2% (308/652), Incidence rate per 100 Person-Years: 32.01, 95% CI 29.55 to 34.47 vs. 31.14, 95% CI 27.66 to 34.62 Chlamydia: 31.5% (411/1306) vs. 32.1% (209/652), Incidence rate per 100 Person-Years: 20.21, 95% CI 18.25 to 22.16 vs. 21.13, 95% CI 18.27 to 23.99 Gonorrhoeae: 19.1% (250/1306) vs. 16.9% (110/652), Incidence rate per 100 Person-Years: 12.29, 95% CI 10.77 to 13.82 vs. 11.12, 95% CI 9.04 to 13.20 Syphilis: 1.3% (17/1306) vs. 0.8% (5/652), Incidence rate per 100 Person-Years: 0.84, 95% CI 0.44 to 1.23 vs. 0.51, 95% CI 0.06 to 0.95 Trichomonas: 17.0% (222/1306) vs. 15.5% (101/652), Incidence rate per 100 Person-Years:10.92, 95% CI 9.48 to 12.35 vs. 10.21, 95% CI 8.22 to 12.20	A vs. B NNRTI resistance mutation, those with newly diagnosed infection: 18.2% (14/77) vs. 16.1% (9/56), p=0.75 Any resistance mutation: 39.0% (30/77) vs. 8.6% (24/56), p=0.65 E138A: 11.7% (9/77) vs. 1.8% (1/56), p=0.07 Minor PI resistance mutation: 26.0% (20/77) vs. 30.4% (17/56), p=0.58 Dapivirine arm, those with newly diagnosed infection Those assigned to PrEP: NNRTI resistance mutations (E138A, A98G, K103N, K101E, V106M): 39.0% (30/77) NRTI resistance mutation: 1.3% (1/77) Major PI resistance mutation: 2.6% (2/77)

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

DISCOVER Mayer, 2020[121]; Ogbuagu, 2021[162] *Oral TAF-FTC Versus TDF-FTC*	A: TAF-FTC (n=2694) B: TDF-FTC (n=2693)	HIV infection (primary [interim] analysis: 100% of patients had completed 48 weeks and 50% had completed 96 weeks): 0.16 vs. 0.34 per 100 person-years, IRR 0.47 (95% CI 0.19 to 1.15); 0.3% (7/2670) vs. 0.6% (15/2665), RR 0.47 (95% CI, 0.19 to 1.14), calculated HIV infection at 96 weeks (all patients had completed 96 weeks): 0.16 vs. 0.30 per 100 person-years, IRR 0.54 (95% CI, 0.23 to 1.26); 0.3% (8/2694) vs. 0.6% (15/2693), RR 0.53 (95% CI 0.23 to 1.26), calculated	Mortality: 0.1% (3/2694) vs. 0.07% (2/2693), RR 1.50 (95% CI 0.25 to 8.97) Serious adverse event: 7.5% (202/2694) vs. 6.9% (186/2693), RR 1.09 (95% CI 0.90 to 1.32) Discontinuation of study drug due to adverse event: 1.5% (40/2694) vs. 1.9% (51/2693), RR 0.78 (95% CI 0.52 to 1.18) Any adverse event: 94% (2523/2694) vs. 94% (2521/2693), RR 1.00 (95% CI 0.99 to 1.01) Rectal chlamydia: 33% (890/2694) vs. 33% (902/2693), RR 0.99 (95% CI 0.91 to 1.06) Oropharyngeal gonorrhea: 32% (871/2694) vs. 31% (838/2693), RR 1.04 (95% CI 0.96 to 1.12) Rectal gonorrhea: 30% (805/2694) vs. 30% (797/2693), RR 0.99 (95 % CI 0.91 to 1.06) Syphilis: 15% (413/2694) vs. 15% (392/2693), RR 1.05 (95% CI 0.93 to 1.20) Urethral chlamydia: 13% (346/2694) vs. 12% (314/2693), RR 1.10 (95% CI 0.95 to 1.27) Any grade 3 or 4 laboratory abnormality: 9.1% (246/2694) vs. 8.9% (240/2693), RR 1.02 (95% CI 0.86 to 1.21) Increased alanine aminotransferase (>5 times upper limit of normal): 1.7% (47/2694) vs. 1.6% (44/2693), RR 1.07 (95% CI 0.71 to 1.60) Any renal adverse event: 10% (263/2694) vs. 10% (266/2693), RR 0.99 (95% CI, 0.84 to 1.16), in primary (interim) analysis Grade ≥3 renal adverse event: 0.07% (2/2694) vs. 0.1% (3/2693), RR 0.67 (95% CI 0.11 to 3.99), in primary (interim) analysis Renal adverse event leading to discontinuation: 0.07% (2/2694) vs. 0.2% (6/2693), RR 0.33 (95% CI 0.07 to 1.65) Proximal renal tubulopathy: 0% (0/2694) vs. 0.04% (1/2693), RR 0.33 (95% CI 0.01 to 8.18, in primary (interim) analysis Creatinine clearance, median percentage change from baseline: -2.3% vs. +1.8%, p<0.0001, in primary (interim) analysis Quantitative proteinuria at 48 hours: 0.04% (1/2694) vs. 0.07% (2/2693), RR 0.50 (95% CI 0.05 to 5.51), in primary (interim) analysis, p=0.005 (rank ANCOVA, adjusting for baseline category) Fracture: 2.2% (60/2694) vs. 2.2% (60/2693), RR 1.00 (95% CI 0.70 to 1.42) Nontraumatic fracture: 0.04% (1/2694) vs. 0.07% (2/2693), RR 0.50 (95% CI 0.05 to 5.51) Hip bone mineral density, percent change from baseline: +0.6% vs. -1.0% in persons ≥25 years (p<0.001) and +1.2% vs. -1.7% in persons <25 years (p=0.04) Spine bone mineral density, percent change from baseline: +0.9% vs. -1.4% in persons ≥25 years (p<0.001) and +1.4% vs. -1.2% in persons <25 years (p=0.14) Diarrhea: 18% (480/2694) vs. 17% (453/2693), RR 1.06 (95% CI 0.94 to 1.19) Nausea: 4.2% (114/2694) vs. 4.6% (123/2693), RR 0.93 (95% CI 0.72 to 1.19), in primary (interim) analysis Acute myocardial infarction: 0.07% (2/2694) vs. 0.04% (1/2693), RR 2.00 (95% CI 0.18 to 22.04), in primary (interim) analysis Increased fasting LDL (>4.92 mmol/L): 2.1% (57/2694) vs. 0.7% (20/2693), RR 2.85 (95% CI 1.72 to 4.73) LDL concentration (median, change from baseline): -0.05 vs. -0.18 mmol/L, p<0.0001	Among 20 patients with HIV infection, 4 patients (all with suspected baseline HIV infection) in TDF-FTC arm had M184 resistance mutations

Appendix B Table 2. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Results

Study name Author, year Type of PrEP	Interventions	Clinical health outcomes	Adverse events	Resistance
			Body weight:, change from baseline (kg): +1.7 vs. +0.5, p<0.0001 Note: outcomes at 96 weeks, except where noted as primary (interim) analysis, for which 100% of patients had completed 48 weeks and 50% had completed 96 weeks	
HPTN 083 Landovitz, 2021[70] *Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC*	A: Cabotegravir 600 mg in a 3 mL IM injectable every 8 weeks (n=2,282) B: Daily TDF-FTC 300 mg + 200 mg (n=2,284)	A vs. B HIV infection: 0.57% (13/2,282) vs. 1.71% (39/2,284); RR 0.33 (95% CI, 0.18 to 0.62); incidence rate per 100 person-years, 0.41 vs. 1.22; HR 0.34 (95% CI 0.18 to 0.62), calculated	A vs. B Serious adverse events: 5.3% (120/2,280) vs. 5.3% (121/2,282), RR 0.99 (95% CI 0.78 to 1.27) Grade 3 or higher adverse events: 31.9% (727/2,280) vs. 33.6% (767/2,282) Hepatic-related discontinuations: 2.1% (47/2,280) vs. 2.1% (48/2,282) Seizures: 0.1% (2/2,280) vs. 0.2% (5/2,282) Decreased creatinine cleareance: 7.0% (159/2,280) vs. 8.3% (190/2,282) Increased aspartate aminotransferase: 2.3% (53/2,280) vs. 3.0% (69/2,282) Increased alanine aminotransferase: 1.0% (23/2,280) vs. 1.4% (32/2,282) Deaths: 0.18% (4/2,280) vs. 0	Cabotegravir: integrase-strand transfer resistance mutation in 1 of 4 baseline infections and 44.4% (4 of 9) incident cases in whom resistance testing was available; No infections during the pharmacokinetic "tail" period. TDF-FTC: 2 baseline infections and 4 of 39 incident infections had K65R, M184V, M184I, or a mixture of M184V and M184I with or without nonnucleloside reverse transcriptase inhibitor mutations
HPTN 084 Delaney-Moretwle, 2022[88] *Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC*	A: Cabotegravir 600 mg in a 3 mL IM injectable every 8 weeks (n=1,592) B: Daily TDF-FTC 300 mg + 200 mg (n=1,586)	A vs. B HIV infection: 0.3% (4/1,592) vs. 2.3% (36/1,586); RR 0.11 (95% CI 0.04 to 0.31; incidence rate per 100 person-years, 0.20 (95% CI 0.06 to 0.52) vs. 1.85 (95% CI 1.30 to 2.57); HR 0.12 (95% C, 0.05 to 0.31)	A vs. B Serious adverse events: 2.0% (33/1,614) vs. 2.0% (33/1,610), RR 1.00 (95% CI 0.62 to 1.61) Grade 3 or higher adverse events: 17.1% (276/1,614) vs. 17.4% (280/1,610) Hepatic-related discontinuation: 0.9% (15/1,614) vs. 1.1% (18/1,610) Seizures: 0 vs. 0.1% (1/1,610) Deaths: 0.2% (3/1,614) vs. 0 Chlamydia: 16.2% (261/1,614) vs. 17.8% (287/1,610), RR 0.91 (95% CI 0.78 to 1.06) Gonorrhea: 7.8% (126/1,614) vs. 7.8% (125/1,610), RR 1.01 (95% CI 0.79 to 1.28) Trichomonas: 7.7% (124/,1614) vs. 6.8% (109/1,610), RR 1.13 (95% CI 0.89 to 1.45) Grade 3 decreased creatinine clearance: 6.8% (110/1,614) vs. 7.8% (125/1,610)	No integrase strand transfer inhibitor resistance mutations among 4 incident infections in the cabotegravir group. Of 36 infections in the TDF-FTC group, 1 M184V and "several" (mainly K103N) resistance mutations occurred

Abbreviations: 3MV=Many Men, Many Voices; ADAPT/HPTN=Alternative Dosing to Augment Pre-Exposure Prophylaxis Pill Taking/HIV Prevention Trials Network; ALT=alanine aminotransferase; aOR=adjusted odds ratio; ART=antiretroviral therapy; AST=aspartate aminotransferase; BMD=bone mineral density; CDC=Centers for Disease Control and Prevention; CI=confidence interval; DEXA=dual energy X-ray absorptiometry; eGFR=estimated glomerular filtration rate; ELISPOT=Enzyme-Linked ImmunoSpot assay; Env=Env peptide pool; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; GFR=glomerular filtration rate; GI=gastrointestinal; HBV=hepatitis B virus; HCV=hepatitis C virus; HR=hazard ratio; HSV=herpes simplex virus; IAVI=International AIDS Vaccine Initiative; IFN-y=interferon gamma; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; IQR=interquartile range; ISCD=International Society for Clinical Densiometry; L2=second lumbar vertebra; L4=fourth lumbar vertebra; LS=lumbosacral spine; NA=not applicable; NNRTI=nonnucleoside reverse transcriptase inhibitor; NNT=number needed to treat; NR=not reported; OR=odds ratio; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; RNA=ribonucleic acid; RR=relative risk; RT=retention time; STI=sexually transmitted infection; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; TFV=tenofovir; TH=thoracic vertebra; VOICE=Vaginal and Oral Interventions to Control the Epidemic; WHO=World Health Organization.

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name Author, year	Interventions	Adherence method of assessment and rate	U.S. factors associated with adherence	Adherence and effectiveness	Subgroups
Bangkok Tenofovir Study Choopanya, 2013[53] and Martin, 2015[153] *Oral PrEP Versus Placebo or No PrEP*	A. Tenofovir 300 mg once daily (n=1,204) B. Placebo (n=1209) Participants could choose directly observed therapy or monthly take-home prescriptions, and switch at monthly followup appointments	Plasma sample detectable (TDF group only, all seroconverters + random sample of uninfected controls): 66% (100/151); seroconverters only: 39% (5/13); uninfected only: 67% (93/138) Drug diaries: participants took study drug a mean of 83.8% of days (SD, 23.0; median, 94.1% of days; IQR, 79.2 to 98.7). No difference by treatment group (p=0.16). Patients were on directly observed therapy 86.9% of the time, median adherence in patients on directly observed therapy was 94.8% and on nondirectly observed therapy was 100%. Proportion of patients who - -Took study drug at least 95% of the time: 46.9% -Took study drug at least 90% of the time: 60.6% -Took study drug 80 to 89% of the time: 13.3% -Took study drug 70 to 79% of the time: 7.3% -Took study drug <70% of the time: range, 1.3% to 5.4%	Reported in Subgroups column	Efficacy (based on HR) in adherent patients on directly observed therapy (i.e., those who took drug for 71% of days and did not miss more than 2 consecutive days): 55.9% (95% CI, -18.8 to 86) (HR, 0.44 [95% CI, 0.14 to 1.19]); excluding 2 tenofovir patients with no detectable plasma tenofovir efficacy, 73.5% (95% CI, 16.6 to 94) (HR, 0.26 [95% CI, 0.06 to 0.83]) Efficacy in adherent patients on directly observed therapy or nondirectly observed therapy, 55.9% (95% CI, -9.8 to 84.4) (HR, 0.44 [95% CI, 0.16 to 1.10]) ≥60% adherence: Efficacy, 48.9% (HR, 0.51) ≥75% adherence: Efficacy, 58.0% (HR, 0.42) ≥97.5% adherence: Efficacy, 83.5% (HR, 0.16) Quantifiable tenofovir plasma concentration: 39% (5/13) in cases and 67% (93/138) in controls; OR, 0.30 (95% CI, 0.09 to 0.98)	A vs. B Sex - efficacy (based on HR) Female: 78.6% (95% CI, 16.8 to 96.7) Male: 37.6% (95% CI, -17.8 to 67.9) Sex - adherence Female: 95.6% (95% CI, 81.1 to 98.9) Male: 93.8% (95% CI, 78.8 to 98.7) Age - efficacy (based on HR) 20 to 29 years: 33.6% (95% CI, -40.1 to 69.8) 30 to 39 years: 29.2% (95% CI, -121.7 to 79.1) ≥40 years: 88.9% (95% CI, 41.1 to 99.4) Age - adherence <40 years: 92.3% (95% CI, 75.5 to 98.2) ≥40 years: 98.2% (95% CI, 93.5 to 99.5) Injected during 12 weeks before enrollment - efficacy (based on HR) Yes: 44.3% (95% CI, -12.5 to 72.4) No: 57.4% (95% CI, -17.0 to 86.6) Shared needles 12 weeks before enrollment - efficacy (based on HR) Yes: 54.7% (95% CI, -44.0 to 87.9) No: 47.6% (95% CI, -2.5 to 74) Unclear if subgroup analyses prespecified

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
Bangkok Tenofovir Study Martin, 2014[152] *Oral PrEP Versus Placebo or No PrEP*	Same as Choopanya 2013	Same as Choopanya 2013	Same as Choopanya 2013	Creatinine clearance was on average 5.7 mL/min lower for participants on tenofovir reporting >80% adherence vs. ≤80% adherence using the Cockcroft-Gault method (results similar for other methods)	A vs. B, mean creatinine clearance (Cockcroft-Gault) at month 60 Male: 90.8 vs. 96.5 mL/min Female: 95.3 vs. 99.1 mL/min Among those on tenofovir, clearance was lower in men than women, p<0.001 Ages 20 to 29 years: 101.2 vs. 107.9 mL/min Ages 30 to 39 years: 92.7 vs. 97.9 mL/min Ages 40 to 59 years: 76.9 vs. 80.4 mL/min Among those on tenofovir, clearance was lower among those age ≥30 years than those ages 20 to 29 years (p<0.001), and the difference increased over time (p=0.002) Injected drugs in the 3 months before enrollment: 90.1 vs. 96.8 mL/min Did not inject drugs in the 3 months before enrollment: 94.4 vs. 97.3 mL/min Creatinine clearance at baseline 60 to 79 mL/min: 68.0 vs. 72.8 mL/min Creatinine clearance at baseline 80 to 99 mL/min: 85.1 vs. 92.8 mL/min Creatinine clearance at baseline ≥100 mL/min: 111.7 vs. 117.8 mL/min Analysis of a subset of participants who stopped tenofovir indicates that the decrease in creatinine clearance was reversible

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
FEM-PrEP Van Damme, 2012[172] and Agot, 2015[128] *Oral PrEP Versus Placebo or No PrEP*	A. Oral TDF-FTC 300/200 mg once daily (n=1,062) B. Placebo, once daily (n=1,058)	Plasma sample, presence of ≥10 ng/mL TDF consistent with dose in last 48 hours (TDF-FTC group only, all seroconverters + random sample of uninfected controls): -Beginning of infection window: 32% (34/105); seroconverters only: 26% (7/27); uninfected only: 35% (27/78) -End of infection window: 33% (42/128); seroconverters only: 21% (7/33); uninfected only: 37% (35/95) -Both visits: 22% (23/105); seroconverters only: 15% (4/27); uninfected only: 24% (19/78)	NA	A vs. B Plasma TDF >10 ng/mL: 15% (4/27) in cases and 24% (19/78) in controls; OR, 0.54 (95% CI, 0.17 to 1.76)	A vs. B <u>Age HIV infection</u> ≥25 years: 4% (11/422) vs. 4% (12/421); RR, 0.91 (95% CI, 0.41 to 2.05) <25 years: 6% (22/602) vs. 6% (23/611): RR, 0.97 (95% CI, 0.55 to 1.72); p=0.91 for interaction Unclear if subgroup analysis prespecified

