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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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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Structured Abstract

Background: Effective prevention strategies for HIV infection are an important public health priority. Pre-exposure prophylaxis (PrEP) involves use of antiretroviral therapy (ART) regularly (e.g., daily) or before and after HIV exposure events to decrease the risk of acquiring HIV infection.

Purpose: To synthesize evidence for the U.S. Preventive Services Task Force (USPSTF) on effects of PrEP on risk of HIV acquisition, mortality, harms, and other clinical outcomes; effects of adherence on PrEP-associated 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 inception to June 2018 and manually reviewed reference lists; additional surveillance for new literature was conducted through January 25, 2019.

Study Selection: Randomized, controlled trials on the benefits and harms of PrEP versus placebo or no PrEP in adults without HIV infection at high risk of becoming infected; studies on the diagnostic accuracy of instruments for predicting incident HIV infection; studies on effects of adherence to PrEP on risk of HIV infection; and studies on rates of adherence to PrEP in U.S. populations.

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, PrEP was associated with decreased risk of HIV infection versus placebo or no PrEP (11 trials; relative risk [RR], 0.46 [95% confidence interval (CI), 0.33 to 0.66; I^2=67%; absolute risk reduction, -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 plus emtricitabine or tenofovir 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). No trial reported effects of nondaily dosing except for one trial of event-driven PrEP (RR, 0.14 [95% CI, 0.03 to 0.63]). There was no difference between PrEP and placebo or no PrEP in risk of serious adverse events (12 trials; RR, 0.93 [95% CI, 0.77 to 1.12]; I^2=56%). PrEP was associated with increased risk of renal adverse events (12 trials; RR, 1.43 [95% CI, 1.18 to 1.75]; I^2=0%; absolute risk difference, 0.56% [95% CI, 0.09% to 1.04%]) and gastrointestinal adverse events (12 trials; RR, 1.63 [95% CI, 1.26 to 2.11]; I^2=43%; absolute risk difference, 1.95% [95% CI, 0.48% to 3.43%]); most adverse events were mild and resolved with discontinuation of PrEP or with longer therapy. The association between PrEP and fracture was not statistically significant (7 trials; RR, 1.23 [95% CI, 0.97 to 1.56]; I^2=0%). There were no differences between PrEP and placebo in risk of sexually transmitted infections, but most trials were blinded. Among women who became pregnant in trials of PrEP,

PrEP was not associated with increased risk of spontaneous abortion (3 trials; RR, 1.09 [95% CI, 0.79 to 1.50]; I^2=0%) or other adverse pregnancy outcomes. Instruments for predicting risk of incident HIV infection had moderate discrimination and require further validation. Adherence to PrEP in U.S. populations of men who have sex with men varied from high to low.

Limitations: Restricted to English language, statistical heterogeneity in some pooled analyses, most randomized trials were conducted in low-income settings, limited evidence on adherence in U.S. populations, and evidence lacking in adolescents and pregnant women.

Conclusions: In adults at increased risk of HIV infection, oral PrEP with tenofovir or tenofovir disoproxil fumarate plus emtricitabine is associated with decreased risk of HIV infection compared with placebo or no PrEP, although effectiveness decreases with inadequate adherence. PrEP is associated with increased risk of renal and gastrointestinal adverse events. Evidence on the accuracy of instruments for identifying persons at high risk of HIV infection is limited, with further validation needed.

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Chapter 1. Introduction and Background

Purpose

Effective prevention strategies for HIV infection are an important public health priority. Pre-exposure prophylaxis (PrEP) involves use of antiretroviral therapy (ART) regularly (e.g., daily) or before and after HIV exposure events (known as “on-demand” or “event-driven” PrEP) to decrease the risk of acquiring HIV infection. The purpose of this report is to synthesize evidence on effects of PrEP on risk of HIV acquisition, mortality, harms, and other clinical outcomes; effects of adherence on PrEP-associated outcomes; and accuracy of methods for identifying potential candidates for PrEP. It will be used by the U.S. Preventive Services Task Force (USPSTF) to develop a new recommendation on PrEP for the prevention of HIV infection, focusing on provision of PrEP in primary care settings.

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 one or more AIDS-defining neoplastic conditions or opportunistic infections.[1] 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.[2]

Prevalence and Burden of Disease/Illness

Since the first cases of AIDS were reported in 1981, more than 700,000 persons diagnosed with AIDS in the United States have died.[3] The Centers for Disease Control and Prevention (CDC) estimates that approximately 1.1 million persons in the United States were living with HIV infection in 2015,[3] including 15 percent who were unaware of their infection.[4] This represents a decrease since 2008, when approximately 20 percent of infected persons were estimated to be unaware of their HIV-infected status.[5-7] The number of new HIV infections annually in the United States has decreased slightly in recent years, from about 42,000 infections in 2011 to 40,000 each year from 2013 to 2016.[3] Approximately 530,000 persons were living with AIDS in 2015.

Groups more affected by HIV infection in the United States include men who have sex with men and black and Hispanic/Latino 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 men who have sex with men, the only risk group to experience a significant increase in incidence during this period ($p<0.001$).[8] In 2016, of total HIV diagnoses, 32,131 (81%) were among adult and adolescent males (age 13 years or older), 7,529 (19%) were among adult and adolescent females, and 122 (0.3%) were among children younger than age 13 years.[3] Persons ages 20 to 34 years accounted for half of the new diagnoses and had the highest incidence of HIV infection (26.2 to 34.8 cases per 100,000 persons). Among adolescents, the incidence of HIV infection rose sharply from ages 13 to 14 years (0.3 cases per 100,000 persons) to ages 15 to 19 years (7.8 cases per 100,000 persons). By race/ethnicity, 44 percent of new diagnoses occurred among black persons, 26 percent among white persons, and 25 percent among Hispanic/Latino persons.[3] Among men, having sex with men is the most common transmission method (83%), followed by heterosexual contact (9.4%), injection drug use (4.0%), and having sex with men and injection drug use together (3.7%). Among females, heterosexual contact is the most common transmission method (87%), followed by injection drug use (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. Factors facilitating sexual transmission include the presence of sexually transmitted infections (STIs), certain sexual practices (e.g., penile-anal or penile-vaginal intercourse without a condom, sex with multiple partners, sex with persons with HIV or at high risk of HIV infection), and high viral load in the infected partner.[9,10] In persons who inject drugs, factors associated with HIV infection include increased frequency or duration of injection behaviors, sharing needles, and backloading (injecting drugs from one syringe into the back of another opened syringe).[11]

The primary HIV infection syndrome usually develops 2 to 4 weeks following initial exposure to HIV.[12] Acute infection is often associated with a clinical syndrome resembling infectious mononucleosis.[13,14] Very early after acute infection, there is rapid virus production that then declines to a set point (which varies between individuals) as the host immune system responds, although continuous rapid virus production and clearance occurs at all stages of infection.[15-20]

Although a small proportion of untreated HIV-infected persons 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.[1] 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.[21,22]

The primary mechanism through which chronic HIV infection causes immune deficiency is via 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.[23] Most patients with CD4 counts over 200 cells/mm^3 are either asymptomatic or have mild disease,[24] although research indicates an increased risk of AIDS or death even in patients with CD4 counts over 500 cells/mm^3.[25] 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.[26-28]

A higher HIV viral load is a strong independent predictor of more rapid progression to AIDS.[26-31] Other predictors of more rapid progression include older age at the time of infection,[21,22,26,27,30,32,

[33] more severe symptoms at the time of primary HIV infection,[34] and other clinical and genetic factors. A factor associated with slow progression is the cysteine-cysteine chemokine receptor 5 delta32 genotype.[35-39]

Risk Factors

Persons at increased risk of HIV infection include men who have sex with men; 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 seeking treatment for other STIs; persons with a history of blood transfusion between 1978 and 1985; persons whose past or current sexual partners are HIV-infected, bisexual, or persons who inject drugs; transgender persons; and persons who do not report one of these risk factors but who request HIV testing.[40-42] 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.[43]

Rationale for Screening/Screening Strategies/Prevention

HIV infection remains incurable 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[44] and others, to identify infected persons; treatment with ART in HIV-infected persons to reduce risk of transmission;[45] and behavioral counseling to reduce high-risk sexual and drug use behaviors.

For persons at substantial risk of HIV infection who are not infected, another promising preventive strategy is PrEP with ART in combination with risk behavior counseling, to reduce risk of acquiring HIV infection.[46] PrEP involves use of ART on an ongoing, regular (e.g., daily) basis or before and after HIV exposure events to lower the likelihood of acquiring HIV infection. It differs from nonoccupational postexposure prophylaxis, which involves use of ART for 28 days after a single high-risk exposure.[47]

Intervention/Treatment

The most commonly studied antiretroviral regimen for PrEP is a daily oral fixed-dose combination of tenofovir disoproxil fumarate (TDF), a prodrug of tenofovir, and emtricitabine (FTC). This combination was selected because of its effectiveness as part of ART 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).[48] In 2012, the U.S. Food and Drug Administration (FDA) approved daily oral TDF-FTC for PrEP in adults at risk of sexual acquisition.[49] In 2018, the FDA expanded the indication for PrEP to include adolescents weighing at least 35 kg (77 lb).[50] Because effectiveness of PrEP depends on adherence,[51] there is also interest in nondaily oral regimens that may enhance adherence while maintaining effectiveness of PrEP, such as on-demand or event-driven[52] (taken before and after an anticipated

HIV exposure event) or intermittent (scheduled, nondaily) dosing of TDF-FTC.[53,54] Research is also ongoing on alternative, nonoral modes of PrEP administration that require infrequent dosing (e.g., long-acting injectables[55] or an intravaginal ring[56]).