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name Author, year	Interventions	Adherence method of assessment and rate	U.S. factors associated with adherence	Adherence and effectiveness	Subgroups
FEM-PrEP Van Damme, 2012[172] and Agot, 2015[128] (Cont'd) *Oral PrEP Versus Placebo or No PrEP*	Same as Van Damme 2012	Self-report only, participants reporting that they usually or always take assigned drug: 95% Pill count only, data consistent with ingestion of study drug: 88% of days Self-reported pill use in the previous 7 days: - ≥10 ng/mL plasma TFV among visits where participants report ≥6 days taking pills: PPV, 38.0 (420/1,105) - ≥0.25 ng/mL plasma TFV among visits where participants report ≥1 days taking pills: PPV, 42.2 (490/1,162) Pill counts during each visit interval: - ≥10 ng/mL plasma TFV and ≥100,000 fmol TFV dp/mL in ULPCs among visits where pill count data indicate ≤1 day without pill use: PPV, 26.2 (249/952) Self-reported pill use in previous 4 weeks: - ≥10 ng/mL plasma TFV and ≥100,000 fmol TFV dp/mL in ULPCs among visits where participants report usually or always taking pills: PPV, 28.7 (329/1,146)	Same as Van Damme 2012	Same as Van Damme 2012	Same as Van Damme 2012

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
FEM-PrEP Mandala, 2014[149] *Oral PrEP Versus Placebo or No PrEP*	Same as Van Damme 2012	Same as Van Damme 2012	Same as Van Damme 2012	Of the 4 participants with grade 2+ creatininemia in the TDF-FTC arm, 1 had excellent adherence, 2 had good adherence, and 1 was not adherent in the interval prior to the event. Of the 8 participants with grade 3+ ALT and/or AST in the TDF-FTC arm, 2 had excellent adherence, 1 had good adherence, and 4 were nonadherent in the interval before the event (and data was not available for 1 participant). TDF-FTC concentration data from a subcohort of 150 women indicated that very few consistently took the study drug, precluding long-term analysis; however, those with ~40% adherence in the first 4 weeks (considered "good") had higher mean change in AST levels from baseline to week 4 (2.90 [95% CI, 0.37 to 5.42]; p=0.05) than those with less than good adherence. No differences were found in ALT, creatinine, or phosphorus during this time period. No differences were found between final drug use interval and 4 weeks after product withdrawal.	In the TDF-FTC arm, proportions of grade 1+ and grade 2+ ALT or AST toxicities were significantly higher in participants who were HBsAb-infected than uninfected, specifically: Grade 1+: 31.6% vs. 22.4%; p<0.007 Grade 2+: 5.6% vs. 2.6%; p<0.047 In the placebo arm, the proportion of grade 1+ ALT or AST toxicities was significantly more frequent in those who were HBsAB-infected than uninfected: 29.5% vs. 17.1%; p<0.001
Grohskopf, 2013[52] (CDC Safety Study) *Oral PrEP Versus Placebo or No PrEP*	A. TDF, 300 mg orally daily, immediately or after a 9-month delay (n=201) B. Placebo, immediately or after a 9-month delay (n=199)	Pill count: 92% (range, 79% to 98%); sensitivity analysis removing participants with temporary drug interruptions 93% (range, 81% to 98%) MEMS 77% (range, 57% to 92%); sensitivity analysis removing participants with temporary drug interruptions 79% (range, 60% to 92%) Adherence by group was NR Persistence: Temporary drug discontinuation: 42% (84/201) Overall (TDF + placebo), 17.6% (70/400) had a permanent drug discontinuation	NR	<u>Safety - grade 3 or 4 adverse event</u> 50% adherence: RR, 1.08 (95% CI, 0.57 to 2.03) 90% adherence: RR, 1.08 (95% CI, 0.57 to 2.03) <u>Safety - fracture</u> 50% adherence: RR, 1.91 (95% CI, 0.51 to 7.17) 90% adherence: RR, 1.90 (95% CI, 0.50 to 7.17)	NR

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
Liu, 2011[148] (companion to Grohskopf, 2013) *Oral PrEP Versus Placebo or No PrEP*	Same as Grohskopf 2013	Same as Grohskoph 2013	Same as Grohskopf 2013	Same as Grohskopf 2013	Same as Grohskopf 2013
IAVI Kenya Study Mutua, 2012[67] *Oral PrEP Versus Placebo or No PrEP*	A. Daily TDF-FTC 300/200 mg (n=24) B. Intermittent (Monday, Friday and within 2 hours postcoital, not to exceed 1 dose/day) TDF-FTC (n=24) C. Daily placebo (n=12) D. Intermittent placebo (n=12)	MEMS: Electronically monitored pill bottle openings and closings and text message self-report Daily regimen: Median unadjusted adherence rate (MEMS data): A vs. C: 82% (IQR, 63–96) vs. 84% (IQR, 63–96); overall 83% (IQR, 63-92) Median adjusted adherence rate (MEMS, adjusted for daily openings and extra pills removed): A vs. C: 92% (IQR, 79–101) vs. 93% (IQR, 84–96); overall 92% (82-99) Intermittent regimen: Median unadjusted adherence rate (MEMS data): B vs. D: 56% (IQR, 31-88) vs. 34% (IQR, 19-72); overall 55% (IQR, 28-78)	NA	NR	Adherence rates did not differ by gender

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
IAVI Uganda Study Kibengo, 2013[68] *Oral PrEP Versus Placebo or No PrEP*	A. Daily TDF-FTC 300/200 mg (n=24) B. Intermittent (Monday, Friday and within 2 hours postcoital, not to exceed 1 dose/day) TDF-FTC 300/200 mg (n=24) C. Daily placebo (n=12) D. Intermittent placebo (n=12)	MEMS: Electronically monitored pill bottle openings and closings and text message self-report Daily regimen: A vs. C Median unadjusted adherence rate (MEMS data): 98% (IQR, 89–100) vs. 96% (IQR, 95–99); p=0.87 Median adjusted adherence rate (MEMS, adjusted for daily openings and extra pills removed): 98% (IQR, 92–100) vs. 98% (IQR, 95–99); p=0.88 Intermittent regimen: B vs. D Median unadjusted adherence rate (MEMS data): 80% (IQR, 74–86) vs. 78% (IQR, 67–86); p=0.60 Median adjusted adherence rate (Monday, Friday doses only): 91% (IQR, 78–102) vs. 88% (IQR, 69–94); p=0.25 Median adjusted adherence rate (MEMS + text reporting, postcoital doses only): 40% (IQR, 23–58) vs. 53% (IQR, 15–79); p=0.45	NA	NR	Adherence rates did not differ by gender

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
IPERGAY Molina, 2015[66] Antoni, 2020[129] *Oral PrEP Versus Placebo or No PrEP*	A. On demand TDF-FTC 300/200 mg (n=199) B. Placebo (n=201) On demand dosing schedule: 1. Two pills 2 to 24 hours before sex 2. Third pill 24 hours after first drug intake 3. Fourth pill 24 hours later Other instructions: For multiple consecutive episodes of sexual intercourse, take one pill per day until the last sexual intercourse, then two postexposure. When resuming PrEP, take a loading dose of two pills unless the last drug intake was less than 1 week earlier, in which case take only one pill.	A vs. B TDF plasma levels detectable over 10 months (among 113 participants): 82% to 100% (86% overall) vs. 0% to 6% FTC plasma levels detectable over 10 months (among 113 participants): 82% to 100% (82% overall) vs. 0% to 6% Returned bottle pill counts, median number of pills taken/month: 15 (IQR, 11–21) vs. 15 (IQR, 9–21); p=0.57 Self-report adherence: -Correct PrEP use (at least one pill taken within 24 hours before sex and one pill taken within 24 hours after sex): 45% (292/649) sexual acts vs. 40% (225/563) sexual acts -Suboptimal PrEP use (any use other than correct use as defined above): 27% (175/649) sexual acts vs. 31% (175/563) sexual acts -No PrEP: 27% (175/649) sexual acts vs. 29% (163/563) sexual acts	NR	Study drugs not detected in plasma of 2 PrEP patients at the time of HIV-1 diagnosis, patients also nonadherent by pill counts (returned 58 and 60 of 60 tablets)	Antoni 2020: A vs B, among men with at least one period of less frequent sex (n=270) HIV incidence per 100 person-years: 0 (95% CI 0 to 5.4) vs. 9.2 (95% CI 3.4 to 20.1); RRR 100% (95% CI 39 to 100%)

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name Author, year	Interventions	Adherence method of assessment and rate	U.S. factors associated with adherence	Adherence and effectiveness	Subgroups
iPrEx Grant, 2010[137] *Oral PrEP Versus Placebo or No PrEP*	A. TDF-FTC 300/200 mg (n=1,251) B. Placebo (n=1,248)	Plasma sample, drug detectable (TDF-FTC group only, all seroconverters + random sample of uninfected controls): 33% (25/77); seroconverters only: 9% (3/34); uninfected only: 51% (22/43) Self-reported pill use: Week 4: mean, 89% vs. 92%; p<0.001; Week 8: mean, 93% vs. 94%; p=0.006; Week 9 to study completion: mean, 95% in both groups Pill use, estimated according to pill count in returned bottles, ≥8 weeks: range, 89% to 95% Pill dispensation date/ quantity, year 1: decreased from 99% to 91%	NR	Efficacy ≥50% pill use: HR, 0.50 (95% CI, 0.30 to 0.82) <50% pill use: HR, 0.68 (95% C,I 0.33 to 1.41); p=0.48 for interaction ≥90% pill use: HR, 0.27 (95% CI, 0.12 to 0.59) <90% pill use: HR, 0.79 (95% CI, 0.48 to 1.31); p=0.02 for interaction	A vs. B Age - HIV incidence <25 years: 3.7% (22/591) vs. 5.6% (37/662); HR, 0.67 (95% CI, 0.40 to 1.14) ≥25 years: 2.1% (14/660) vs. 4.6% (27/586); HR, 0.41 (95% CI, 0.24 to 0.87; p=0.36 for interaction Race/ethnicity - HIV incidence Non-Hispanic: 1.1% (4/351) vs. 2.3% (8/342); HR, 0.48 (95% CI, 0.14 to 1.60) Hispanic: 3.6% (32/900) vs. 6.2% (56/906); HR, 0.57 (95% CI, 0.37 to 0.89); p=0.79 for interaction Risk behaviors, unprotected receptive anal intercourse - HIV incidence Yes: 3.1% (23/732) vs. 7.4% (56/753); HR, 0.42 (95% CI, 0.26 to 0.68) No: 2.5% (13/519) vs. 1.6% (8/495); HR, 1.59 (95% CI, 0.66 to 3.84); p=0.01 for interaction Subgroup analyses prespecified
iPrEx Deutsch, 2015[134] *Oral PrEP Versus Placebo or No PrEP*	*Transgender women only* A. TDF-FTC 300/200 mg (n=170) B. Placebo (n=169)	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	A vs. B Transgender women only - HIV infection: 7% (11/170) vs. 6% (10/169); HR. 1.1 (95% CI. 0.5 to 2.7) MSM only - HIV infection: HR. 0.50 (95% C.I 0.34 to 0.75) Transgender women vs. MSM, p=0.09 for interaction Subgroup analysis not prespecified

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
iPrEx Liu, 2014[147] *Oral PrEP Versus Placebo or No PrEP*	Same as Grant 2010	PBMC sampling - random set of total sample (n=2,499; no stratification by randomization group): Proportion with detectable drug, week 8: 55% (95% CI, 49% to 60%) Proportion with drug never detected during longitudinal followup: 31% Proportion with drug inconsistently detected during longitudinal followup: 39% Proportion with drug always detected, longitudinal followup: 30% -San Francisco site only (n=140; 6% of total sample): Proportion with detectable drug, week 8: 90% (95% CI, 76% to 96%) Proportion with drug never detected during longitudinal followup: 1% Proportion with drug inconsistently detected during longitudinal followup: 27% Proportion with drug always detected, longitudinal followup: 67% -Boston site only (n=87; 3% of total sample): Proportion with detectable drug, week 8: 72% (95% CI, 56% to 84%)	Factors associated with drug detection at week 8: Age ≤20 vs. 21 to 25 years: OR, 2.44 (95% CI, 1.24 to 4.77) Age ≤20 vs. 26 to 30 years: OR, 2.18 (95% CI, 1.06 to 4.49) Age ≤20 vs. >30 years: OR, 2.86 (95% CI, 1.36 to 6.03) Factors associated with some drug detection during longitudinal followup vs. no drug detection: Age ≤20 vs. 21 to 25 years: OR, 4.04 (95% CI, 1.66 to 9.85) Age ≤20 vs. 26 to 30 years: OR, 3.42 (95% CI, 1.21 to 9.67) Age ≤20 vs. >30 years: OR, 5.13 (95% CI, 1.87 to 14.07) Factors associated with drug always detected during longitudinal followup vs. never detected: Age ≤20 vs. 21 to 25 years: OR, 6.32 (95% CI, 2.09 to 19.09) Age ≤20 vs. 26 to 30 years: OR, 4.74 (95% CI, 1.26 to 17.76)	Same as Grant 2010	Same as Grant 2010

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name Author, year	Interventions	Adherence method of assessment and rate	U.S. factors associated with adherence	Adherence and effectiveness	Subgroups
			Age ≤20 vs. >30 years: OR, 33.24 (95% CI, 9.91 to 111.45) No condomless receptive anal intercourse vs. condomless receptive anal intercourse: OR, 3.25 (95% CI, 1.54 to 6.85)		
iPrEx Marcus, 2014[150] *Oral PrEP Versus Placebo or No PrEP*	*HSV-2 negative substudy only* *A.* TDF-FTC 300/200 mg (n=692) B. Placebo (n=691)	Same as Grant 2010	Same as Grant 2010	A vs. B HSV-2 infection, TFV-DP ≤16: HR, 1.0 (95% CI, 0.4 to 2.5) HSV-2 infection, TFV-DP >16: HR, 1.0 (95% CI, 0.3 to 3.5)	Same as Grant 2010
iPrEx Mulligan, 2015[159] *Oral PrEP Versus Placebo or No PrEP*	*BMD substudy only* A. TDF-FTC 300/200 mg (n=247) B. Placebo (n=251)	Proportion of TDF-FTC patients with tenofovir (TFV) or FTC detected in plasma: 24 weeks: 57% 48 weeks: 48% 72 weeks: 53%	Same as Grant 2010	TVF-DP >16 (average, 43) fmol/106 PBMCs (indicative of consistent dosing), mean change in spine BMD: -1.42% (SD, 0.29%); mean change in hip BMD, -0.85% (SD, 0.19%); p<0.001 for both vs. placebo	Same as Grant 2010
iPrEx Solomon, 2014[168] *Oral PrEP Versus Placebo or No PrEP*	Renal substudy only A. TDF-FTC 300/200 mg (n=563) B. Placebo (n=574)	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
iPrEX Solomon 2016[169] *Oral PrEP Versus Placebo or No PrEP*	HBV Substudy	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010
Partners PrEP Baeten, 2012[51] *Oral PrEP Versus Placebo or No PrEP*	A. Once-daily TDF 300 mg + placebo TDF-FTC (n=1,571) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=1,565) C. Placebo TDF + placebo TDF-FTC (n=1,570) All participants received a comprehensive package of HIV-1 prevention services and were offered HBV vaccination	Detectable plasma tenofovir level: 35% (6/17) in TDF converters, 25% (3/12) in TDF-FTC converters, and 82% (737/901) in 901 samples from 198 controls Monthly pill counts of returned study tablets: 98% of dispensed study bottles were returned across study groups A vs. B vs. C: Bottles with ≥50% taken: 99% vs. 99% vs. 99% Bottles with ≥75% taken: 98% vs. 98% vs. 99% Bottles with ≥90% taken: 92% vs. 93% vs. 92% Bottles with ≥95% taken: 84% vs. 84% vs. 85%	NR	Detectable vs. nondetectable plasma tenofovir level: HR, 0.14 (95% CI, 0.05 to 0.43) for TDF patients and 0.10 (95% CI, 0.02 to 0.44) for TDF-FTC patients	Sex TDF vs. placebo Female: HR, 0.29 (95% CI, 0.13 to 0.63) Male: HR, 0.37 (95% CI, 0.17 to 0.80); p=0.65 for interaction Sex TDF-FTC vs. placebo Female: HR, 0.34 (95% CI, 0.16 to 0.72) Male: HR, 0.16 (95% CI, 0.06 to 0.46); p=0.24 for interaction Age TDF vs. placebo <25 years: HR, 0.28 (95% CI, 0.01 to 1.01) ≥25 years: HR, 0.34 (95% CI, 0.18 to 0.61) p=0.79 for interaction Age TDF-FTC vs. placebo <25 years: HR, 0.59 (95% CI, 0.21 to 1.61) ≥25 years: HR, 0.17 (95% CI, 0.07 to 0.37) p=0.06 for interaction Unprotected sex with study partner TDF vs. placebo Yes: HR, 0.47 (95% CI, 0.25 to 0.89) No: HR, 0.13 (95% CI, 0.04 to 0.44) p=0.05 for interaction Unprotected sex with study partner TDF-FTC vs. placebo Yes: HR, 0.27 (95% CI, 0.12 to 0.58) No: HR, 0.22 (95% CI, 0.08 to 0.58) p=0.77 for interaction Unclear if subgroup analyses prespecified
Partners PrEP Celum 2014[120] *Oral PrEP Versus Placebo or No PrEP*	A. Once-daily TDF 300 mg + placebo TDF-FTC (n=528) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=513)	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name Author, year	Interventions	Adherence method of assessment and rate	U.S. factors associated with adherence	Adherence and effectiveness	Subgroups
Partners PrEP Donnell, 2014[135] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	*TDF arm only (n=472 samples)* Plasma tenofovir concentration: >0.3 ng/mL: 82% >10 ng/mL: 78% >40 ng/mL: 70% No detectable tenofovir: 18% Pill count coverage >80%: 92% *TDF-FTC arm only (n=502 samples)* Plasma tenofovir concentration: >0.3 ng/mL: 79% >10 ng/mL: 74% >40 ng/mL: 69% No detectable tenofovir: 21% Pill count coverage >80%: 96%	Same as Baeten 2012	TDF HIV seroconverters (17 samples, n=17) vs. HIV uninfected (455 samples, n=96) Tenofovir >0.3 ng/mL: 41% (7/17) vs. 83% (378/455); aRR, 82% (95% CI, 46% to 94%); HR, 0.18 (95% CI, 0.06 to 0.54) Tenofovir >10 ng/mL: 41% (7/17) vs. 79% (361/455); aRR, 77% (95% CI, 31% to 92%); HR, 0.23 (95% CI, 0.08 to 0.69) Tenofovir >40 ng/mL: 24% (4/17) vs. 72% (328/455); aRR, 87% (95% CI, 59 to 96%); HR, 0.13 (95% CI, 0.04 to 0.41) Tenofovir detected: 41% (7/17) vs. 83% (378/455); OR, 0.14 (95% CI, 0.05 to 0.39) Pill count coverage >80%: 71% (12/17) vs. 95% (431/455); OR, 0.13 (95% CI, 0.04 to 0.41) TDF-FTC HIV seroconverters (12 samples) vs. HIV uninfected (490 samples, n=100) Tenofovir >0.3 ng/mL: 17% (2/12) vs. 80% (394/490); aRR, 93% (95% CI, 60% to 99%) Tenofovir >10 ng/mL: 17% (2/12) vs. 76% (369/490); aRR, 91% (95% CI, 46% to 99%) Tenofovir >40 ng/mL: 17% (2/12) vs. 70% (342/490); aRR, 88% (95% CI, 31% to 98%) Tenofovir detected: 17% (2/12) vs. 80% (394/490); OR, 0.05 (95% CI, 0.01 to 0.23) Pill count coverage >80%: 58% (7/12) vs. 97% (474/490); OR, 0.05 (95% CI, 0.01 to 0.17) Combined PrEP arms HIV seroconverters (39 samples, n=39) vs. HIV uninfected (945 samples, n=196) Tenofovir >0.3 ng/mL: 41% (9/29) vs. 83% (772/945); aRR, 82% (95% CI, 46% to 94%); OR, 0.10 (95% CI, 0.05 to 0.23) Tenofovir >10 ng/mL: 41% (9/29) vs. 79% (730/945); aRR, 77% (95% CI, 31% to 92%); OR, 0.13 (95% CI, 0.06 to 0.30) Tenofovir >40 ng/mL: 24% (6/29) vs. 72% (670/945); aRR, 87% (95% CI, 59% to 96%); OR, 0.11 (95% CI, 0.04 to 0.27) Tenofovir detected: 41% (9/29) vs. 83% (772/945); OR, 0.10 (95% CI, 0.05 to 0.23) Pill count coverage >80%: 71% (19/29) vs. 95% (905/945); OR, 0.08 (0.04 to 0.19)	Same as Baeten 2012