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, in addition to attenuating HIV prevention benefits. PrEP could induce antiretroviral resistance as a result of inadequate treatment in HIV-infected persons who inadvertently receive PrEP or in HIV-uninfected persons who acquire infection while on PrEP. Adverse effects of TDF include negative effects on bone mass and kidney function.[57-59]

Current Clinical Practice

In 2014, the United States Public Health Service issued a guideline recommending PrEP with TDF-FTC in adults at high risk of infection, including men who have sex with men with a high number of sexual partners or inconsistent condom use, men who have sex with men and heterosexual persons in HIV-serodiscordant relationships, other high-risk heterosexual persons, and persons who inject drugs and share injection equipment; the guideline was updated in 2017.[60] The guideline also includes TDF alone as an option for PrEP in persons who inject drugs and heterosexual men and women. Criteria for PrEP in different HIV risk categories are shown in **Table 1**. The guideline recommends that providers engage in shared decisionmaking with pregnant women who are beginning or continuing PrEP during pregnancy.[60] Although FDA labeling information and perinatal antiretroviral treatment guidelines permit use of TDF-FTC during pregnancy, the guideline notes that data on safety of PrEP use during pregnancy are limited. The guideline states that data on the efficacy and safety of PrEP in adolescents are insufficient, but were developed before expansion of FDA approval of TDF-FTC for PrEP in adolescents weighing at least 35 kg.

A 2012 World Health Organization guideline recommends PrEP in persons at high risk of sexual acquisition of HIV infection.[61] The World Health Organization has also issued an implementation tool for PrEP.[62]

Recent data indicate that implementation of PrEP in the United States remains limited. The CDC estimated approximately 1.2 million persons were eligible for PrEP in 2015 (492,000 men who have sex with men, 115,000 persons who inject drugs, and 624,000 heterosexually active adults), but only an estimated 125,000 had active PrEP prescriptions.[63,64] Evidence from clinicians in the United States, particularly among primary care providers, indicate gaps in knowledge and uptake of PrEP.[65] A survey of more than 500 providers in 10 U.S. cities during 2014 to 2015 found that compared with HIV providers, primary care providers were less likely to have heard of PrEP (76% vs. 98%), feel familiar with prescribing PrEP (28% vs. 76%), or had prescribed it (17% vs. 64%).[66] Primary care providers were also less comfortable than HIV providers with discussing sexual activities (75% vs. 98%). Barriers to prescribing by primary care providers included limited knowledge about PrEP and concerns about insurance coverage. A 2015 survey of academic primary care providers (n=266) found that 93 percent were familiar with PrEP; of those, about one-third reported adoption of PrEP.[67] Adopters were more likely to provide care to more than 50 HIV-infected patients, report good or excellent knowledge of PrEP, perceive PrEP as safe, and not perceive PrEP as increasing risky behaviors. Another survey of 280 primary care providers from high HIV incidence areas in 10 U.S. cities found that one-third had discussed PrEP and 17 percent had prescribed PrEP.[68] Prescribing was associated with greater knowledge about PrEP, positive attitudes toward PrEP, and confidence in prescribing PrEP.

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[69] 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 surveyed for input, and the draft research plan was posted for public comment before finalization.

Key Questions

1. What are the benefits of PrEP in persons without pre-existing HIV infection versus 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 population subgroups?
   b. How do the benefits of PrEP differ by dosing strategy or regimen?
2. 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?
3. What are rates of adherence to PrEP in U.S. primary care–applicable settings?
4. What is the association between adherence to PrEP and effectiveness for preventing HIV acquisition?
5. What are the harms of PrEP versus placebo or no PrEP when used for the prevention of HIV infection?

Contextual Questions

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

1. What factors are associated with increased or decreased adherence to PrEP?
2. What is the risk of infection with antiretroviral drug–resistant HIV in persons treated with PrEP, and what is the effect of infection with PrEP-related, antiretroviral drug–resistant HIV on treatment outcomes?

Search Strategies

We searched MEDLINE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Embase from inception through June 2018. Search strategies are available in **Appendix A1**. We also reviewed reference lists of relevant articles.

After June 2018, we conducted surveillance through article alerts and targeted searches of high-impact journals to identify major studies that may affect conclusions. The last surveillance was conducted on January 25, 2019. Surveillance identified no primary research meeting inclusion criteria for this review.

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.

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 PrEP interventions addressed in this report are oral daily TDF-FTC, the only antiretroviral regimen currently approved by the FDA for PrEP, as well as alternative TDF-FTC dosing schedules (e.g., event-driven [on-demand][52] or intermittent dosing[53,54]), which are not approved by the FDA but have been evaluated in randomized, controlled trials (RCTs) and adopted in some countries. 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, a large trial found no clear difference between TDF and TDF-FTC in effects on risk of HIV acquisition,[70] and it is an option for PrEP in persons who inject drugs and heterosexual men and women in the 2017 United States Public Health Service guideline.[60] We conducted stratified analyses for all outcomes according to the regimen used (TDF-FTC or TDF) as well as the dosing regimen (daily or event-driven/intermittent). We did not include other oral PrEP regimens (e.g., regimens with tenofovir alafenamide or containing maraviroc[71]) or delivery methods (e.g., long-acting injectables,[55] intravaginal ring,[72-74] or vaginal gel[75-77]), which are not approved by the FDA or recommended in other countries. The main comparison was PrEP versus placebo; one trial compared PrEP with no (delayed) PrEP.[78] To address effects of dosing method on effectiveness, we also included randomized trials of daily versus nondaily (intermittent or event-driven) PrEP.