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Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
Partners PrEP Haberer, 2013[138] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	*Adherence substudy only* A vs. B vs. C Unannounced pill count: unannounced visit to participants' home on randomly selected day every month for the first 6 months and quarterly thereafter: 97% vs. 98% vs. 98% MEMS: electronic recording of date and time of pill bottle openings: 90% vs. 92% vs. 91%	NA	NR	NA
Partners PrEP Heffron, 2014[139] *Oral PrEP Versus Placebo or No PrEP*	A. TDF or FTC B. Placebo	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	A vs. B HIV infection Women using hormonal contraception (DMPA), HIV-1 infection: aHR, 0.35 (95% CI, 0.12 to 1.05) Women not using hormonal contraception, HIV-1 infection: aHR, 0.25 (95% CI, 0.07 to 0.84) Men with female partners using hormonal contraception, HIV-1 infection: aOR, 0.10 (95% CI, 0.00 to 0.77) Men with female partners not using hormonal contraception, HIV-1 infection: aOR, 0.18 (95% CI, 0.08 to 0.62)
Partners PrEP Lehman, 2015[146] *Oral PrEP Versus Placebo or No PrEP*	*Seroconverters only* A. Once-daily TDF 300 mg + placebo TDF-FTC (n=39) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=25) C. Placebo TDF + placebo TDF-FTC (n=58)	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012

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Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
Partners PrEP Matthews, 2014[154] *Oral PrEP Versus Placebo or No PrEP*	Oral TDF and TDF-FTC PrEP; placebo; risk reduction counseling, couples counseling, and condoms	TDF or TDF-FTC testing: -Pregnant: 71% -Not pregnant: 81% aHR, 0.81 (95% CI, 0.43 to 1.52) Pill count: -Pregnant: 97% -Not pregnant: 98% aRR, 0.99 (95% CI, 0.98 to 1.00) High adherence rating: -Pregnant: 98% -Not pregnant: 99%	Partners PrEP data suggest that women were willing to use PrEP around time of conception, even in absence of safety and efficacy data for prevention. Periconception adherence was highest at 5 months prior to pregnancy. Qualitative data suggest this may have been partially due to partner involvement	NR	Same as Baeten 2012
Partners PrEP Mugo, 2014[157] *Oral PrEP Versus Placebo or No PrEP*	*HIV-uninfected women only* A. Once daily TDF 300 mg (n=595) B. Once daily TDF-FTC 300/200 mg (n=565) C. Once daily placebo (n=621)	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012

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Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
Partners PrEP Mugwanya, 2015[158] *Oral PrEP Versus Placebo or No PrEP*	A. Once daily TDF 300 mg (n=1,548) B. Once daily TDF-FTC 300/200 mg (n=1,545) C. Once daily placebo (n=1,547)	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	A vs. B vs. C <u>Mean eGFR (mL/min/1.73 m^2)</u> Female (n=586 vs. 557 vs. 611): -0.43 vs. -0.69 vs. +1.04; difference: A vs. C, -1.47 (95% CI, -2.92 to -0.02); B vs. C, -1.73 (95% CI, -3.23 to -0.23) Male (n=962 vs. 988 vs. 936): +0.66 vs. +0.25 vs. +1.75; difference: A vs. C, -1.09 (95% CI, -2.09 to -0.08); B vs. C, -1.50 (95% CI, -2.5.3 to -0.49) Ages 18 to 34 years (n=879 vs. 846 vs. 834): +0.29 vs. -0.39 vs. +1.28; difference: A vs. C, -0.99 (95% CI, -2.19 to 0.21); B vs. C, -1.67 (95% CI, -2.88 to -0.46) Ages 35 to 44 years (n=471 vs. 491 vs. 508): +0.33 vs. -0.21 vs. +1.78; difference: A vs. C, -1.45 (95% CI, -2.87 to -0.02); B vs. C, -1.99 (95% CI, -3.45 to -0.54) Age ≥45 years (n=198 vs. 208 vs. 205): -0.82 vs. +0.27 vs. +0.76; difference: A vs. C, -1.58 (95% CI, -3.49 to 0.34); B vs. C, -0.49 (95% CI, -2.56 to 1.58) <u>Serum GFR decline ≥25% from baseline</u> Male: aHR: A vs. C, 1.04 (95% CI, 0.39 to 2.78); B vs. C, 1.41 (95% CI, 0.50 to 3.45) Female: aHR: A vs. C, 1.51 (95% CI, 0.68 to 3.38); B vs. C, 1.56 (95% CI, 0.70 to 3.48) p<0.05 for interaction Ages 18 to 34 years: aHR: A vs. C, 1.54 (95% CI, 0.60 to 3.98); B vs. C, 1.37 (95% CI, 0.50 to 3.67) Ages 35 to 44 years: aHR: A vs. C, 1.07 (95% CI, 0.42 to 2.69); B vs. C, 1.56 (95% CI, 0.67 to 3.67) Age ≥45 years: aHR: A vs. C, 1.46 (95% CI, 0.24 to 8.76); B vs. C, 2.11 (95% CI, 0.40 to 10.94); p<0.05 for interaction

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Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
Partners PrEP Murnane, 2013[161] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	High-risk, unprotected sex in prior 3 months - transmission events A vs. B: 5/896 vs. 20/857 B vs. C: 3/893 vs. 20/857 High-risk, partner plasma HIV-1 RNA >50,000 copies/mL - transmission events A vs. B: 4/269 vs. 18/289 B vs. C: 4/271 vs. 18/289 High-risk, STI in either partner A vs. B: 8/1,063 vs. 22/1,079 B vs. C: 7/1,057 vs. 22/1,079 High-risk, risk score >5 A vs. B: 7/347 vs. 28/380 B vs. C: 6/354 vs. 28/380 Women with partner HIV-1 plasma >50,000 copies/mL A vs. B: 2/144 vs. 13/154 B vs. C: 4/146 vs. 13/154 Women, age <30 years A vs. B: 4/202 vs. 17/194 B vs. C: 5/188 vs. 17/194 Women, risk score >5 A vs. B: 4/140 vs. 16/165 B vs. C: 5/140 vs. 16/165

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Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
Partners PrEP Murnane, 2015[160] *Oral PrEP Versus Placebo or No PrEP*	Same as Baeten 2012	*TDF or TDF-FTC arm only* Proportion of patients with pill coverage 80% to 107%: Returned pill count (up to 2 excess doses allowed/month) and/or unreturned pills assumed to be taken/Total number of pills expected to have been taken: Month 1 (n=299): 80% Month 3 (n=301): 81% Month 6 (n=305): 84% Month 12 (n=262): 87% Month 18 (n=188): 86% Month 24 (n=120): 91% Proportion of patients with plasma tenofovir level >40 ng/mL: Month 1 (n=299): 77% Month 3 (n=301): 70% Month 6 (n=305): 68% Month 12 (n=262): 65% Month 18 (n=188): 59% Month 24 (n=120): 68%	NA	A vs. C 100% predicted adherence: HR, 0.19 (95% CI, 0.07 to 0.56) 90% predicted adherence: HR, 0.22 (95% CI, 0.10 to 0.54) B vs. C 100% predicted adherence: HR, 0.12 (95% CI, 0.03 to 0.52) 90% predicted adherence: HR, 0.16 (95% CI, 0.05 to 0.45) Predicted adherence based on sample of patients with plasma tenofovir concentration in logistic model	Same as Baeten 2012
Partners PrEP Were, 2014[173] *Oral PrEP Versus Placebo or No PrEP*	*HIV-uninfected men only* A. Once-daily TDF 300 mg + placebo TDF-FTC (n=986) B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=1,013) C. Placebo TDF + placebo TDF-FTC (n=963)	NR	NA	NR	NR

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Study name Author, year	Interventions	Adherence method of assessment and rate	U.S. factors associated with adherence	Adherence and effectiveness	Subgroups
Project PrEPare ATN 082 Hosek, 2013[141] *Oral PrEP Versus Placebo or No PrEP*	A. PrEP with daily TDF-FTC (n=20) + 3MV behavioral HIV prevention intervention B. Placebo (daily) + 3MV behavioral intervention (n=19). C. 3MV behavioral intervention, alone (n=19)	Self-reported medication adherence: mean, 62% (range, 43% to 83%) across arms. Detectable plasma TDF in TDF-FTC arm: Week 4: 63.2% Week 24: 20%	NR	NR	NR
PROUD McCormack, 2016[118] *Oral PrEP Versus Placebo or No PrEP*	A. Immediate PrEP with daily TDF-FTC 245/200 mg (n=275) B. Deferred PrEP for 1 year (n=269)	Tenofovir detected in plasma of 100% (52/52) of random sample of participants who reported taking PrEP. Proportion receiving only one prescription: 5% (14/275) Proportion with interrupted/ missed doses due to adverse events: 8% (21/275) Sufficient study drug (defined as adequate prescription to last 1 month beyond next scheduled appointment) prescribed 88% of total followup time	NR	NR	NR

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
Study of TDF Peterson, 2007[55] *Oral PrEP Versus Placebo or No PrEP*	A. TDF, 300 mg orally daily (n=469) B. Placebo (n=467) All participants received HIV posttest counseling, and received condoms and risk reduction counseling at every monthly visit	No between-group data reported; maximum overall adherence was 69% based on pill counts	NA	NR	NR
TDF2 Thigpen, 2012[170] *Oral PrEP Versus Placebo or No PrEP*	A. Oral TDF-FTC 300/200 mg, once daily (n=611) B. Placebo, once daily (n=608)	Plasma tenofovir level detectable in 50% (2/4) of seroconverters and 80% (55/69) of nonseroconverters in TDF-FTC group Plasma FTC level detectable in 50% (2/4) of seroconverters and 81% (56/69) of nonseroconverters in TDF-FTC group Pill count: 84% vs. 84% Self-reported adherence for previous 3 days: 94% vs. 94%	NA	Detectable tenofovir level: 50% (2/4) vs. 80% (55/69); OR, 0.25 (95% CI, 0.03 to 1.97) Detectable FTC level: 50% (2/4) vs. 81% (56/69); OR, 0.23 (95% CI, 0.03 to 1.80)	A vs. B Sex: HIV infection Female: 3% (7/280) vs. 5% (14/277); RR, 0.49 (95% CI, 0.02 to 1.21) Male: 0.6% (2/331) vs. 3% (10/331); RR, 0.20 (95% CI, 0.4 to 0.91) p=not significant for interaction (value NR) Unclear if subgroup analysis prespecified

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
TDF2 Chirwa, 2014[133] *Oral PrEP Versus Placebo or No PrEP*	Same as Thigpen 2012	Same as Thigpen 2012	Same as Thigpen 2012	Same as Thigpen 2012	Of the 33 who acquired HIV during the course of the study, no resistance mutations were identified in their first RNA-positive samples or in any of their samples from subsequent study visits; 1 participant in the placebo group had low levels (<1%) of the K65R mutation, a level of expression attributable to replication error at and around codon 65 that has been observed with ART-naive HIV subtype C infections; 1 of the 3 participants who screened falsely negative at study entry and received TDF-FTC until HIV was diagnosed at month 7 developed the M184V mutation—this was retrospectively found to have occurred 1 month after study entry, and the A62V and K65R mutations occurred between 4 and 7 months after study entry; all mutations were at high levels.
VOICE Marrazzo, 2015[54] *Oral PrEP Versus Placebo or No PrEP*	A. Oral TDF 300 mg and TDF-FTC placebo (n=1,007) B. Oral TDF-FTC 300/200 mg and TDF placebo (n=1,003) C. Oral TDF placebo and oral TDF-FTC placebo (n=1,009) *Interventions outside the scope of this review:* D. Vaginal 1% TFV gel (n=1,007) E. Vaginal placebo gel (n=1,003) (all daily)	Proportion of patients with detectable tenofovir at quarterly plasma sample: 30% vs. 29% vs. NA vs. 25% vs. NA Proportion of patients with no detectable TDF in any quarterly plasma sample: 58% vs. 50% vs. NA vs. 57% vs. NA Clinic-based product count: 84% vs. 88% vs. 90% vs. 83% vs. 84% Self report based on face-to-face interview: 91% vs. 90% vs. 91% vs. 90% vs. 90% Self report based on computer-assisted interview: 87% vs. 87% vs. 88% vs. 88% vs. 89%	NA	Tenofovir ever detected in plasma: TDF arm: 26% (14/54) among cases and 44% (68/156) among controls; aRR, 0.55 (95% CI, 0.26 to 1.14); OR, 0.60 (95% CI, 0.33 to 1.10) TDF-FTC arm: 39% (24/61) among cases and 52% (77/148) among controls; aRR, 0.83 (95% CI, 0.39 to 1.76); OR, 0.45 (95% CI, 0.23 to 0.90)	Association with detectable TVF in patients assigned to PrEP Age >25 years: aOR, 2.17 (95% CI, 1.36 to 3.47) Living situation Married: aOR, 2.96 (95% CI, 1.04 to 8.38) Having more than one child: aOR, 2.03 (95% CI, 1.24 to 3.33) Independent income: aOR, 1.78 (95% CI, 1.08 to 2.93) Association with risk of HIV infection among patients assigned to placebo: Age >25 years: aOR, 0.35 (95% CI, 0.22 to 0.54) Living situation Married: aOR, 0.12 (95% CI, 0.04 to 0.41) Having more than one child: aOR, 0.44 (95% CI, 0.28 to 0.67) Independent income: aOR, 0.63 (95% CI, 0.44 to 0.91)

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
VOICE Mirembe, 2016[156] *Oral PrEP Versus Placebo or No PrEP*	A. TDF (n=172) B. TDF-FTC (n=174) C. Placebo (n=172)	Tenofovir was detected in at least one plasma sample from 57% (194/342) of participants; available from 4 visits for 71%, from more than 4 visits for 5%, and from 1 to 3 quarterly followup visits for 23%	Same as Marrazzo 2015	For active arm participants with drug detection at 75% to 100% of visits (n=81 for active arms combined) at week 48: Net change in BMD, lumbosacral spine: average -1.0% to -1.4% for the TDF, TDF-FTC, and combined active drug recipients compared with placebo (all p<0.05) Net change in BMD, thoracic vertebra: average 0.7% to -0.9% for active treatment compared with placebo (p<0.05) A vs. B vs. A + B vs. C >3% decrease in BMD, spine: 40% (17/43) vs. 25% (13/51) vs. 36% (29/81) vs. 18% (22/119) (p=0.012 for TDF vs. placebo and p=0.008 for combined active arms vs. placebo) >3% decrease in BMD, hip: no differences For those with ≥75% detection, BMD results were similar to those at 48 weeks active discontinuation	Same as Marrazzo 2015

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
ADAPT/ HPTN 067 Bekker 2018[130] *Event Driven Versus Daily Oral PrEP*	A. Daily TDF-FTC (n=59) B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex; n=59) C. Event-driven TDF-FTC (one tablet both before and after sex; n=60)	Pill count (EDM) defined as having at least one PrEP dose within 4 days (96 hours) before and within 1 day (24 hours) after sex events, adjusted according to patient self-report Plasma TDF PBMC measure of TDF-DP	NA	A vs. B vs. C EDM-adjusted adherence: 75% vs. 65% vs. 53%; MD, A vs. B: 10.0% (95% CI, 3.8% to 16.0%); A vs. C: 22.0% (95% CI, 15.3% to 30.0%) % with plasma TDF detected (≥0.31 ng/mL): -Week 10: 93% (55/59) vs. 84% (48/57) vs. 78% (29/37) -Week 18: 81% (44/54) vs. 80% (43/54) vs. 70% (21/30) -Week 30: 68% (38/56) vs. 56% (31/55) vs. 53% (17/32) % with plasma TDF ≥2 pills/week (≥2.5 ng/mL): -Week 10: 78% (46/59) vs. 67% (38/57) vs. 54% (20/37) -Week 18: 57% (31/54) vs. 57% (31/54) vs. 37% (11/30) -Week 30: 54% (30/56) vs. 36% (20/55) vs. 31% (10/32) % with plasma TDF 7 pills/week (≥35.5 mg/mL): -Week 10: 58% (34/59) vs. 19% (11/57) vs. 5% (2/35) -Week 18: 44% (24/54) vs. 17% (9/54) vs. 23% (7/30) -Week 30: 38% (21/56) vs. 15% (8/55) vs. 13% (4/32) % with PBMC TDF-DP ≥2 pills/week (≥5.2 fmol/10^6 cells): -Week 10: 84% (49/58) vs. 78% (45/58) vs. 68% (25/37) -Week 18: 72% (41/57) vs. 64% (35/55) vs. 33% (10/30) -Week 30: 54% (30/56) vs. 45% (25/55) vs. 39% (12/31) % with PBMC TDF-DP 7 pills/week (≥16.8 fmol/10^6 cells): -Week 10: 74% (43/58) vs. 43% (25/58) vs. 32% (12/37) -Week 18: 53% (30/57) vs. 36% (20/55) vs. 23% (7/30) -Week 30: 52% (29/56) vs. 22% (12/55) vs. 23% (7/31)	<u>Age ≤25 years</u> % with plasma TDF ≥2 pills/week (≥2.5 ng/mL): -Week 10: 83% (19/23) vs. 67% (6/9) vs. 44% (8/18) -Week 30: 69% (11/16) vs. 43% (3/7) vs. 25% (3/12) % with plasma TDF 7 pills/week (≥35.5 mg/mL): -Week 10: 61% (14/23) vs. 33% (3/9) vs. 6% (1/18) -Week 30: 56% (9/16) vs. 14% (1/7) vs. 0% (0/12) % with PBMC TDF-DP ≥2 pills/week (≥5.2 fmol/10^6 cells): -Week 10: 87% (20/23) vs. 67% (6/9) vs. 67% (12/18) -Week 30: 69% (11/16) vs. 57% (4/7) vs. 25% (3/12) % with PBMC TDF-DP 7 pills/week (≥16.8 fmol/10^6 cells): -Week 10: 65% (15/23) vs. 44% (4/9) vs. 33% (6/18) -Week 30: 69% (11/16) vs. 29% (2/7) vs. 17% (2/12) <u>Age >25 years</u> % with plasma TDF ≥2 pills/week (≥2.5 ng/mL): -Week 10: 76% (13/17) vs. 57% (8/14) vs. 63% (12/19) -Week 30: 62% (8/13) vs. 47% (8/17) vs. 35% (7/20) % with plasma TDF 7 pills/week (≥35.5 mg/mL): -Week 10: 53% (9/17) vs. 14% (2/14) vs 5% (1/19) -Week 30: 23% (3/13) vs. 18% (3/17) vs. 20% (4/20) % with PBMC TDF-DP ≥2 pills/week (≥5.2 fmol/106 cells): -Week 10: 76% (13/17) vs. 71% (10/14) vs. 68% (13/19) -Week 30: 62% (8/13) vs. 53% (9/17) vs. 47% (9/19) % with PBMC TDF-DP 7 pills/week (≥16.8 fmol/106 cells): -Week 10: 76% (13/17) vs. 29% (4/14) vs. 32% (6/19) -Week 30: 62% (8/13) vs. 35% (6/17) vs. 26% (5/19)