The population of interest for PrEP was HIV-uninfected persons at higher risk of HIV acquisition. The review assessed evidence on PrEP in adults, including HIV-uninfected pregnant women and HIV-uninfected women seeking to become pregnant with an HIV-infected partner, as well as adolescents (defined as ages 13 to <18 years). Patient subgroups of interest were based on demographic characteristics (age, sex, race/ethnicity, and pregnancy status) and HIV risk category. For the Key Question on risk assessment, we included studies on the diagnostic accuracy of provider or patient assessment instruments to predict HIV acquisition, to identify potential candidates for 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 C virus infection, renal insufficiency, fractures, gastrointestinal adverse events, and pregnancy-related outcomes. HSV infection is 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.[79,80] We also addressed the association between adherence and effectiveness of PrEP and rates of adherence to PrEP in U.S. primary care–applicable settings. Methods for measuring adherence include patient diaries and self-report, pill counts, adherence monitoring devices, drug levels (e.g., plasma or dried blood spots), and prescription fill data. A Contextual Question addresses factors (e.g., demographic factors or sexual or drug use behaviors) associated with increased or decreased adherence to PrEP.[81] Condom use was not included as an outcome because effects on rates of HIV and other STIs are directly addressed. A Contextual Question addresses 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. This is 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 resistance due to PrEP on clinical outcomes appears to be very limited.[82]

To assess applicability, we abstracted data regarding 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.

We included randomized trials of PrEP versus placebo or no PrEP. For evaluation of adherence, we also included longitudinal U.S.-based PrEP implementation studies.[83,84]

Data Abstraction and Quality Rating

For studies meeting inclusion criteria, we created data abstraction forms to summarize characteristics of study populations, interventions, comparators, adherence, and method 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. For one trial that reported total numbers of adverse events, we contacted the study funding agency for per-person adverse event rates.[85]

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**).[69] 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 are biologically plausible.[86] For each study, quality assessment was performed by two team members. Any disagreements were resolved by consensus.

Data Synthesis

We conducted meta-analyses to calculate risk ratios for effects of PrEP on HIV infection, mortality, and harms using the DerSimonian and Laird random-effects model with Review Manager Version 5.3 software (The Cochrane Collaboration Nordic Cochrane Centre, Copenhagen, Denmark). Statistical heterogeneity was assessed using the I^2 statistic.[87] When the I^2 was greater than 30 percent, sensitivity analysis was performed with the profile likelihood method using Stata/IC Version 13.1 (StataCorp, College Station, TX), as the DerSimonian and Laird model can result in overly narrow confidence intervals (CIs) in this situation.[88] We conducted additional sensitivity and stratified analyses based on study quality, PrEP drug regimen (TDF or TDF-FTC), HIV risk category (men who have sex with men, persons who inject drugs, 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.[89] We analyzed effects of study-level adherence as a categorical variable in a stratified analysis (≥70%, >40% to <70%, or ≤40%)[90] and as a continuous variable through meta-regression, and constructed a plot of adherence against effectiveness (log RR). Adherence was based on, in order of preference, 1) the proportion of all PrEP patients (or a random sample) with detectable plasma tenofovir levels; 2) the proportion of PrEP nonseroconverters with detectable plasma tenofovir levels, based on a random or matched (to seroconverters) sample, or the mean proportion of PrEP doses taken; 3) medication electronic monitoring system data; 4) pill counts; or 5) self-report. We performed sensitivity analysis restricted to studies that assessed adherence based on drug levels. 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).[91]

For all Key Questions, the overall quality of evidence was determined using the approach described in the USPSTF Procedure Manual.[69] 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.[69]

External Review

The draft report was reviewed by content experts (**Appendix A7**), USPSTF members, Agency for Healthcare Research and Quality Project Officers, and collaborative partners, and posted for public comment. The report was revised in response to comments before finalization.

Response to Public Comments

The draft report was posted for public comment from November 20, 2018 to December 26, 2018, and few comments were received. In response to the comments, we added a reference to the WHO implementation tool,[62] clarified that STI testing in persons taking PrEP is every 3 to 6 months, and for studies of PrEP in adolescents,[92-94] corrected the trial names in the evidence tables and clarified funding sources.

Chapter 3. Results

A total of 3,116 references from electronic database searches and manual searches of recently published studies were reviewed and 308 full-text papers were evaluated for inclusion. Across all Key Questions, 14 RCTs (in 37 articles[52-54,70,76,78,85,94-123]), eight observational studies,[81,92,93,124-128] and seven studies of diagnostic accuracy of HIV risk prediction instruments[129-135] were included. 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 Versus Placebo or No PrEP (Including Deferred PrEP) on the Prevention of HIV Infection and Quality of Life?