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
ADAPT/ HPTN 067 Grant, 2018[136] *Event Driven Versus Daily Oral PrEP*	A. Daily TDF-FTC (n=119) B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex; n=119) C. Event-driven TDF-FTC (one tablet both before and after sex; n=119)	Pill count, varied according to study arm: Daily arm: 1 tablet/day; time-driven arm: 1 tablet every 4 days + an additional tablet taken within 24 hours after sex; event-driven arm: 1 tablet within 48 hours before sex and another tablet taken within 24 hours after sex Plasma tenofovir Adherence, drug levels: TFV-DP ≥326 fmol/punch (consistent with ≥2 doses/week) on visits when sex was reported in the prior week, daily PrEP: 48%; time-driven PrEP: 31%; event-driven PrEP 17% A vs. B: p=0.11; A vs. C: p=0.004 Adherence, other method: Medication event monitoring system, daily PrEP: 62%; time-driven PrEP: 47%; event-driven PrEP: 41% Proportion with ≥90% adherence, daily PrEP: 25%; time-based PrEP: 0%; event-driven PrEP: 2% Persistence: Temporarily or permanently discontinued PrEP due to side effects: 2.2% (4/179)	NR	A vs. B vs. C Bangkok site Adherence: 85.4% vs. 79.4% vs. 65.1% Proportion with ≥90% adherence: 48.3% (29/60 vs. 23.7% (14/59) vs. 6.8% (4/59) Proportion of visits with plasma TDF consistent with ≥2 pills on visits when sex was reported in the prior week: 97.6% (81/83) vs. 98.7% (77/78 vs. 95.7% (67/70); A vs. B: p=0.11; A vs. C: p=0.004 Harlem site Adherence: 65.1% vs. 46.5% vs. 41.3% Proportion with ≥90% adherence: 25.4% (15/59 vs. 0% (0/60) vs. 1.7% (1/59) Proportion of visits with plasma TDF consistent with ≥2 pills on visits when sex was reported in the prior week: 48.5% (33/68) vs. 30.9% (21/68 vs. 16.7% (11/68); A vs. B: p=0.11; A vs. C: p=0.004	NR

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
Kwan, 2021[144] *Event Driven Versus Daily Oral PrEP*	A: Once-daily TDF (n=59) B: On-demand TDF (n=60)	A vs. B (self report) Coverage of days with condomless anal intercourse: Median 9 (IQR 3-31) vs. 14 (IQR, 2-22) Proportion of days covered by PrEP: median 92.3% (IQR, 77.8-100%) vs. 91.9% (IQR, 75.0-100%)	Age <30 years, receptive sexual role, sex partner on PrEP at baseline, sought sexual partners at week 24	NR	Men with >90% vs. ≤90% of days of condomless anal intercourse covered by PrEP
ASPIRE Baeten, 2016[73] *Dapivirine Vaginal Ring Versus Placebo Ring*	A. Dapivirine Ring (n=1313) B. Placebo (1316)	Dapivirine plasma level >95 pg/mL, dapivirine group: 82% Dapivirine level <23.5 mg in returned ring: 84%	NR	NR	NR
Ring Study Nel, 2016[74] *Dapivirine Vaginal Ring Versus Placebo Ring*	A. Dapivirine Ring (n=1307) B. Placebo (652)	Dapivirine plasma level ≥95 pg/mL: 84% Residual dapivirine ringe level ≤23.5 pg: 83% Dapivirine plasma level >95 pg/mL and residual dapivirine ring level ≤23.5 mg: ≥73%	NR	NR	NR

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**U.S. factors associated with adherence**	**Adherence and effectiveness**	**Subgroups**
DISCOVER Mayer, 2020[121] Ogbuagu, 2021[162] *Oral TAF-FTC Versus TDF-FTC*	A: TAF-FTC (n=2694) B: TDF-FTC (n=2693)	TAF-FTC vs. TDF-FTC Self-reported adherence ≥95%: 78%-82% vs. 78-82% Self-reported adherence ≥80%: 96%-98% vs. 97%-98% Pill count (median adherence): 98% (IQR 93%-100%) vs. 98% (IQR 93.5%-100%) Dried blood spot samples, TFV-DP level consistent with ≥4 tablets/week: 88%-96% vs. 84%-93%, primary (interim) analysis Persistence (did not discontinue): 78.2% (21072/2694) vs. 79.8% (2150/2693)	Not reported	Not reported	Transgender women: No cases of HIV infection in either group Age <25 years: IRR 1.23 (95% CI 0.28 to 5.49) Age ≥25 years: IRR 0.25 (95% CI 0.078 to 0.90); p for interaction=0.11 Black race: IRR 0.33 (95% CI 0.03 to 3.15) Not Black race: IRR 0.50 (95% CI 0.19 to 1.34); p for interaction=0.73 Hispanic/Latinx ethnicity: IRR 1.08 (95% CI 0.22 to 5.35) Not Hispanic/Latinx ethnicity: IRR 0.33 (95% CI 0.11 to 1.01); p for interaction=0.23 United States: IRR 0.17 (95% CI 0.04 to 0.77) Not United States: IRR 1.60 (95% CI 0.38 to 6.68), p for interaction=0.04 Recreational drug use: IRR 0.60 (95% CI 0.22 to 1.66) No recreational drug use: IRR 0.20 (95% CI 0.02 to 1.72), p for interaction=0.37 Binge alcohol use: IRR 0.29 (95% CI 0.06 to 1.41) No binge alcohol use: IRR 0.63 (95% CI 0.21 to 1.91); p for interaction=0.44 ≤3 unprotected receptive anal intercourse partners: IRR 0.39 (95% CI 0.10 to 1.47) >3 unprotected receptive anal intercourse partners: IRR 0.52 (95% CI 0.15 to 1.78); p for interaction=0.75 Note: stratified analyses conducted for primary (interim) analysis, for which 100% of patients had completed 48 weeks and 50% had completed 96 weeks

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Study name Author, year	Interventions	Adherence method of assessment and rate	U.S. factors associated with adherence	Adherence and effectiveness	Subgroups
HPTN 083 Landovitz, 2021[70] *Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC*	A: Cabotegravir 600 mg in a 3 mL IM injectable every 8 weeks (n=2,282) B: Daily TDF-FTC 300 mg + 200 mg (n=2,284)	*Oral TDF-FTC (random sample)* Tenofovir plasma level >40 ng/mL (consistent with daily doses in last week): 74.2% Tenofovir plasma level >0.31 ng/mL: 86.0% Tenofovir dried blood spot level consistent with ≥4 doses/week: 72.3% *Injectable cabotegravir* "Covered" by cabotegravir (injections with delay of <2 weeks): 91.5% of person-years Permanently discontinued, cabotegravir vs. TDF-FTC: 19.5% (445/2282) vs. 20.3% (463/2284)	NR	NR	NR
HPTN 084 Delany-Moretwle, 2022[88] *Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC*	A: Cabotegravir 600 mg in a 3 mL IM injectable every 8 weeks (n=1,592) B: Daily TDF-FTC 300 mg + 200 mg (n=1,586)	*Oral TDF-FTC (random sample of 405 participants)* Plasma tenofovir detectable (≥0.31 ng/mL): 55.9% Plasma tenofovir consistent with daily use (≥40 ng/mL): 41.9% Dried blood spot tenofovir level consistent with ≥4 doses/week (≥700 fmol/punch): 18% Dried blood spot tenofovir level detectable: 61.9% *Injectable cabotegravir* Received injection with a delay of less than 2 weeks: 93% Premature discontinuation, cabotegravir vs. TDF-FTC: 5.3% (85/1614) vs. 6.8% (110/1610)	NR	NR	HIV infection reported by age (<25 or ≥25 years; p for interaction=0.53), BMI (>30 kg/m^2 or ≤30 kg/m^2; p for interaction=0.47), and contraceptive method (DMPA, NET-EN, Implant, or Other; p for interaction=0.87)

Appendix B Table 3. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Additional Information on Adherence and Subgroups

Abbreviations: 3MV=Many Men, Many Voices; ADAPT/HPTN=Alternative Dosing to Augment Pre-Exposure Prophylaxis Pill Taking/HIV Prevention Trials Network; aHR=adjusted hazard ratio; ALT=alanine aminotransferase; aOR=adjusted odds ratio; aRR=adjusted risk ratio; ART=antiretroviral therapy; AST=aspartate aminotransferase; BMD=bone mineral density; CDC=Centers for Disease Control and Prevention; CI=confidence interval; DMPA=depot medroxyprogesterone acetate; EDM=electronic drug monitoring; eGFR=estimated glomerular filtration rate; FTC=emtricitabine; GFR=glomerular filtration rate; HR=hazard ratio; HSV=herpes simplex virus; IAVI=International AIDS Vaccine Initiative; iPrEx=Pre-Exposure Prophylaxis Initiative; IM=intramuscular; IQR=interquartile range; MEMS=medication event monitoring system; MSM=men who have sex with men; NA=not applicable; NR=not reported; OR=odds ratio; PBMC=peripheral blood mononuclear cell; PPV=positive predictive value; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; RNA=ribonucleic acid; RR=relative risk; SD=standard deviation; STI=sexually transmitted infection; TAF=tenofovir alafenamide;TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; TFV=tenofovir; TFV-DP=tenofovir-diphosphate; ULPC=upper layer packed cell; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

Appendix B Table 4. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Quality Assessment

Study name Author, year Type of PrEP	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential (>10%)/high (>20%)?	Analyze persons in the groups in which they were random-ized?	Quality
Bangkok Tenofovir Study Choopanya, 2013[53] *Oral PrEP Versus Placebo or No PrEP*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
FEM-PREP Van Damme, 2012[172] *Oral PrEP Versus Placebo or No PrEP*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Grohskopf, 2013[52] *Oral PrEP Versus Placebo or No PrEP*	Yes, per Liu 2011	Yes, per Liu 2011	Race differed (greater percentage Black race in placebo arm; p=0.001)	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
IAVI Kenya Study Mutua, 2012[67] *Oral PrEP Versus Placebo or No PrEP*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
IAVI Uganda Study Kibengo, 2013[68] *Oral PrEP Versus Placebo or No PrEP*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
IPERGAY Molina, 2015[66] *Oral PrEP Versus Placebo or No PrEP*	Yes	Yes	Yes (except race)	Yes	Yes	Unclear	Yes	Yes	No	Yes	Good

Appendix B Table 4. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Quality Assessment

Study name Author, year Type of PrEP	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential (>10%)/high (>20%)?	Analyze persons in the groups in which they were random-ized?	Quality
iPrEX Grant, 2010[137] *Oral PrEP Versus Placebo or No PrEP*	Yes	Yes	Yes	Yes	Yes	Yes, see protocol	Yes	Yes	No	Yes	Good
Partners PrEP Baeten, 2012[51] *Oral PrEP Versus Placebo or No PrEP*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Project PrEPare ATN 082 Hosek 2013[141] *Oral PrEP Versus Placebo or No PrEP*	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Yes	Fair
PROUD McCormack, 2016[118] *Oral PrEP Versus Placebo or No PrEP*	Yes	Unclear	Yes	Yes	No	No	No	Yes	No	Yes	Fair
Study of TDF Peterson, 2007[55] *Oral PrEP Versus Placebo or No PrEP*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
TDF2 Thigpen, 2012[170] *Oral PrEP Versus Placebo or No PrEP*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
VOICE Marrazzo, 2015[54] *Oral PrEP Versus Placebo or No PrEP*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good

Appendix B Table 4. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Quality Assessment

Study name Author, year Type of PrEP	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential (>10%)/high (>20%)?	Analyze persons in the groups in which they were random-ized?	Quality
ADAPT/HPTN Bekker 2018[130], Grant, 2018[136] *Event Driven Versus Daily Oral PrEP*	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Fair
Kwan, 2021[144] *Event Driven Versus Daily Oral PrEP*	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Fair
ASPIRE Baeten, 2016[73] *Dapirivine Vaginal Ring Versus Placebo Ring*	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Good
Ring Study Nel, 2016[74] *Dapirivine Vaginal Ring Versus Placebo Ring*	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Good
DISCOVER Mayer, 2020[121] Ogbuagu, 2021[162] *Oral TAF-FTC Versus TDF-FTC*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
HPTN 083 Landovitz, 2021[70] *Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC*	Yes; "electronically"	Unclear; likely yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good

Appendix B Table 4. HIV Pre-Exposure Prophylaxis Randomized, Controlled Trials: Quality Assessment

Study name Author, year Type of PrEP	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential (>10%)/high (>20%)?	Analyze persons in the groups in which they were random-ized?	Quality
HPTN 084 Delany-Moretwle, 2022[88] *Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC*	Yes	Unclear; likely yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good

Abbreviations: ADAPT/HPTN=Alternative Dosing to Augment Pre-Exposure Prophylaxis Pill Taking/HIV Prevention Trials Network; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; IAVI=International AIDS Vaccine Initiative; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

Appendix B Table 5. Diagnostic Accuracy of HIV Risk Assessment Tools: Study Characteristics

Study, Year Followup	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
Beymer, 2017[131] Mean 1.8 years	Retrospective cohort MSM who were negative at baseline and had at least one subsequent test; no formal testing protocol	MSM	Derivation cohort: Los Angeles LGBT center (2009 to 2014) cohort Age <25 years: 26% Ages 25 to 29 years: 26% Ages 30 to 39 years: 28% Age ≥40 years: 21% White: 48% Hispanic: 32% Black: 7.8%	Derivation cohort: 9,481	Derivation cohort: 3.9% (370/9,481)	1) Race/ethnicity 2) History of any STI 3) Condom use during receptive anal sex, last partner 4) Race/ethnicity, last partner 5) Age difference, last partner 6) Number sex partners, last 3 months 7) Intimate partner violence 8) Ecstasy use, prior 12 months 9) Methamphetamine use, prior 12 months 10) Nitrates use, prior 12 months Scoring of items unclear, total
Hoenigl, 2015[140] SDET score Duration of followup not applicable due to cross-sectional design; utilized risk behavior data from prior 12 months	Retrospective cross-sectional MSM who underwent HIV testing and classified as EAH or no EAH	MSM	San Diego "Early Test" (2008 to 2014) cohort Age (median, years): 30 in acute and early HIV infection, 33 in those who remained uninfected White: 67% Asian: 8% Black: 6% Hispanic ethnicity: 27% Cohort randomly split in 2:1 ratio into derivation and validation cohorts	Derivation cohort: 5,568 Validation cohort: 2,758	Entire cohort: 2.4% (200/8,326) for acute and early HIV infection	1) ≥10 male partners (0 or 2) 2) Condomless receptive anal intercourse and ≥5 male partners (0 or 3) 3) Condomless receptive anal intercourse with HIV-infected partner (0 or 3) 4) Bacterial STI (0 or 2)
Jones, 2017[142] 1) ARCH-MSM 2) Menza 3) SDET Up to 24 months (mean/ median NR)	Cohort Non-Hispanic, Black and White MSM who were HIV-negative at baseline and had HIV testing every 6 months or until HIV-infected for 24 months	MSM	Involve[men]t study cohort Age (mean, years): 27 White: 54% Black: 46%	562	5.7% (32/562); 6 were determined to be acutely infected at baseline (included in analysis)	1) ARCH-MSM: See Smith 2012 (drug use questions modified from last 6 to last 12 months) 2) SDET: See Hoenigl 2015 3) Menza: See Menza 2009 (drug use question modified from last 6 to last 12 months)

Appendix B Table 5. Diagnostic Accuracy of HIV Risk Assessment Tools: Study Characteristics