Summary

- PrEP was associated with decreased risk of HIV infection versus placebo or no PrEP in populations at higher risk of acquiring HIV (11 trials; 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).[52,53,70,76,78,85,97,100,117,119,120]
- There was a strong association between degree of adherence and PrEP effectiveness (p<0.00001 for interaction)
    - Adherence ≥70%: 6 trials; RR, 0.27 [95% CI, 0.19 to 0.39]; I^2=0%[52,53,70,78,85,119]
    - Adherence >40% to <70%: 3 trials; RR, 0.51 [95% CI, 0.38 to 0.70]; I^2=0%[97,100,117]
    - Adherence ≤40%: 2 trials; RR, 0.93 [95% CI, 0.72 to 1.20]; I^2=0%[76,120]
- PrEP was consistently associated with decreased risk of HIV infection when trials were stratified according to risk category, study duration, setting (high- or low-income), and study quality, and in subgroup analyses based on age[70,97,100,120] and sex.[70,97,119]
- Effects of 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%); one trial of men who have sex with men[52] evaluated event-driven (as opposed to daily) PrEP (RR, 0.14 [95% CI, 0.03 to 0.63]).
- PrEP was associated with a statistically nonsignificant trend toward reduced risk of mortality versus no PrEP or placebo (9 trials; RR, 0.81 [95% CI, 0.59 to 1.11]; I^2=0%).[70,76,78,85,97,100,117,119,120]
- No trial reported effects of PrEP versus placebo or no PrEP on quality of life.

Evidence

Twelve RCTs (reported in 29 publications[52-54,70,76,78,85,95-98,100,102-104,106-109,111-115,117-121]) evaluated PrEP versus placebo or no PrEP (**Table 2; Appendix B Tables 1–3**). Two trials[53,54] 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 RCTs randomized patients to

PrEP or placebo. The other trial randomized patients to immediate PrEP versus delayed PrEP (no PrEP for 1 year, after which patients received PrEP).[78] Six trials[54,70,76,117,119,120] enrolled men and women at increased risk of HIV infection via heterosexual contact, four trials[52,78,85,100] enrolled men who have sex with men or transgender women, one trial[53] enrolled both men who have sex with men and high-risk women, and one trial[97] enrolled persons who inject drugs. 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[85,97,117] evaluated TDF 300 mg, six trials[52-54,100,119,120] evaluated TDF 300 mg-FTC 200 mg, one trial[78] evaluated TDF 245 mg-FTC 200 mg, and two trials[70,76] included arms for both TDF 300 mg alone and TDF 300 mg-FTC 200 mg. PrEP was prescribed daily in 11 trials[53, 54,70,76,78,85,97,100,117,119, 120] and dosing was intermittent or event-driven in three trials (two of which also included daily dosing arms).[52-54] 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 was taken within 1 week.[52] 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.[53,54] 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.[78]

Seven trials were conducted in Africa,[53,54,70,76,117,119,120] one in Thailand,[97] two in Europe or Canada,[52,78] one in the United States,[85] and one trial was international (~10% of patients from U.S. sites).[100] The trial conducted in the United States (n=400) evaluated daily TDF versus placebo in men who have sex with men;[85] the two trials conducted in Europe and Canada[52,78] and the international trial[100] also focused on men who have sex with men. All trials of persons at higher risk of HIV infection via heterosexual contact were conducted in Africa, and the only trial of persons who inject drugs was conducted in Thailand.[97] 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 without a prescription at pharmacies at low cost. 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,[78] three trials reported that study medications were donated by industry,[53,54,120] and one trial noted that two investigators received royalties or funding from industry.[119] One trial[78] 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.

HIV Infection

Results of analyses on effects of PrEP versus placebo or no PrEP on risk of HIV infection are summarized in **Table 3**. Among 12 trials of PrEP versus placebo or no PrEP[52-54,70,76,78,85,97,100,117, 119,120] one small (n=72) trial[54] reported no cases of HIV infection with either PrEP or placebo. In the other 11 trials, 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[78] 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.[89,100]

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)[76,120] 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%;[52,53,70,78,85,119] adherence >40% to <70%: 3 trials; RR, 0.51 [95% CI, 0.38 to 0.70]; I^2=0%;[97,100,117] and adherence ≤40%: 2 trials; RR, 0.93 [95% CI, 0.72 to 1.20]; I^2=0%[76,120]) and stratification eliminated statistical heterogeneity (**Table 3; Figure 3**).[52,53,70,76,78,85,97,100,117,119,120]

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. Issues related to adherence are further addressed in Key Questions 3 and 4 and Contextual Question 1.