Study, Year Followup	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
Krakower, 2019[143] Duration of followup NR	Cohort Development cohort, Atrius health years 2007 to 2015 Prospective validation cohort, Atrius health year 2016 External validation cohort, Fenway Health 2011 to 2016	General population (>15 years of age)	Development cohort Age: 35.0 years Gender: Male 42.9%, female 57.0%, transgender or gender nonconforming NR, unknown 0.2% Race/ethnicity: White 60.0%, Black 5.2%, American Indian/Alaskan Native 0.1%, Asian 5.8%, Native Hawaiian/Other Pacific Islander <0.1%, Other 3.3%, Hispanic or Latinx 2.9%, unknown 22.6% At least 1 EHR predictor variable suggestive of HIV risk: 34.5% Incident HIV: <0.1% PrEP use: <0.1% Prospective validation cohort Age: 39.1 years Gender: Male 42.5%, female 57.5%, transgender or gender nonconforming NR, unknown <0.1% Race/ethnicity: White 72.7%, Black 6.9%, American Indian/Alaskan Native 0.1%, Asian 6.4%, Native Hawaiian/Other Pacific Islander <0.1%, Other 4.0%, Hispanic or Latinx 3.2%, unknown 6.7% At least 1 EHR predictor variable suggestive of HIV risk: 45.7% Incident HIV: <0.1% PrEP use: <0.1% External validation cohort Age: 34.5 years Gender: Male 62.3%, female 31.0%, transgender or gender nonconforming 6.7, unknown 0 Race/ethnicity: White 68.3%, Black 8.1%, American Indian/Alaskan Native 0.2%, Asian 7.1%, Native Hawaiian/Other Pacific Islander 0.4%, Other 10.2%, Hispanic or Latinx 5.6%, unknown 0 At least 1 EHR predictor variable suggestive of HIV risk: NA Incident HIV: 1.3% PrEP use: 5.4%	Development cohort: n=1,155,966 Prospective validation cohort: n=537,257 External validation cohort: n=33,404	Development cohort: <0.1% (n=150) Prospective validation cohort: <0.1% (n=16) External validation cohort: 1.3% (n=423)	LASSO algorithm (coefficient), based on electronic health record data: Diagnosis codes: 1) Syphilis of any site or stage except late latent (1.00) 2) HIV counseling n previous 2 years (1.10) 3) Contact with or exposure to venereal disease (0.29) Lab tests and results 4) No. of positive gonorrhea tests in previous 2 years (3.07) 5) No. of chlamydia tests (-0.15) 6) No. of HIV tests (0.12) 7) No. of HIV ELISA tests (0.16) 8) No. of HIV tests in previous 2 years (0.23) 9) No. of HIV RNA tests in previous year (0.15) 10) Testing for acute HIV (1.82) 11) Testing for acute HIV in previous 2 years (0.16) Prescriptions 12) Intramuscular penicillin G benzathine (1.80) 13) Intramuscular penicillin G benzathine in previous year (1.36) 14) Intermuscular penicillin G benzathine in previous 2 years (0.21) 15) Buprenorphine and naloxone in previous 2 years (0.20) Demographics and registration data 16) Years of previous HER data (-0.07) 17) At least 1 year of previous HER data (-0.63) 18) At least 2 years of previous HER data (-0.40) 19) Any data on primary language (-0.08) 20) English as primary language (-0.42) 21) Black race (1.06) 22) White race (-0.66) 23) Male gender (1.87)

Appendix B Table 5. Diagnostic Accuracy of HIV Risk Assessment Tools: Study Characteristics

Study, Year Followup	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
Lancki, 2018[145] 1) ARCH-MSM 2) CDC criteria 3) Gilead indications Mean 0.77 years	Cohort Self-identified as African American or Black, ages 16 to 29 years, oral or anal intercourse with a man within the past 24 months, located on South Side of Chicago, HIV-uninfected, testing at baseline and at 9-month intervals over 18 months	MSM	uConnect study cohort Age (mean, years): NR White: 0% Black: 100%	300	11% (33/300)	1) ARCH-MSM: See Smith 2012 (drug use questions modified from last 6 to last 12 months) 2) CDC criteria: Any male sex partner in past 6 months, not in a monogramous partnership with a recently tested, HIV-uninfected man and one of the following: a) Any anal sex without condoms (receptive or insertive) b) Any STI diagnosed or reported in past 6 months c) In an ongoing sexual partnership with an HIV-positive male partner 3) Gilead indications: a) Inconsistent or no condom use b) Diagnosis of STI c) Exchange of sex for commodities d) Use of illicit drugs or alcohol dependence (excluding marijuana) e) Incarceration f) Partners of unknown HIV-1 status with any of the factors listed above
Marcus, 2019[151] Up to 3 years (validation cohort), (mean/ median NR)	Cohort Development cohort: Kaiser Permanente Northern California 2007-2014 Prospective validation cohort: Kaiser Permanente Northern California 2015-2017 data	General population (≥18 years of age)	Development cohort: Age, mean: 44.6 years Gender: Male 46.5% Race/ethnicity: White 51.9%, Hispanic 19.3%, Asian 17.2%, Black 7.4%, other 4.1%, unknown 6.8% Sexual orientation among known: heterosexual 96.4%, gay or lesbian 2.9%, bisexual 0.7% Unknown sexual orientation: 84.4% Validation cohort: Age, mean: 37.4 years Gender: Male 49.0% Race/ethnicity: White 44.0%, Hispanic 24.3%, Asian 23.0%, Black 6.4%, other 2.3%, unknown 5.8% Sexual orientation among known: heterosexual 95.5%, gay or lesbian 3.4%, bisexual 1.1% Unknown sexual orientation: 59.7%	3,750,664 Development cohort: 3,143,963 Validation cohort: 606,701	0.02% (784/3,750,664) within 3 years	LASSO algorithm (coefficient), based on electronic health record data: Demographics and social history 1) Male 2) MSM 3) Sexually active 4) Age 50-59 5) Age ≥60 6) Black 7) Hispanic 8) Asian 9) Other race/ethnicity 10) Neighborhood deprivation index (NDI), Quintile 2 11) NDI, Quintile 3 12) NDI, Quintile 4 13) Received care in one of three cities with high HIV incidence 14) Resided in one of eight urban ZIP codes with high HIV incidence Laboratory tests and results 15) Positive urine test for methadone 16) Positive urine test for cocaine 17) No. of HIV testing episodes in previous 2 years

Appendix B Table 5. Diagnostic Accuracy of HIV Risk Assessment Tools: Study Characteristics

Study, Year Followup	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
						18) No. of HIV antibody or RNA tests in previous 2 years 19) No. of tests for rectal gonorrhea or chlamydia 20) No. of positive tests for rectal gonorrhea or chlamydia in previous 2 years 21) No. of positive tests for urethral chlamydia in previous 2 years 22) No. of positive tests for urethral gonorrhea in previous 2 years 23) No. of RPR or treponemal tests for syphilis in previous 2 years 24) No. of reactive RPR or positive treponemal tests for syphilis in previous 2 years Medication use 25) Medications for erectile dysfunction 26) No. of penicillin G benzathine injections with syphilis test within 90 days in previous 2 years Diagnoses 27) No. of anal wart diagnoses 28) Depression 29) Any psychiatric diagnosis 30) Transgender-related diagnosis 31) High-risk sexual behavior (homosexual) 32) High-risk sexual behavior (not specified) 33) Exposure to HIV 34) HIV counseling 35) HIV education
Menza, 2009[155] Median 3 years (validation cohort)	Retrospective cohort In derivation cohort, MSM were HIV-negative at baseline and had at least one subsequent HIV test; no formal testing protocol In validation cohort, MSM were HIV-negative at baseline and underwent retesting every 6 months	MSM	Derivation cohort: Public Health-Seattle and King County STI Clinic (2001 to 2008) repeat testers cohort Age <40 years: 80% Age ≥40 years: 20% White, Asian, or Pacific Islander: 77% Other race: 23% Gonorrhea on STI testing: 12% Chlamydia on STI testing: 8.8% Methamphetamine use in past 6 months: 6.7%	Derivation cohort: 1,903 Validation cohort: 2,081	Derivation cohort: 5.3% (101/1,903) Validation cohort: 6.9% (144/2,081)	1) Gonorrhea, chlamydia, or syphilis, or a history of these infections (0 or 4 points) 2) Used methamphetamine or inhaled nitrites in the past 6 months (0 or 11 points) 3) Unprotected anal intercourse with an HIV-infected partner or unknown HIV status in the past year (0 or 1 point) 4) 10 or more male sexual partners in the prior year (0 or 3 points)

Appendix B Table 5. Diagnostic Accuracy of HIV Risk Assessment Tools: Study Characteristics

Study, Year Followup	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
			Inhaled nitrites in past 6 months: 8.9% Crack/cocaine in past 6 months: 2.8% Validation cohort: Project EXPLORE (1999 to 2001) RCT, control arm (behavioral intervention trial) Age <40 years: 76% Age ≥40 years: 24% White, Asian, or Pacific Islander: 75% Other race: 25% Gonorrhea on STI testing: 3.0% Chlamydia on STI testing: 4.2% Methampetamine in past 6 months: 11% Inhaled nitrites in past 6 months: 28% Crack/cocaine use in past 6 months: 2.3%			
Ridgway, 2021[164] Duration of followup NR	Retrospective cohort Cohort was cisgender women with a new positive HIV test in the ED between January 1, 2011 and April 30, 2018	Cisgender women	Age, median: 38 years (IQR 29-47) Black: 95.2% (20/21)	21	21 (100%)	Calculated from data available in electronic medical record: 1) Male sex (7 points) 2) Chief complaint related to STI-associated symptoms (6 points) 3) Age ≤20 years (13 points) 4) Age 21-24 years (8 points) 5) Positive STI in previous 6 months (21 points) 6) MSM (21 points)
Scott, 2020[165] Sexual Health Promotion (SexPro) tool mysexpro.org Ranged from 1-3 years (validation cohorts)	Cohort Development cohort: EXPLORE trial 1991 to 2003 , US Validation cohorts: VAX0004 trial from 1998 to 2002, HPTN061 cohort study from 2009 to 2013, HVTN505 trial from 2009 to 2013	MSM, inclusive of Black MSM	EXPLORE vs. VAX004 vs. HPTN061 vs. HVTN505 Age <35 years: 60.9%, 48.8%, 44.8%, 68.3% Race/ethnicity: Black 7.4%, 3.4%, 100%, 18.3%, Latinx 14.8%, 0.7%, 7.7%, 8.5% Heavy (defined) alcohol use: 10.2% vs. 10.7%, 40.4%, 15.2% Methamphetamine use: 12.8%, 9.1%, 9.3%, 5.7% Popper use: 36.7 vs. 32.8%, 10.4%, 24.7%	Development cohort: =4,069 Validation cohorts: Total 8,047 (VAX004 n=4,878 vs. HPTN061 n=973 vs. HVTN505 n=2,196)	Development cohort: 217 Validation cohorts: Total 433 (VAX004 343 vs. HPTN061 25 vs. HVTN505 65)	Final model (score 1-20, with 20=lowest HIV risk): 1) Age ≤35 2) Black race 3) Latinx ethnicity 4) No. of receptive anal intercourse episodes without a condom with HIV positive or unknown status partners 5) No. of receptive anal intercourse episodes with a condom with HIV positive or unknown status partners 6) No. of insertive anal intercourse episodes without a condom with HIV positive or unknown status partners 7) No. of HIV-negative anal sex partners

Appendix B Table 5. Diagnostic Accuracy of HIV Risk Assessment Tools: Study Characteristics

Study, Year Followup	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
			STI: 6.5%, 9.7%, 4.8%, 4.7%			8) 1 HIV-negative sex partner only 9) Heavy alcohol use 10) Methamphetamine use 11) Popper use 12) Gonorrhea, syphilis, or chlamydia diagnosis
Smith, 2012[166] HIRI-MSM (now ARCH-MSM) Up to 4 years (mean/ median NR)	Retrospective cohort In derivation and validation cohorts, MSM were HIV-negative at baseline and underwent retesting every 6 months	MSM	Derivation cohort: VAXGEN 004 (1998 to 1999) RCT (HIV vaccine trial) Ages 18 to 28 years: 19% Ages 29 to 49 years: 48% Ages 41 to 48 years: 22% Age ≥49 years: 11% Non-Hispanic White: 86% Amphetamine use: 8.2% Popper use: 27% Validation cohort: Project EXPLORE (1999 to 2001) RCT (behavioral intervention trial) Age ≤25 years: 18% Ages 26 to 30 years: 22% Ages 31 to 35 years: 22% Age ≥36 years: 39% Non-Hispanic White: 75% Amphetamine use: 12% Popper use: 33%	Derivation cohort: 4,386 Validation cohort: 3,368	Derivation cohort: 7.2% (318/4,386) Validation cohort: 4.3% (144/3,368)	1) Age (0 to 8 points) 2) Total number of male partners, prior 6 months (0 to 7 points) 3) Total number of infected male partners, prior 6 months (0 to 8 points) 4) Times had unprotected receptive anal intercourse with any HIV status partner, prior 6 months (0 or 10 points) 5) Used amphetamines, prior 6 months (0 or 5 points) 6) Used poppers, prior 6 months (0 or 3 points)
Smith, 2015[167] ARCH-IDUs Median 5.85 years	Retrospective cohort Patients who reported drug use in the last 11 years and HIV-uninfected, underwent testing every 6 months	PWID	Derivation cohort: ALIVE (1988 to 2008) cohort Age <30 years: 17% Ages 30 to <40 years: 46% Ages 40 to <50 years: 27% Age ≥50 years: 7.9% Injected heroin: 75% Injected cocaine: 74% Methadone maintenance: 11% MSM: 1.8%	Derivation cohort: 1,904	Derivation cohort 11% (205/1,904)	1) Age (0 to 38 points) 2) In the last 6 months, in methadone maintenance program (0 or 31 points) Next 5 items receive 0 or 1 points on injection subscore: 3) In the last 6 months, inject heroin 1 or more times 4) In the last 6 months, inject cocaine 1 or more times 5) In the last 6 months, share cooker 1 or more times 6) In the last 6 months, share needle 1 or more times 7) In the last 6 months, visit shooting gallery 1 or more times Add 5 injection subscores, 0=score 0, 1=score 7, 2=score 21, 3=score 24, 4=score 24, 5=score 31

Appendix B Table 5. Diagnostic Accuracy of HIV Risk Assessment Tools: Study Characteristics

Study, Year Followup	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
Tordoff, 2020[171] A: Seattle PrEP Score B: Menza C: HIRI-MSM D: SDET E: CDC 2018 Mean 7.6 years	Retrospective cohort Derivation and validation cohorts consisted of2 STD clinic data sets	MSM	Derivation cohort (n=13,527; visits 37,814) Age, median: 33 years Race/ethnicity: White 65.3%, Black 11.0%, Asian 5.6%, Hispanic 5.0%, Native American/Alaskan Native 1.2%, Multiracial/other/unknown 11.8% STI diagnoses: Urethral gonorrhea 3.6%, rectal gonorrhea 3.2%, pharyngeal gonorrhea 3.5%, urethral chlamydia 3.1%, rectal chlamydia 3.5%, pharyngeal chlamydia 0.4%, syphilis 2.4%, herpes 15.2% No. of sex partners, median: 5 Any condomless anal intercourse: 51.3% Any condomless receptive anal intercourse: 39.6% Any insertive anal intercourse: 43.2% Any HIV-infected partners: 12.8% Any anonymous partners: 20.4% Substance use: Methamphetamine 5.2%, inhaled nitrate (“poppers”) 11.6% Validation cohort data set (n=9,234; visits 18,908) Age, median: 33 years Race/ethnicity: White 65.6%, Black 10.6%, Asian 6.0%, Hispanic 4.9%, Native American/Alaskan Native 1.2%, Multiracial/other/unknown 11.9% STI diagnoses: Urethral gonorrhea 3.6%, rectal gonorrhea 3.4%, pharyngeal gonorrhea 3.4%, urethral chlamydia 3.2%, rectal chlamydia 3.4%, pharyngeal chlamydia 0.4%, syphilis 2.3%,	Derivation cohort: 13,527 Validation cohort: 9,234	Derivation cohort: 1.2% (440/13,527) Validation cohort: 1.1% (200/9,234)	Seattle PrEP Score model (all items based on prior 12 months) 1) Methamphetamine use* (1 point) 2) Condomless receptive anal intercourse* (1 point) 3) ≥10 sex partners* (1 point) 4) Composite: gonorrhea or syphilis diagnosis or self-reported STI history* (1 point) Menza score Smith’s HIRI-MSM Hoenigl’s SDET CDC 2018 1) Any condomless anal intercourse (1 point) 2) Any HIV-positive sex partner (1 point) 3) Self-reported history of bacterial STI (1 point) 4) Injection drug use in past 6 months (1 point)

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Study, Year Followup	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
			herpes 14.7% No. of sex partners, median: 5 Any condomless anal intercourse: 51.5% Any condomless receptive anal intercourse: 39.45% Any insertive anal intercourse: 43.4% Any HIV-infected partners: 13.0% Any anonymous partners: 21.0% Substance use: Methamphetamine 5.2%, inhaled nitrate (“poppers”) 11.0%			

Abbreviations: ARCH-IDUs=Assessing the Risk of Contracting HIV in Injection Drug Users; ARCH-MSM=Assessing the Risk of Contracting HIV in Men Who Have Sex With Men; CDC=Centers for Disease Control and Prevention; EAH=early or acute HIV infection; ED=emergency department; EHR=electronic health record; ELISA=enzyme-linked immunosorbent assay; EXPLORE=A Randomized Clinical Trial of the Efficacy of a Behavioral Intervention to Prevent Acquisition of HIV Among Men Who Have Sex With Men; HIRI-MSM=HIV Incidence Risk Index for Men Who Have Sex With Men; HPTN=HIV Prevention Trials Network; HVTN= HIV Vaccine Trials Network; IQR=interquartile range; LASSO=Least Absolute Shrinkage and Selection Operators; LGBT=lesbian, gay, bisexual, and transgender; MSM=men who have sex with men; NDI=Neighborhood deprivation index; NR=not reported; PrEP=pre-exposure prophylaxis; PWID=persons who inject drugs; RCT=randomized, controlled trial; RNA=ribonucleic acid; RPR=rapid plasma regain; SDET=San Diego Early Test; STD=sexually transmitted disease; STI=sexually transmitted infection.

Appendix B Table 6. Diagnostic Accuracy of HIV Risk Assessment Tools: Results

Study, Year	Cutoff	Proportion meeting cutoff	Sensitivity	Specificity	AUROC	Comments
Beymer, 2017[131]	Ranged from ≥1 to ≥40 A: ≥3 B: ≥5 C: ≥7 D: ≥10 E: ≥15	Derivation cohort A: 83.4% B: 50.8% C: 30.9% D: 15.4% E: 6.2%	Derivation cohort A: 96.4% B: 74.6% C: 58.6% D: 39.5% E: 17.7%	Derivation cohort A: 11.9% B: 50.2% C: 70.2% D: 85.6% E: 94.3%	NR	Akaike Information Criterion score 6,094 vs. 6,162 for CDC 2014 criteria; 6,150 for ARCH-MSM; 6,072 for Menza (lower score indicates better goodness-of-fit)
Hoenigl, 2015[140] SDET score	A: ≥3 B: ≥5 C: ≥6 D: ≥8 E: ≥10	Derivation cohort NR Validation cohort A: 38% B: 24% C: 8.7% D: 4.6% E: 1.2%	Derivation cohort NR Validation cohort A: 70% B: 60% C: 37% D: 25% E: 10%	Derivation cohort NR Validation cohort A: 63% B: 77% C: 92% D: 96% E: 99%	Derivation cohort NR Validation cohort, 0.70 (95% CI, 0.62 to 0.78)	None
Jones, 2017[142] A: ARCH-MSM B: Menza C: SDET	A: ≥10 B: ≥1 C: ≥5	A: 47.1% B: 62.6% C: 17.5%	A: 62.5% Black: 58.3% White: 75.0% B: 62.5% Black: 54.2% White: 87.5% C: 25.0% Black: 16.7% White: 50.0%	A: 56.7% Black: 66.4% White: 49.0% B: 41.1% Black: 41.5% White: 40.8% C: 83.9% Black: 88.5% White: 80.3%	A: 0.62 (95% CI, 0.52 to 0.72) Black: 0.63 (95% CI, 0.51 to 0.75) White: 0.67 (95% CI, 0.47 to 0.88) B: 0.51 (95% CI, 0.41 to 0.60) Black: 0.49 (95% CI, 0.36 to 0.62) White: 0.60 (95% CI, 0.44 to 0.75) C: 0.55 (95% CI, 0.44 to 0.66) Black: 0.52 (95% CI, 0.39 to 0.65) White: 0.66 (95% CI, 0.46 to 0.87)	None
Krakower, 2019[143]	A: ≥1 (70th percentile of HIV risk) B: ≥2 (80th percentile) C: ≥8 (90th percentile) D: ≥13 (95th percentile)	NR	Development/ prospective validation/ external validation cohorts A: 96.0%/100%/100% B: 94.7%/100%/98.1% C: 77.3%/93.8%/91.3% D: 67.3%/62.5%/80.4%	Development/ prospective validation/ external validation cohorts A: 70.3%/67.6%/2.0% B: 80.4%/75.8%/26.8% C: 90.0%/91.0%/44.2% D: 95.0%/95.4%/59.1%	Development cohort 0.86 (95% CI 0.82 to 0.90) Prospective validation cohort 0.91 (95% CI 0.81 to 1.00) External validation cohort 0.77 (95% CI 0.74 to 0.79)	

Appendix B Table 6. Diagnostic Accuracy of HIV Risk Assessment Tools: Results

Study, Year	Cutoff	Proportion meeting cutoff	Sensitivity	Specificity	AUROC	Comments
Lancki, 2018[145] A: ARCH-MSM B: CDC criteria C: Gilead indications	A: ≥10 B: Met criteria C: One or more criteria	A: 72% B: 49% C: 86%	Unweighted A: 85% B: 52% C: 94% Weighted A: 76% B: 30% C: 93%	Unweighted A: 30% B: 52% C: 15% Weighted A: 36% B: 59% C: 22%	A: 0.57 B: 0.51 C: 0.54	None
Marcus, 2019[151]	High or very high risk scores defined as predicted probability of incident HIV within 3 years of 0.20% to 0.99% and ≥1.0%, respectively A:Full Lasso model B: MSM status and STI positivity testing, and treatment C: STI positivity, testing, and treatment D: MSM status and STI positivity E: MSM status F: STI positivity	Validation cohort No. of patients flagged: A: 2.2% B: 0.76% C: 0.24% D: 0.63% E: 0.62% F: 0.17% % of incident HIV cases identified: A: 38.6% B: 28.9% C: 20.5% D: 25.3% E: 25.3% F: 6.0%	Validation cohort A: 59.1% B: 42.7% C: 16.2% D: 38.8% E: 38.1% F: 6.4%	Validation cohort A: 97.8% B: 99.2% C: 99.8% D: 99.4% E: 99.4% F: 99.8%	C-statistic: Validation cohort A: 0.84, 95% CI 0.80 to 0.89 B: 0.73, 95% CI 0.66 to 0.79 C: 0.69, 95% CI 0.63 to 0.75 D: 0.63 95% CI 0.58 to 0.68 E: 0.62, 95% CI 0.58 to 0.67 F: 0.58, 95% CI 0.54 to 0.62	
Menza, 2009[155]	Ranged from ≥0 to ≥19 A: ≥1 B: ≥3 C: ≥5 D: ≥8 E: ≥12	Derivation cohort A: 71.3% B: 64.1% C: 31.3% D: 18.5% E: 11.8% Validation cohort A: 71.9% B: 58.6% C: 36.1% D: 34.7% E: 25.0%	Derivation cohort A: 83% B: 79% C: 48% D: 33% E: 26% Validation cohort A: 86% B: 76% C: 53% D: 51% E: 44%	Derivation cohort A: 30% B: 38% C: 71% D: 84% E: 91% Validation cohort A: 29% B: 43% C: 65% D: 67% E: 77%	Derivation cohort, 0.69 (95% CI, 0.60 to 0.74) Validation cohort, 0.66 (95% CI, 0.61 to 0.71)	Results based on 4-year estimates

Appendix B Table 6. Diagnostic Accuracy of HIV Risk Assessment Tools: Results

Study, Year	Cutoff	Proportion meeting cutoff	Sensitivity	Specificity	AUROC	Comments
Ridgway, 2021[164]	A: ≥16	A: 9.5% (2/21)	A: 9.5%	NR	NR	Calculated HIV risk score from electronic medical record data available from prior ED visits
Scott, 2020[165]	A. 13 B: 15 C: 16 D: 17 E: 18 Note: Study reports diagnostic accuracy for scores ranging from 1 to 20; selected cutoffs presented.	NR	Development cohort A. 63.1 B: 74.2 C: 81.1 D: 92.2 E: 96.3 Validation cohort, VAX004 A. 44.6 B: 55.1 C: 64.4 D: 80.5 E: 97.4 Validation cohort, HPTN061 A. 80.0 B: 92.0 C: 100 D: 100 E: 100 Validation cohort, HVTN505: A. 53.8 B: 64.6 C: 75.4 D: 90.8 E: 100	Development cohort A. 79.6 B: 69.5 C: 59.6 D: 45.9 E: 25.7 Validation cohort, VAX004 A. 84.5 B: 75.3 C: 67.4 D: 51.5 E: unclear Validation cohort, HPTN061 A. 34.3 B: 16.1 C: 0 D: 0 E: 0 Validation cohort, HVTN505: A. 74.9 B: 61.9 C: 51.8 D: 38.6 E: 8.8	Development cohort: C-statistic=79.5; AUC=0.80 Validation cohort, VAX004: C-statistic=73.1; AUC=0.73 Validation cohort, HPTN061: C-statistic=71.0; AUC=0.71 Validation cohort, HVTN505: C-statistic=71.9; AUC=0.72	

Appendix B Table 6. Diagnostic Accuracy of HIV Risk Assessment Tools: Results

Study, Year	Cutoff	Proportion meeting cutoff	Sensitivity	Specificity	AUROC	Comments
Smith, 2012[166] HIRI-MSM (now ARCH-MSM)	Ranged from ≥1 to ≥48 A: ≥1 B: ≥3 C: ≥5 D: ≥10 E: ≥15	Derivation cohort A: 97.2% B: 91.8% C: 89.6% D: 56.8% E: 41.5% Validation cohort A: 91.7% B: 91.7% C: 86.0% D: 62.4% E: 45.0%	Derivation cohort A: 100% B: 99.0% C: 98.4% D: 84.4% E: 73.9% Validation cohort A: 97.9% B: 97.9% C: 95.1% D: 81.2% E: 73.6%	Derivation cohort A: 3.1% B: 9.1% C: 11.4% D: 84.4% E: 60.7% Validation cohort A: 8.4% B: 8.4% C: 14.0% D: 37.7% E: 55.3%	Derivation cohort, 0.738 Validation cohort, 0.721	None
Smith, 2015[167] ARCH-IDUs	Range from 1 to 100 A: ≥30 B: ≥40 C: ≥46 D: ≥50 E: ≥60	Derivation cohort A: 89.9% B: 61.5% C: 57.8% D: 56.6% E: 35.9%	Derivation cohort A: 98.5% B: 87.7% C: 86.2% D: 85.2% E: 70.4%	Derivation cohort A: 10.1% B: 38.8% C: 42.5% D: 43.7% E: 64.5%	Derivation cohort, 0.72	None
Tordoff, 2020[171] A: Seattle PrEP Score B: Menza C: HIRI-MSM D: SDET E: CDC 2018	Seattle PrEP score: ≥2 Menza score: ≥2 Smith's HIRI-MSM: ≥10 Hoenigl's SDET: ≥5 CDC 2018: Condomless anal intercourse or STD in last 6 months and HIV-positive sex-partner or injection drug use in last 6 months	Seattle PrEP score Derivation: 30.7% Validation: 31.2% Combined: 30.9% Menza score Combined: 86.7% Smith's HIRI-MSM Combined: 62.7% Hoenigl's SDET Combined: 33.1% CDC 2018 Combined: 66.0^	Seattle PrEP score Derivation: 62.3% Validation: 46.3% Combined: 57.1% Menza score Combined: 91.7% Smith's HIRI-MSM Combined: 76.6% Hoenigl's SDET Combined: 56.6% CDC 2018 Combined: 90.7%	Seattle PrEP score Derivation: 69.6% Validation: 69.0% Combined: 69.4% Menza score Combined: 13.3% Smith's HIRI-MSM Combined: 37.4% Hoenigl's SDET Combined: 67.1% CDC 2018 Combined: 34.3%	Seattle PrEP score Derivation: 0.69 (95% CI 0.64 to 0.73) Validation: 0.60 (95% CI 0.54 to 0.66) Combined: 0.66 (95% CI 0.62 to 0.69) Menza score Combined: 0.66 (95% CI 0.62 to 0.70) Smith's HIRI-MSM Combined: 0.61 (95% CI 0.57 to 0.65) Hoenigl's SDET Combined: 0.62 (95% CI 0.59 to 0.67) CDC 2018 Combined: 0.62 (0.60 to 0.65)	Seattle PrEP Score, by race/ethnicity *Sensitivity/specificity* White: 56.5%/68.2% All non-White: 58.0%/71.3% Black: 47.6%/75.7% Asian: 83.3%/72.7% Hispanic: 46.2%/65.3% Native American/Alaskan Native: 66.7%/71.1% Multiracial/other/unknown: 63.2%/70.4% *AUC* White: 0.64 (95% CI 0.60 to 0.69) All non-White: 0.68 (95% CI 0.62 to 0.74) Black: 0.62 (95% CI 0.49 to 0.76) Asian: 0.91 (95% CI 0.66 to 0.95) Hispanic: 0.59 (95% CI 0.43 to 0.74) Native American/Alaskan Native: 0.68 (95% CI 0.42 to 0.95) Multiracial/other/unknown: 0.72 (95% CI 0.64 to 0.79)

Abbreviations: ARCH-IDUs=Assessing the Risk of Contracting HIV in Injection Drug Users; ARCH-MSM=Assessing the Risk of Contracting HIV in Men Who Have Sex With Men; AUC=area under curve; AUROC=area under the receiver operating characteristic curve; CDC=Centers for Disease Control and Prevention; CI=confidence interval; ED=emergency

Appendix B Table 6. Diagnostic Accuracy of HIV Risk Assessment Tools: Results

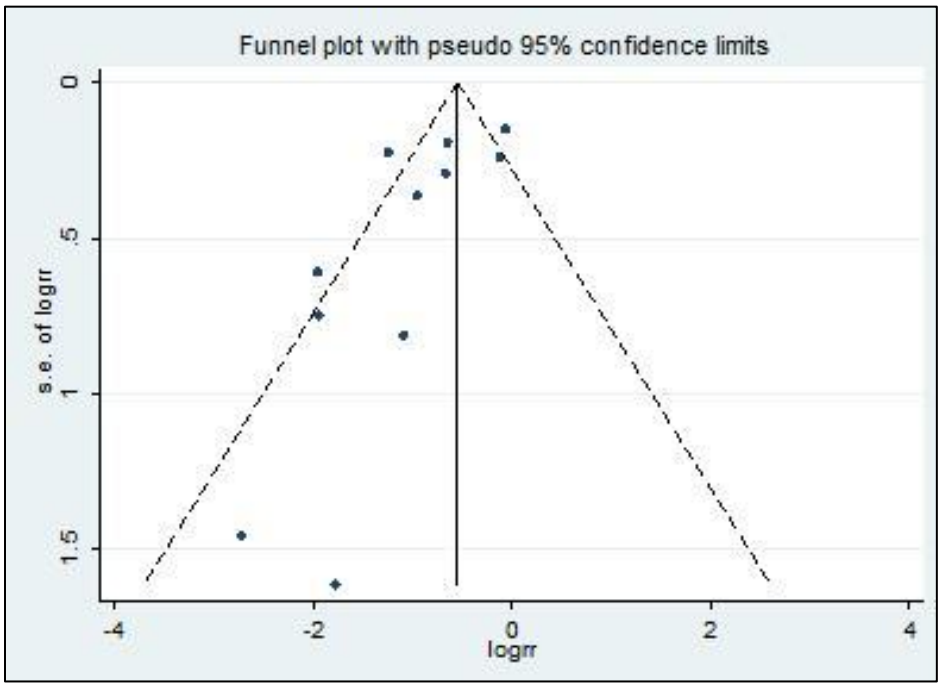
department; HIRI-MSM=HIV Incidence Risk Index for Men Who Have Sex With Men; HPTN=HIV Prevention Trials Network; HVTN= HIV Vaccine Trials Network; LASSO=Least Absolute Shrinkage and Selection Operators; MSM=men who have sex with men; NR=not reported; PrEP=pre-exposure prophylaxis; SDET=San Diego Early Test; STD=sexually transmitted diease; STI=sexually transmitted infection.

Appendix B Table 7. Diagnostic Accuracy of HIV Risk Assessment Tools: Quality Assessment

Study, Year	Consecutive or random sample?	Prespecified threshold?	Low attrition and missing data?	Accurate reference standard?	Test evaluated in a sample independent from the one used to develop the test?	Quality rating
Beymer, 2017[131]	Yes	No	Unclear	Yes	No	Fair
Hoenigl, 2015[140]	Yes	No	Unclear	Unclear	Yes	Fair
Jones, 2017[142]	Yes	Yes	Unclear	Yes	Yes	Fair
Krakower, 2019[143]	Yes	No	Unclear	Yes	Yes	Fair
Lancki, 2018[145]	Yes	Yes	No	Yes	No (for CDC and Gilead criteria)	Fair
Marcus, 2019[151]	Yes	No	Unclear	Yes	Yes	Fair
Menza, 2009[155]	Yes	No	Unclear	Yes	Yes	Fair
Ridgway, 2021[164]	Yes	Yes	Unclear	Yes	Unclear	Fair
Scott, 2020[165]	Yes	No	Unclear	Yes	Yes	Fair
Smith, 2012[166]	Yes	No	Unclear	Yes	Yes	Fair
Smith, 2015[167]	Yes	No	Unclear	Yes	No	Fair
Tordoff, 2020[171]	Yes	Yes (validation cohort)	Unclear	Yes	Yes	Fair

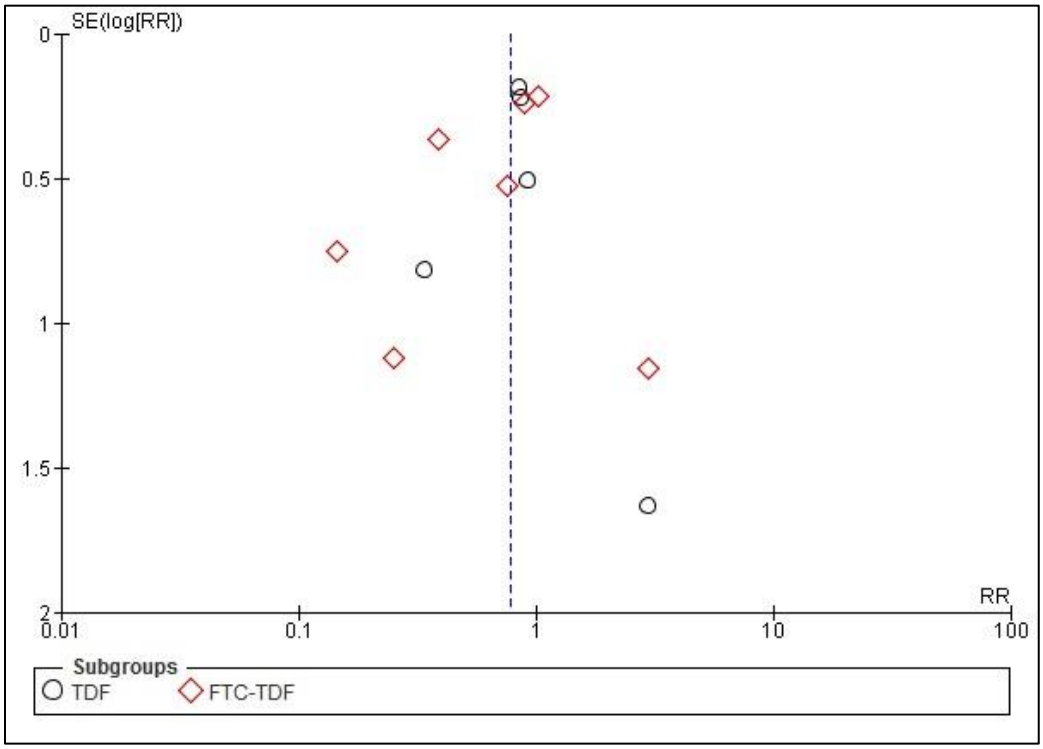
Abbreviation: CDC=Centers for Disease Control and Prevention.

Appendix C Figure 1. Funnel Plot: HIV Infection



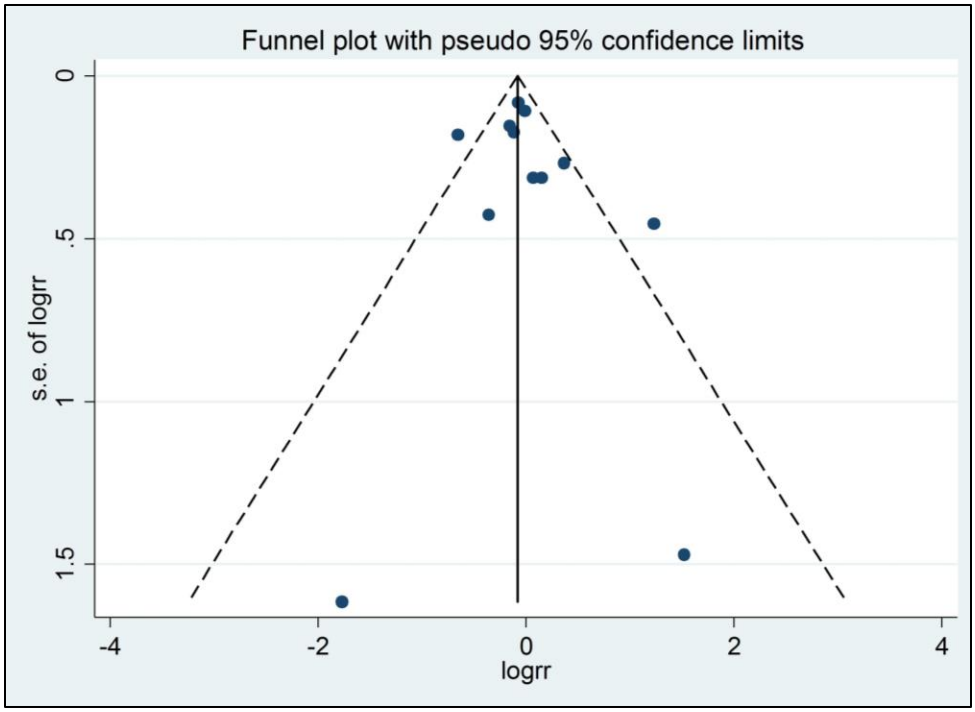
Abbreviation: s.e.=standard error.