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%),[52,53,117] 1 year or more 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%),[78,100,119,120] 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%),[70,76,85,97] or whether trials reported receipt of industry support (3 trials; RR, 0.58 [95% CI, 0.27 to 1.22]; I^2=54%)[53,119,120] versus only reporting governmental or nonprofit funding (8 trials; RR, 0.39 [95% CI, 0.23 to 0.64]; I^2=77%)[52,70,76,78,85,97,100,117] (**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%)[52,78,85] 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**).[53,54,70,76,97,100,117,119,120] All three trials conducted in the United States, Europe, or Canada reported high adherence and enrolled men who have sex with men.

Mortality

Nine trials[70,76,78,85,97,100,117,119,120] of PrEP versus placebo or no PrEP reported mortality; one other trial reported no deaths with or without PrEP,[52] and two small, short-term trials (n=72 each; followup 4 months) did not report mortality.[53,54] 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%); risk estimates from individual trials were imprecise (**Figure 7**). There was no funnel plot asymmetry (**Appendix C Figure 2**). Results 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]).

Quality of Life

No trial reported effects of PrEP versus placebo on quality of life.

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

HIV Infection

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%),[54,70,76,117,119,120] men who have sex with men or transgender women (4 trials; RR, 0.23 [95% CI, 0.08 to 0.62]; I^2=64%),[52,78,85,100] or persons who inject drugs (1 trial; RR, 0.52 [95% CI, 0.29 to 0.92]; p=0.43 for interaction) (**Figure 8**),[97] although evidence of effectiveness in persons who inject drugs 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.[76,120]

Five trials performed within-study subgroup analyses of PrEP effectiveness (**Table 4**).[70,97,100,119,120] Four trials[70,97,100,120] found no clear differences in PrEP effectiveness in subgroups defined according to age, and three trials[70,97,119] found no clear differences between males and females. A post-hoc analysis of the iPrEx trial[100] found that PrEP was effective in men who have sex with men (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).[98] 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.[100] Among three trials conducted in the United States, Europe, or Canada, the proportion of participants who were white ranged from 73 to 91 percent.[52,78,85]

Data were limited regarding effects of risk behaviors on effectiveness of PrEP. One trial found PrEP was effective in transgender women and men who have sex with men 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).[100] 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.[70] This trial also found both TDF and TDF-FTC associated with similar effectiveness when analyzed according to sexual risk behaviors and viral load (**Appendix B Table 1**).[115] A trial of persons who inject drugs (the Bangkok Tenofovir Study) found no association between drug injection or needle sharing in the 12 weeks before enrollment and effectiveness of PrEP.[97]

Mortality

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%),[70,76,119,120] men who have sex with men or transgender women (4 trials; RR, 0.87 [95% CI, 0.22 to 3.41]; I^2=0%),[78,85,100,117] and persons who inject drugs (1 trial; RR, 0.85 [95% CI, 0.58 to 1.23]) (**Figure 9**).[97]

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

HIV Infection

Estimates of effectiveness of 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%)[70,76,85,97,117] 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**).[52,53,70,76,78,100,119,120] Among the trials that used intermittent or event-driven dosing, one trial[54] reported no HIV events and one trial[53] combined results for intermittent/event-driven and daily dosing of PrEP arms. The third trial (IPERGAY)[52] found event-driven PrEP associated with a lower risk of HIV infection than placebo in men who have sex with men (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 10**),[70,76,78,85,97,100,117,119,120] 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]).[53,70,78,85, 119] 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 compared daily with intermittent (twice a week, plus a dose after sex) or event-driven (dosing before and after sex) PrEP with TDF-FTC in men who have sex with men or transgender women[123] (n=357) and heterosexual African women[122] (n=178)

(**Appendix B Table 1**), but was not powered to evaluate effects of dosing on HIV infection risk (five total postrandomization cases across all risk groups and dosing regimens).

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 UK: Immediate or Deferred (PROUD) trial, PrEP was more effective than no PrEP at reducing risk of HIV infection in men who have sex with men (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%) in persons randomized to PrEP.[78] 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;[52,70,100] PrEP was effective in all three trials (RR, 0.14 to 0.53).

Mortality

Estimates of effectiveness of PrEP versus placebo or no PrEP on mortality 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 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

- Three studies of different instruments for predicting incident HIV infection in men who have sex with men reported moderate discrimination (area under the receiver operating characteristic curve [AUROC], 0.66 to 0.72); a study of a fourth instrument reported better goodness of fit than with two instruments evaluated in other studies (AUROC not reported).[129-132] Two studies found poorer discrimination of risk prediction instruments in black men who have sex with men (AUROC, 0.49 to 0.63).[134,135] All studies had methodological limitations and all prediction instruments require further validation.
- One study that retrospectively applied a 10-item instrument for predicting incident HIV infection in persons who inject drugs reported an AUROC of 0.72, but had methodological limitations and required validation.[133]
- No study evaluated a U.S.-applicable instrument for predicting incident HIV infection in women or men at risk of HIV infection via heterosexual contact.
- No study evaluated an instrument for predicting incident HIV infection in persons not preidentified as belonging to an HIV risk category.