Appendix C Figure 2. Funnel Plot: Mortality



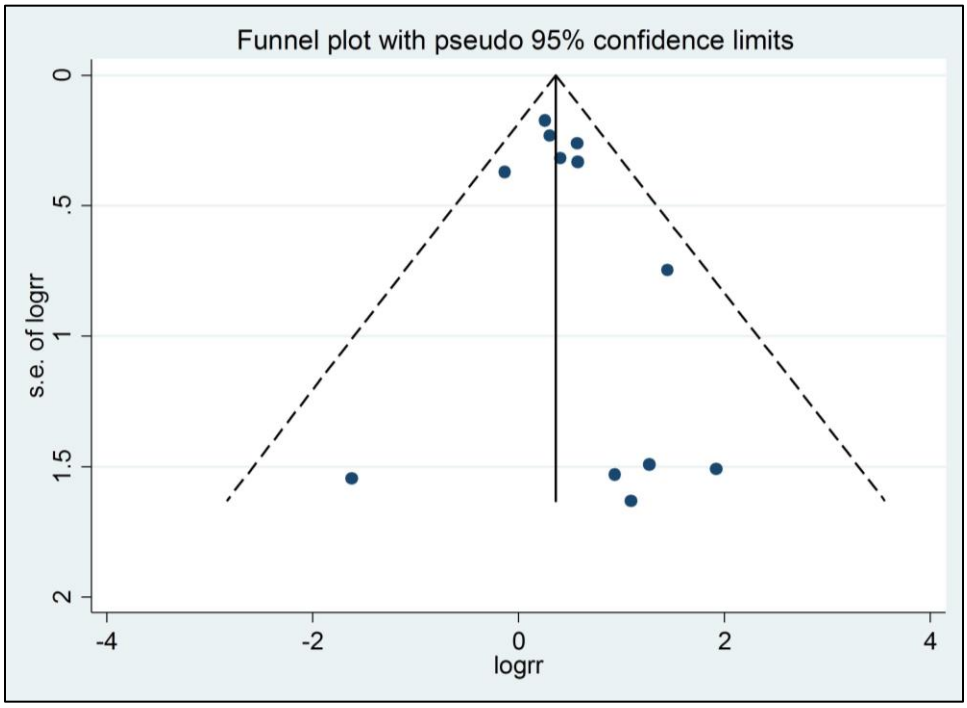
Abbreviations: FTC=emtricitabine; RR=relative risk; SE=standard error; TDF=tenofovir disoproxil.

Appendix C Figure 3. Funnel Plot: Serious Adverse Events



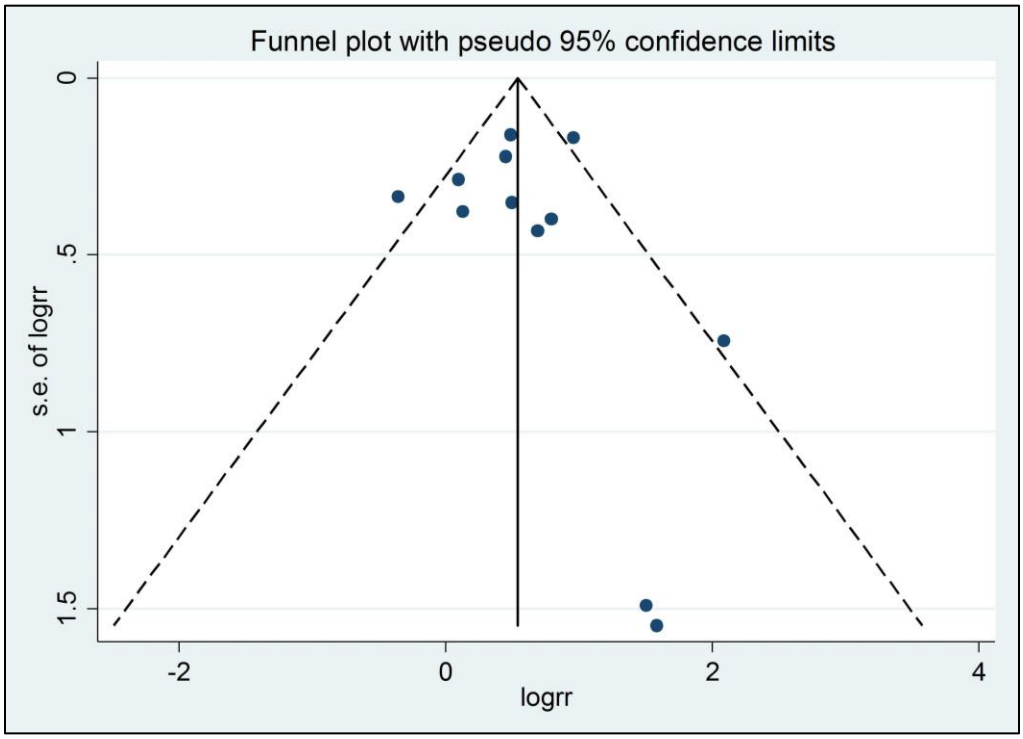
Abbreviation: s.e.=standard error.

Appendix C Figure 4. Funnel Plot: Renal Adverse Events



Abbreviation: s.e.=standard error.

Appendix C Figure 5. Funnel Plot: Gastrointestinal Adverse Events



Abbreviation: s.e.=standard error.

Appendix D Table 1. Rates of Adherence and Persistence to PrEP in U.S. Primary Care Settings

Study, year Type of PrEP	Study design	N	Population	Years PrEP Adminis-tered	Adherence: Drug levels	Adherence: Self report	Adherence: Other method	Persistence
ANCHOR Brokus, 2021[263] *Oral PrEP*	Treatment series	29	People with OUD receiving HCV treatment Median age: 54 years Male: 72% Black: 90% Heterosexual: 93%	NR	TFV-DP DBS detectable at week 4 94% (17/18); consistent with ≥4 pills/week 68% at week 24 and 25% at week 36	7 pills/week: 52.2% (12/23) at 4 weeks, 47.6% (10/21) at 12 weeks, 62.5% (5/8) at 48 weeks ≥4 pills/week: 73.9% (17/23) at 4 weeks, 71.4% (15/21) at 12 weeks, 87.5% (7/8) at 48 weeks	NR	Retention: 86.2% (25/29) at week 4, 72.4% (21/29) at week 12, 44.8% (13/29) at week 24, 31.0% (9/29) at week 36
Blackstock, 2017[196] *Oral PrEP*	Treatment series	21	Heterosexual women receiving PrEP Median age: 35 years Non-Latinx Black: 29% Latinx: 38% Other/not documented race/ethnicity: 33%	2015-2016	NR	NR	NR	Retained in care (PrEP care-related clinic visit or phone note within 1 month of clinic visit): 61.1% (13/21) at 3 months, 37.5% (8/21) at 6 months
Chan, 2016[187] *Oral PrEP*	Treatment series	267	MSM (89%), MSF (5.2%), FSM (6.7%) Mean age: 32 years White: 44% Black/African American: 41% Asian: 2.8% Other: 13% Hispanic or Latinx: 12%	2014	NR	≥4 pills in last week: 92% (106/115) at 3 months, 92% (73/79) at 6 months 100% adherence in last week: 72% (83/115) at 3 months, 79% (64/81) at 6 months 100% adherence in last month: 49% (56/115) at 3 months, 56% (44/79) at 6 months	NR	Retained in care 3 months after initial prescription: 73% (124/171) at 3 months, 60% (102/171) at 6 months
CDC Safety Study Grohskopf, 2013[52] *Oral PrEP*	RCT	373	MSM Median age: 38 years White: 80% African American: 11% Asian/Pacific Islander: 5.0% Other race: 5.0% Hispanic ethnicity: 8.0%	2005–2007	NR	NR	Medication event monitoring system: 79% (range, 60% to 92%) Pill count: 93% (range, 81% to 98%)	Temporary drug discontinuation: 42% (84/201) Overall (TDF + placebo), 17.6% (70/400) had a permanent drug discontinuation

Appendix D Table 1. Rates of Adherence and Persistence to PrEP in U.S. Primary Care Settings

Study, year Type of PrEP	Study design	N	Population	Years PrEP Adminis-tered	Adherence: Drug levels	Adherence: Self report	Adherence: Other method	Persistence
Clement, 2021[191] *Oral PrEP*	Treatment series	271	PrEP users at two health centers MSM: 81% Transgender: 5.2% Male: 86% Black: 47% White: 34% Hispanic/Latinx: 11%	2013-2018	NR	NR	NR	Discontinuation (missed more than 2 quarterly visits with no additional visits by the end of follow-up): 47.2% (128/271) Intermittent care (missed more than 2 quarterly visits, but at least one visit within six months by the end of the study):11.4% (31/271) Continuous care (not discontinuing PrEP and less than 6 months between all visits): 41.3% (112/271)
Coy, 2019[189] *Oral PrEP*	Treatment series	7148	PrEP users in national pharmacy database Male: 97% 18 to 24 years: 11% 25 to 29 years: 22% 30 to 39 years: 35% 40 to 49 years: 20% 50+ years: 12% Race/ethnicity: NR	Initiated in 2015	NR	NR	NR	Persistence (at least 16 days of PrEP filled per 30-day period, for at least three-quarters of a period [9 months of a 12 month period or 18 months of a 24 month period]): 56% (4030/7148) in year 1; 41% (2951/7148) in year 2 (among those persistent in year 1, 63% [2521/4030] persistent in year 2)
Hojilla, 2021[107] *Oral PrEP*	Treatment series	13,906	Persons linked to PrEP care in an integrated health system Mean age not reported; 18-25 20%, 26-35 40%, 35-45 21%, >45 20% Male 95%, female 5% White: 49% Latinx: 22% Asian: 15% Black: 7%	2012-2019	NR	NR	NR	Discontinued (>120 days without PrEP based on pharmacy refill records) at least once: 52.5% (95% CI 48.9% to 55.7%) Discontinued at 2 years: 38.4% (95% CI 37.2% to 39.6%) Reinitiated PreP, among those who discontinued at least once: 60.2% (95% CI 52.2% to 68.3%)

Appendix D Table 1. Rates of Adherence and Persistence to PrEP in U.S. Primary Care Settings

Study, year Type of PrEP	Study design	N	Population	Years PrEP Adminis-tered	Adherence: Drug levels	Adherence: Self report	Adherence: Other method	Persistence
Hosek, 2017[184] Project PrEPare, ATN 110 *Oral PrEP*	Treatment series	200	MSM Mean age: 20 years Latinx: 26% Non-Latinx Black/African American: 66% Non-Latinx White: 29% Non-Latinx other race: 5%	2013	Dried blood spot samples with TFV-DP level ≥700 fmol/punch Week 4: 56% Week 8: 58% Week 12: 53% Week 24: 47% Week 36: 41% Week 48: 34% Any TFV-DP level detected: 92% at week 4, 69% at week 48 TFV-DP level ≥350 fmol/punch Week 4: 78% Week 8: 77% Week 12: 72% Week 24: 57% week 36: 58% Week 48: 49%	NR	NR	NR
Hosek, 2017[183] Project PrEPare, ATN 113 *Oral PrEP*	Treatment series	72	MSM Mean age: 16 years White: 14% Black/African American: 29% White Hispanic: 21% Other race/ethnicity: 33%	2013–2014	Dried blood spot samples with TFV-DP level ≥700 fmol/punch Week 4: 54% Week 8: 47% Week 12: 49% Week 24: 28% Week 36: 17% Week 48: 22% TFV-DP level ≥350 fmol/punch Week 4: 69% Week 8: 66% Week 12: 59% Week 24: 36% Week 36: 28% Week 48: 26%	NR	NR	NR

Appendix D Table 1. Rates of Adherence and Persistence to PrEP in U.S. Primary Care Settings

Study, year Type of PrEP	Study design	N	Population	Years PrEP Adminis-tered	Adherence: Drug levels	Adherence: Self report	Adherence: Other method	Persistence
Hosek, 2013[141] Project PrEPare, ATN 082 *Oral PrEP*	Double-blind medication pilot RCT with third nonmedication control group	58	MSM, ages 18–22 years, at least 2 episodes of unprotected anal sex in past 12 months Male: 100% Black: 50% vs. 63% vs. 47% Other/mixed race: 40% vs. 32% vs. 42% Hispanic ethnicity: 35% vs. 32% vs. 53% Unprotected anal sex with a man in past 30 days: 45% vs. 37% vs. 42%	NR	TDF-FTC arm only Proportion of patients with detectable plasma TDF: Week 4: 63% Week 24: 20%	TDF-FTC arm only Mean adherence: 62% (range, 43% to 83%)	NR	NR
Huang, 2021[190] *Oral PrEP*	Treatment series	11,807	PrEP users in a commercially insured cohort and Medicaid-insured cohort Median age not reported Age 25-44 years: 61% (commercial) and 63% (Medicaid) Male: 98% (commercial) and 78% (Medicaid) Black: NR (commercial) and 26% (Medicaid) White: NR (commercial) and 44% (Medicaid)	2012-2017	NR	NR	NR	Median persistence (no gap >30 days): 13.7 months (commercial) and 6.8 months (Medicaid) Persisted for 12 months: 54.0% (commercial) and 29.9% (Medicaid)

Appendix D Table 1. Rates of Adherence and Persistence to PrEP in U.S. Primary Care Settings

Study, year Type of PrEP	Study design	N	Population	Years PrEP Adminis-tered	Adherence: Drug levels	Adherence: Self report	Adherence: Other method	Persistence
Krakower, 2019[194] *Oral PrEP*	Treatment series	663	Patients prescribed PrEP at a health center specializing in healthcare for sexual and gender minorities Male: 96% Female: 0.5% Transgender female or trans-feminine identifying: 3.0% Transgender male or trans-masculine identifying: 0.6% White (non-Hispanic): 73% Black: 6.5% Asian or Pacific Islander: 3.6% Hispanic or Latinx: 6.6%	2014-2015	NR	NR	NR	Continuous PrEP use (no interruption in PrEP >7 days): 60% One or more discontinuations (interruption in PrEP >7 days): 36% Discontinuation without re-initiation: 18%
Landovitz, 2017[186] PATH-PrEP *Oral PrEP*	Treatment series	301	MSM and transgender women Median age: 36 years White: 50% Hispanic: 28% Black: 11% Asian/Pacific Islander:6% Other race: 5%	2013–2016	Dried bloodspot samples with TFV-DP ≥700 fmol/punch: Week 4: 83.1% Week 12: 83.4% Week 24: 75.7% Week 36: 71.6% Week 48: 65.5%	NR	NR	NR

Appendix D Table 1. Rates of Adherence and Persistence to PrEP in U.S. Primary Care Settings

Study, year Type of PrEP	Study design	N	Population	Years PrEP Adminis-tered	Adherence: Drug levels	Adherence: Self report	Adherence: Other method	Persistence
Liu, 2016[177] The Demo Project *Oral PrEP*	Treatment series	557	MSM (98%) and transgender women (1.4%) Mean age: 35 years White: 48% Latinx: 34% Black: 7.2% Asian: 4.7%	2012–2015	Dried blood spot samples with TFV-DP level ≥700 fmol/punch Week 4: 86% Week 12: 85% Week 24: 82% Week 36: 85% Week 48: 80% ≥2 dried blood spot samples meeting threshold: 62.5% (170/272) TFV-DP level ≥350 fmol/punch, ≥2 dried blood spot samples meeting threshold: 97% (264/272)	Adherence self-rated "very good" or "excellent" at 87% (1,959/2,242) of visits	Pill count: 81.6% Medication ratio (number of dispensed pills/the number of days between visits): 85.9%	Interruption in PrEP: 15.1% (84/556) Interruption in PrEP without restarting: 13.1% (73/556)
Montgomery, 2016[185] *Oral PrEP*	Treatment series	50	MSM (95%) Mean age: 34 years Non-Hispanic White: 58% Non-Hispanic Black: 26% Hispanic or Latinx: 26% Other race: 8%	2013–2014	Dried blood spot samples with TFV-DP level ≥700 fmol/punch at mean of 4.4 months: 90% (19/21) TFV-DP level ≥350 fmol/punch: 95% (20/21)	Mean proportion of doses taken in last 7 days, at 3 months: 89% (6.2/7) Mean proportion of doses taken in last 30 days, at 6 months: 89% (26.8/30)	NR	Taking PrEP: 88% (38/43) at 3 months, 82% 31/38) at 6 months
Morgan, 2018[193] *Oral PrEP*	Treatment series	197	MSM 16 to 29 years of age Race/ethnicity: Not reported for baseline population	2015-2017	NR	NR	NR	Discontinued PrEP: 33.0% (65/197)
Serota, 2020[192] *Oral PrEP*	Treatment series	131	Non-Hispanic Black MSM 18 to 29 years of age	2015-2017	NR	NR	NR	Discontinuation : 69% Final discontinuation (discontinuation without restarting): 40%

Appendix D Table 1. Rates of Adherence and Persistence to PrEP in U.S. Primary Care Settings