Evidence

Seven studies evaluated instruments developed and validated in U.S. cohorts for predicting incident HIV infection[129-135] (**Appendix B Tables 5 and 6**). Six studies evaluated risk prediction instruments in men who have sex with men[129-132,134,135] and one study in persons who inject drugs.[133] Samples sizes (including development and validation cohorts) ranged from 300 to 9,481 patients (total N=32,311). For men who have sex with men, studies evaluated the predictive utility of four different instruments (number of criteria ranged from 4 to 10), as well as CDC criteria for PrEP and recommendations from the TDF-FTC package insert. In the cohorts used to develop risk assessment instruments for men who have sex with men, black participants comprised 6 and 7.8 percent of the population in two studies;[129,130] one study reported that 23 percent of the population was nonwhite, Asian, or Pacific Islander;[131] and one study reported a nonwhite proportion of 14 percent.[132] Two studies evaluated the performance of previously developed risk assessment in men who have sex with men cohorts in which 46 percent[135] or all participants[134] were black. The instrument for predicting risk in persons who inject drugs had seven items and was developed using a cohort of primarily (93%) black participants. In the cohorts used to develop and validate the risk prediction instruments, the incidence of HIV infection ranged from 2.4 to 11 percent in men who have sex with men; HIV incidence was 11 percent in the study in persons who inject drugs.

All studies had methodological shortcomings (**Appendix B Table 7)**. In all studies, risk assessment instruments were applied to previously collected data; in some cases, the criteria had to be modified based on the data available. In six studies, new HIV infections were identified in the study sample by repeat testing using a longitudinal (cohort) design. In the other study, which evaluated a risk prediction instrument for men who have sex with men, new HIV infections were identified based on a single test for markers for acute or early HIV infection.[130] Three studies used cohorts that included persons who had HIV testing before the year 2000.[131-133] In five studies, the predictive utility of risk assessment instruments was tested (validated) in cohorts independent from the one used to develop the instrument.[130-132,134,135] In two studies, accuracy was only reported for the cohort used to develop the instrument.[129,133] Cutoffs to define a positive test were predefined in two studies.[134,135]

Although three studies evaluated instruments for predicting risk of incident HIV infection in heterosexual women or men, including pregnant and postpartum women, all were developed and validated in African cohorts and have not been tested in the United States or U.S.-applicable settings.[136-138] No study evaluated instruments for predicting risk of HIV infection in persons not preidentified as having an HIV risk factor (e.g., men who have sex with men, injection drug use, or high-risk heterosexual behaviors). One study evaluated patients attending a clinic for lesbian, gay, bisexual, and transgender persons[129] and one study evaluated patients attending an STI clinic;[131] the other studies evaluated persons enrolled in research studies.

Men Who Have Sex With Men

Six studies evaluated risk prediction instruments in men who have sex with men.[129-132,134,135] 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 ART in an HIV-infected sexual partner.

For three instruments, discrimination was similar, with AUROCs in the original validation cohorts ranging from 0.66 to 0.72.[130-132] A fourth study[129] 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[131,132] or criteria from the 2014 CDC guidelines for offering PrEP in men who have sex with men.[60] 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. Two studies reported poorer discrimination of various risk assessments instruments in black men who have sex with men, with AUROCs ranging from 0.49 to 0.63.[134,135]

The six-item Assessing the Risk of Contracting HIV in Men Who Have Sex With Men (ARCH-MSM) instrument was included in the CDC PrEP guideline as a potential tool to identify eligible candidates.[132] 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. Based on a suggested post-hoc cutoff of 10 or greater (range, 0 to 48), 62.4 percent of men in the validation cohort 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 cohorts used to validate and develop the ARCH-MSM instrument were older (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 the same validation cohort as ARCH-MSM.[131] A cutoff score of 3 or greater with this instrument provided comparable sensitivity (76%) and specificity (43%) to ARCH-MSM 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 San Diego Early Test (SDET) (score range, 0 to 10 points) was developed using a more contemporary (2008–2014) cohort.[130] As noted earlier, HIV incidence was estimated based on markers for acute or early HIV infection on a single test. A cutoff score of 1 or greater resulted in a sensitivity (73%) and specificity (48%) 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).[129] 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. 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 men who have sex with men (any anal sex without condoms in past 6 months, any STI diagnosed or reported in past 6 months, or ongoing sexual relationship with an HIV-infected partner).[60] In the study by Beymer et al, goodness of fit was slightly better with the Los Angeles LGBT Center instrument than the CDC criteria.[129]

Two studies found that risk prediction instruments performed more poorly in black men who have sex with men. In one study of men who have sex with men, 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 the subgroup of black men who have sex with men, and from 0.60 to 0.67 in white men who have sex with men.[135] In the other study, the AUROC for the ARCH-MSM was 0.57 in black men who have sex with men, and similar using criteria derived from the CDC recommendations (AUROC, 0.51) or the PrEP package insert (AUROC, 0.54).[134]

Persons Who Inject Drugs

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 persons who inject drugs in Baltimore.[133] The instrument includes items on age, enrollment in a methadone maintenance program, and drug use behaviors. In the sample used to develop the instrument, the 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-IDU has not been evaluated in a separate validation cohort.