Study, year Type of PrEP	Study design	N	Population	Years PrEP Adminis-tered	Adherence: Drug levels	Adherence: Self report	Adherence: Other method	Persistence
Van Epps 2018[188] *Oral PrEP*	Treatment series	1,086	Indication for PrEP NR Mean age NR; 39% age <35 years; 35% ages 35–49 years; 21% ages 50–64 years; 6% ages 65–79 years 4% female 22% Black; 67% White; 6% other	2012–2016	NR	NR	Median proportion of days/year covered by PrEP prescription: 74% (IQR, 40% to 92%)	Discontinued PrEP in first year (defined as 120-day gap): 44% (364/825)
Zarwell, 2021[195] *Oral PrEP*	Treatment series	294	Transgender man (80%) or woman (20%) 16 to 26 years: 29% 27+ years: 71% Black: 10% White: 51% Latinx: 18%	2017-2018	NR	NR	NR	Discontinued (among those ever having received PrEP): 49% (25/51)
HIV Preventio Trials Network (HPTN) 067/ADAPT Grant 2018[136] *Event Driven Versus Daily Oral PrEP*	RCT	179	MSM (97%), transgender women (2%), gender queer (1%) Mean age NR; 30% ages 18–24 years; 18% ages 25–29 years; 21% ages 30–39 years; 32% age ≥40 years 70% Black; 13% White; 3% Asian; 3% Native American; 21% other; 25% Hispanic (participants could self-identify in more than one category)	2012–2014	TFV-DP ≥326 fmol/punch (consistent with ≥2 doses/week) on visits when sex was reported in the prior week, daily PrEP: 48%; time-driven PrEP: 31%; event-driven PrEP 17%	NR	Medication event monitoring system, daily PrEP: 62%; time-driven PrEP: 47%; event-driven PrEP: 41% Proportion with ≥90% adherence, daily PrEP: 25%; time-based PrEP: 0%; event-driven PrEP: 2%	Temporarily or permanently discontinued PrEP due to side effects: 2.2% (4/179)

Appendix D Table 1. Rates of Adherence and Persistence to PrEP in U.S. Primary Care Settings

Study, year Type of PrEP	Study design	N	Population	Years PrEP Adminis-tered	Adherence: Drug levels	Adherence: Self report	Adherence: Other method	Persistence
DISCOVER Mayer, 2020[121] Ogbuagu, 2021[162] *Oral TAF-FTC Versus TDF-FTC*	RCT	5,387 (3,220 U.S.)*	MSM (99%), transgender women who have sex with men (1%) Median age: 34 years White: 84% Black: 9% Asian: 4% Hispanic or Latinx: 24%	2016-2017	TAF-FTC vs. TDF-FTC: TFV-DP DBS level consistent with ≥4 tablets/week: 88%-96% vs. 84%-93%, primary (interim) analysis	TAF-FTC vs. TDF-FTC: 78%-82% vs. 78-82%	TAF-FTC vs. TDF-FTC: Based on pill count, median adherence 98% (IQR 93%-100%) vs. 98% (IQR 93.5% to 100%)	Did not discontinue: 78.2% (2107/2694) vs. 79.8% (2150/2693)
HIV Preventio Trials Network (HPTN) 083 Landovitz, 2021[70] *Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC*	RCT	4,570 (1,698 U.S.)*	MSM (87%), transgender women who have sex with men (12%) Median age: 26 years Race/ethnicity (US patients): 50% Black	2016-2020	*Oral TDF-FTC (random sample)* TFV concentration >40 ng/mL: 74.2%; TFV concentration >0.31 ng/mL: 86.0%; TFV-DP in DBS consistent with ≥4 doses/week: 72.3%	NR	*Injectable cabotegravir* "Covered" by cabotegravir (injections with delay of <2 weeks): 91.5% of person-years	Did not permanently discontinue: 19.5% (445/2282) vs. 20.3% (463/2284)

*Adherence/persistence is not reported separately for U.S. patients.

Abbreviations: ANCHOR= Anal Cancer/HSIL Outcomes Research; CDC=Centers for Disease Control and Prevention; CI=confidence interval; DBS=dried blood spots; FSM=females who have sex with males; FTC=emtricitabine; HCV=hepatitis C virus; HPTN= HIV Prevention Trials Network; IQR=interquartile range; MSM=men who have sex with men; MSF=men who have sex with females; NR=not reported; OUD=opioid use disorder; PrEP=pre-exposure prophylaxis; RCT=randomized, controlled trial; TAF=tenofovir alafenamide; TVF-DP=tenofovir disoproxil fumarate-diphosphate; TDF-FTC=tenofovir disoproxil fumarate-emtricitabine; U.S.=United States.

Appendix D Table 2. Rates of Antiretroviral Drug Resistance in Patients Taking PrEP

Study Author, year Study design Type of PrEP	PrEP regimen	Resistance mutations among persons with newly diagnosed HIV infection	Resistance mutations among persons randomized to PrEP
Bangkok Tenofovir Study Choopanya 2013[53] RCT *Oral PrEP*	TDF daily (n=1,204)	TDF vs. placebo* K65R, K70E: 0% (0/17) vs. 0% (0/35)	0% (0/1204)
FEM-PrEP Van Damme 2012[172] RCT *Oral PrEP*	TDF-FTC daily (n=1,024)	TDF-FTC vs. placebo† K65R, K70E: 0% (0/33) vs. 0% (0/35) M184V mutation: 9.1% (3/33) vs. 2.9% (1/35) M184I mutation: 3.0% (1/33) vs. 0% (0/35)	0.4% (4/1024)
Grohskopf, 2013[52] RCT *Oral PrEP*	TDF daily (n=201)	TDF vs. placebo K65R: 0% (0/0) vs.0% (0/7)	0% (0/201)
IPERGAY Molina 2015[66] RCT *Oral PrEP*	TDF-FTC on demand (n=199)	TDF-FTC (n=2) vs. placebo (n=14) No resistance mutations identified	0% (0/199)
iPrEx Grant 2010[137] RCT *Oral PrEP*	TDF-FTC daily (n=1,251)	TDF-FTC vs. placebo‡ M184V alone: 2.6% (1/38) vs. 0% (0/72) M184I: 2.6% (1/38) vs. 0% (0/72) Multidrug resistance (M184V, T215Y, and K103N): 0% (0/38) vs. 1.4% (1/72)	0.2% (2/1,251)
Partners PrEP Baeten 2012[51] RCT *Oral PrEP*	A: TDF daily (n=1,572) B: TDF-FTC daily (n=1,568)	TDF vs. TDF-FTC vs. placebo§ K65R: 5.0% (1/20) vs. 0% (0/15) vs. 0% (0/57) K70E: 0% (0/20) vs. 0% (0/15) vs. 0% (0/57) K65N: 5.0% (1/20) vs. 0% (0/15) vs. 0% (0/57) M184I: 0% (0/20) vs. 0% (0/15) vs. 0% (0/57) M184V: 0% (0/20) vs. 6.7% (1/15) vs. 0% (0/57)	0.1% (3/3,140) overall 0.1% (2/1,572) TDF 0.06% (1/1,568) TDF-FTC
PROUD McCormack, 2016[118] RCT *Oral PrEP*	TDF-FTC daily (n=268)	TDF-FTC vs. deferred PrEP‖ K65R or K70G: 0% (0/5) vs. NR M184I or M184V: 40% (2/5) vs. NR	0.7% (2/268)
Study of TDF Peterson 2007[55] RCT *Oral PrEP*	TDF daily (n=427)	TDF vs. placebo¶ No drug resistance mutations identified in 1 patient randomized to TDF (no resistance testing performed in 1 other patient randomized to TDF who became infected)	NR
TDF2 Thigpen 2012[170] RCT *Oral PrEP*	TDF-FTC daily (n=601)	TDF-FTC vs. placebo Multidrug resistance (M184V, K65R, and A62V): 10% (1/10)# vs. 0% (0/26) K65R alone: 0% (0/10) vs. 3.8% (1/26)	0.2% (1/601)
VOICE Marrazzo 2015[54] RCT *Oral PrEP*	A: TDF daily (n=172) B: TDF-FTC daily (n=174)	TDF vs. TDF-FTC vs. placebo** K65R: 0% (0/70) vs. 0% (0/71) vs. 0% (0/69) K70E: 0% (0/70) vs. 0% (0/71) vs. 0% (0/69) M184V: 0% (0/70) vs. 4.2% (3/71) vs. 0% (0/69) M184I: 0% (0/70) vs. 1.4% (1/71) vs. 0% (0/69)	1.2% (4/346) overall 0% (0/172) TDF 2.3% (4/174) TDF-FTC

Appendix D Table 2. Rates of Antiretroviral Drug Resistance in Patients Taking PrEP

Study Author, year Study design Type of PrEP	PrEP regimen	Resistance mutations among persons with newly diagnosed HIV infection	Resistance mutations among persons randomized to PrEP
iPrEx-OLE Grant 2014[198] Observational *Oral PrEP*	TDF-FTC daily (n=1225)	M184V: 3.6% (1/28)	0.1% (1/1,225)
Hosek 2017[184] Project PrEPare, ATN 110 Observational *Oral PrEP*	TDF-FTC daily (n=200)	Antiretroviral drug resistance (not specified): 0% (0/4)	0% (0/200)
Hosek 2017[183] Project PrEPare, ATN 113 Observational *Oral PrEP*	TDF-FTC daily (n=78)	Antiretroviral drug resistance to TDF or FTC: 0% (0/3)	0% (0/78)
Liu 2016[177] Observational *Oral PrEP*	TDF-FTC daily (n=383)	Antiretroviral drug resistance to TDF or FTC: 0% (0/2)	0% (0/383)
Montgomery 2016[185] Observational *Oral PrEP*	TDF-FTC daily (n=35)	M184V, D67N, T215S, and K219Q: 100% (1/1)	2.0% (1/50)
ASPIRE Baeten, 2016[73] RCT *Dapivirine Vaginal Ring*	Dapivirine 25 mg vaginal ring (n=1,313)	NNRTI mutations (HIV-1 acquired after enrollment): Overall: 12% (8/68) V90I: 2.9% (2/68) E138A: 4.4% (3/68) K101E, K103S, V106M, V108I, E138G, V179D, V179I/T, H221Y: 1.5% each (1/68)	0.6% (8/1313)
HOPE Baeten, 2021[112] (ASPIRE open-label extension) *Dapivirine Vaginal Ring*	Dapivirine 25 mg vaginal ring (n=731)	NNRTI mutations: 20% (7/35 infections) L103A: 11.4% (4/35) A98G: 2.9% (1/35) G138A: 2.9% (1/35) V179A: 5.7% (2/35) V106M: 2.9% (1/35)	1.4% (7/731)
Ring Study Nel, 2016[74] RCT *Dapivirine Vaginal Ring*	A. Dapivirine ring (n=1,307)	Any HIV-1 drug resistance mutation: 39.0% (30/77) NNRTI resistance mutations (E138A, A98G, K103N, K101E, V106M, V090I, V108I, E138Q, Y181C, Y188C, H221Y): 18.2% (14/77) NRTI resistance mutation: 1.3% (1/77) Major PI resistance mutation: 2.6% (2/77) Minor PI resistance mutation: 26.0% (20/77)	Any HIV-1 drug resistance mutation: 2.3% (30/1307) NNRTI resistance mutation: 1.1% (14/1307)
DREAM Nel, 2021[111] Ring Study open-label extension *Dapivirine Vaginal Ring*	A. Dapivirine ring (n=941)	NNRTI mutations (A98G, G138A, L101G, L103A): 29.4% (5/17) NRTI mutations: 0% (0/17) Major PI mutation: 5.9% (1/17) (Denominator was 17/22 persons with seroconversion with successful population-based HIV-1 genotyping)	0.5% (5/941)

Appendix D Table 2. Rates of Antiretroviral Drug Resistance in Patients Taking PrEP

Study Author, year Study design Type of PrEP	PrEP regimen	Resistance mutations among persons with newly diagnosed HIV infection	Resistance mutations among persons randomized to PrEP
DISCOVER Mayer, 2020[121] Ogbuagu, 2021[162] *Oral TAF-FTC Versus TDF-FTC*	A: TAF-FTC (n=2694) B: TDF-FTC (n=2693)	M184: 20% (4/20); all infections occurred in TDF-FTC arm in persons with suspected baseline HIV infection (Denominator was 20 of 23 patients with HIV infection with successful genotypic resistance testing)	Overall: 0.07% (4/5387) A: TAF-FTC: 0% (0/2694) B: TDF-FTC: 1.5% (4/2693) (all suspected of having infection at baseline)
HPTN 083 Landovitz, 2021[70] *Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC*	A: Cabotegravir 600 mg in a 3 mL IM injectable every 8 weeks (n=2,282) B: Daily TDF-FTC 300 mg + 200 mg (n=2,284)	A: Cabotegravir (INSTI resistance mutation): 44.4% (4/9) among incident cases in whom resistance testing was available (1/4 cases with baseline infection had INSTI resistance mutation). Q148R (n=3), Q148K (n=1), E138K (n=2), E138A, K103N, L74I, G140A. No infections during the pharmacokinetic "tail" period. B: TDF-FTC (K65R, M184V, M184I, or a mixture of M184V and M184I with or without NNRTI resistance mutation): 10.3% (4/39) among incident infections (2/3 cases with baseline infection had drug resistance mutation)	A: Cabotegravir (INSTI resistance mutations): 0.2% (4/2282) B: TDF-FTC: 0.2% (4/2284)
HPTN 084 Delany-Moretwle, 2022[88] *Long-acting Injectable Cabotegravir Versus Daily Oral TDF-FTC*	A: Cabotegravir 600 mg in a 3 mL IM injectable every 8 weeks (n=1,592) B: Daily TDF-FTC 300 mg + 200 mg (n=1,586)	A: Cabotegravir: INSTI resistance mutations: 0% (0/4 incident infections) B: TDF-FTC: M184V: 2.8% (1/36 infections) and "several" (mainly K103N) resistance mutations occurred	A: Cabotegravir (INSTI resistance mutations): 0% (0/1592) B: TDF-FTC (M184V): 0.06% (1/1586)

*Includes two persons in placebo group who were HIV-infected at enrollment.
†Excludes one person on PrEP and four persons in placebo group who were HIV-infected at enrollment.
‡Includes 2 persons in TDF-FTC and 8 persons in placebo group who were HIV-infected at enrollment; all cases of resistance occurred in persons who were HIV-infected at enrollment.
§ Includes 5 persons on TDF, 3 persons on FTC-TDF, and 6 persons on placebo who had HIV infection at enrollment; K65R and M184V mutations occurred in persons with HIV infection at randomization.
‖Includes 2 persons in TDF group who were HIV-infected at enrollment or at 4-week visit; both mutations occurred in both persons.
¶Includes 1 person in TDF-FTC group and 2 persons in placebo group who were HIV-infected at enrollment.
#HIV-infected at enrollment.
**Includes 5 patients randomized to TDF, 9 patients randomized to TDF-FTC, and 1 patient randomized to placebo who were HIV-infected at time of enrollment; two cases of M184V mutations and 1 case of M184I mutation occurred in persons who were HIV infected at time of enrollment.
Abbreviations: FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; NR=not reported; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; IM=intramuscular; INSTI=integrase-strand transfer inhibitor; iPrEx=Pre-Exposure Prophylaxis Initiative; iPrEx-OLE=Pre-Exposure Prophylaxis Initiative–Open Label Extension; NNRTI=non-nucleoside reverse transcriptase inhibitors; PI=protease inhibitor; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; TAF=tenofovir alafenamid; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

Appendix D Table 3. Primary Care Interventions to Increase HIV PrEP Utilization

Author, year	Setting Country Recruitment	Study design	Population	Who gave intervention	Intervention	N	Findings
Chan 2021[216]	STI clinic US Recruited at STI clinic	RCT	MSM at risk for HIV (≥10 on HIRI-MSM)	STI clinic counselor	Brief (15-20 min) motivational interviewing intervention followed by <10 min telephone booster session vs. treatment as usual	86	Participants in the intervention group vs. the treatment as usual group were significantly more likely to schedule an appointment to further discuss PrEP with a prescriber (OR 6.0, 95% CI 2.3 to 15.6), attend the prescriber appointment (OR 3.6, 95% CI 1.5 to 8.9), and receive and accept a prescription for PrEP (OR 3.6, 95% CI 1.5 to 8.9)
Desrosiers 2019[214]	Clinic US Recruited online via social networking apps	RCT	Young Black MSM	Counselor and physician assistant	PrEP counseling (20-45 mins) and information vs. control (received information only)	50	Initiated PrEP by 3 months: 24% (6 people) in the intervention group vs. 0% control, p=0.023
Doblecki-Lewis 2019[217]	Research site US Recruited from hospital outpatient clinics and online via social networking app	RCT	Persons interested in PrEP	Patient navigator	Strengths-based case management (SBCM) intervention (1 45-60 minute session and option to attend 4 additional visits and/or phone/text message contact) vs. passive referral	61	Initiated PrEP by 12 weeks: 40% (12 people) in the intervention group vs. 29% (9 people) control, p=0.367 Saw PrEP provider by 12 weeks: 53% (16 people) in the intervention group vs. 33% (10 people) control, p=0.096
Harawa 2020[215]	Addiction center US Recruited via public venues and online	RCT	Black MSM	Various	Passport to Wellness HIV prevention full intervention vs. same intervention lacking peer support 1) all participants received a customized wellness plan (or Passport) that included referrals to health and support services and incentives for accessing those services; 2) all participants were awarded incentives for providing documentation of completed Passport activities; 3) participants assigned to the Peer Mentor (PM) intervention arm were also paired with a trained Peer who provided support, encouragement, and navigation; and 4) individuals assigned to this arm were also given the opportunity to attend social/education group outings	80	Use of PrEP in the prior 6 months: Increased from 0% to 22% for participants in the full intervention arm vs. from 0% to 9% for participants in the non-peer mentor arm, p=ns

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Author, year	Setting Country Recruitment	Study design	Population	Who gave intervention	Intervention	N	Findings
Meyer 2021[218] OPTIONS study	Addiction treatment center US Recruited at addiction treatment center	Non-randomized study	Women with substance use disorders in addiction treatment	Researcher	Patient-centered PrEP decision aid vs. enhanced standard care	164	Likely to see a provider for PrEP: 15.7% intervention group vs. 6.2% control; p=0.05
Teixeria da Silva 2021[213]	Clinics US Recruited from STI clinics and social networking apps	RCT	Black MSM and Black transgender women	Social work interventionist	Partner Services PrEP, a brief information-motivation-behavioral skills model intervention (60 mins plus up to 4 booster sessions) vs. usual services	146	Initiated PrEP within 3 months (EMR data): 20% (14 people) intervention group vs. 11% (7 people) control, p=0.15 Initiated PrEP within 12 months (EMR data): 37% (24 people) intervention group vs. 27% (17 people) control, p=0.25 Initiated PrEP within 3 months (self-report data): 24% (16 people) intervention group vs. 11% (7 people) control, p=0.05 Days to PrEP linkage within 12 months (EMR data): 27 days intervention group vs. 192 days control, p=0.05 Linked to PrEP within 3 months (EMR data): 24% (17 people) intervention group vs. 11% (7 people) control, p=0.04

Abbreviations: CI=confidence interval; EMR=electronic medical record; HIRI-MSM= HIV Incidence Risk Index for men who have sex with men; MSM=men who have sex with men; ns=not significant; OR=odds ratio; PM=peer mentor; PrEP=pre-exposure prophylaxis; RCT=randomized, controlled trial; SBCM=strengths-based case management; STI=sexually transmitted infection; U.S.=United States.