The 2014 CDC guideline includes recommended indications for PrEP in persons who inject drugs (any sharing of injection or drug preparation equipment in past 6 months, been in a methadone or buprenorphine treatment program in past 6 months, or risk of sexual acquisition); we did not identify any formal assessment of the CDC criteria.[60]

Men and Women at Increased Risk of HIV Infection Via Heterosexual Contact

Three studies evaluated instruments for predicting risk of HIV infection in men and women at increased risk of HIV infection via heterosexual contact but did not meet inclusion criteria because they were developed using data from African cohorts. One instrument focused on serodiscordant couples,[137] one in women,[138] and one in pregnant women.[136] The 2014 CDC guideline includes recommended indications for PrEP in men and women at increased risk of HIV infection via heterosexual contact (men who have sex with both women and men, infrequent use of condoms during sex with one or more partners of unknown HIV status who are known to be at substantial risk of HIV infection, or being in an ongoing sexual relationship with an HIV-infected partner), but we did not identify any formal assessment of these criteria.[60]

Key Question 3. What Are Rates of Adherence to PrEP in U.S. Primary Care–Applicable Settings?

Summary

- Three observational studies of U.S. men who have sex with men (mean age, 34 to 36 years) found adherence to PrEP of 66 to 90 percent, based on a tenofovir-diphosphate (TFV-DP) level of 700 fmol/punch or greater on dried blood spot samples (consistent with ≥4 doses/week).[81,126,127]
- Two observational studies of younger U.S. men who have sex with men (mean age, 16 to 20 years) found adherence to PrEP of approximately 50 percent at 12 weeks and 22 to 34 percent at 48 weeks, based on a TFV-DP level of 700 fmol/punch or greater on dried blood spot samples (consistent with ≥4 doses/week).[92,93] The proportion with a TFV-DP level of 350 fmol/punch or greater (consistent with ≥2 doses/week) was 49 and 26 percent at 48 weeks.
- An RCT of U.S. men who have sex with men found adherence was higher with daily (48%) than intermittent (31%) or event-driven (17%) PrEP during weeks in which sex was reported, based on a TFV-DP level of 326 fmol/punch or greater on dried blood spot samples (consistent with ≥2 doses/week).[123]
- In two studies of U.S. men who have sex with men, adherence based on self-report was highly correlated with adherence based on drug levels on dried blood spot samples.[85,124]
- No study evaluated rates of adherence to PrEP in U.S. persons who inject drugs or women and men at increased risk of HIV infection via heterosexual contact.

Evidence

Ten studies evaluated rates of adherence to PrEP in U.S. primary care and primary care–applicable settings (**Table 5**).[81,85,92-94,123,124,126-128] Three studies were RCTs (**Appendix B Tables 1-3**)[85,94, 123] and seven were observational studies (**Appendix B Tables 8–10**).[81,92,93,124,126-128] Six studies assessed adherence based on drug levels from dried blood spot samples,[81,92,93,123,126,127] one used plasma drug levels,[94] three used self-report,[81,124,127] two used a medication event monitoring system,[85,123] one used pill counts,[85] and one used prescription refill data.[128] In the RCTs, the number of participants randomized to PrEP ranged from 20 to 373 (total N=572),[85,94,123] and in the observational studies, the number of participants on PrEP ranged from 35 to 1,086 (total N=2,605).[81,92-94,124,126,127] Two RCTs evaluated daily TDF-FTC in men who have sex with men[85,94] and one RCT evaluated daily, intermittent, or event-driven TDF-FTC in men who have sex with men (97%) and transgender women (1.1%).[123] The observational studies all evaluated TDF-FTC. The largest observational study (n=1,086) did not report HIV risk behaviors or indications for PrEP.[128] In the other observational studies, all or nearly all (≥89%) of the population was men who have sex with men. One large (n=557) observational study, the Demo Project, enrolled men who have sex with men (98%) and transgender women (1.4%);[81] two smaller studies enrolled a small proportion of heterosexual men and women.[124,127] Two observational studies reported injection drug use in 1.6 to 3 percent of participants,[81,126] one reported no patients with a history of injection drug use,[127] and the other studies did not report injection drug use status. The duration of PrEP use ranged from 6 months to 2 years. One RCT was rated good quality and the other fair quality.[85,94] Methodological shortcomings in the fair-quality RCT included unclear randomization and allocation concealment methods; in addition, it was unclear if outcomes assessors were blinded.[93,94] The observational studies were all rated fair quality. Methodological shortcomings included unclear enrollment of a consecutive or random sample, failure to describe blinding of data analysts, and high attrition (**Appendix Tables 4 and 11**).[81,92,93,124,126,127]

Six studies assessed PrEP drug levels based on intracellular drug concentrations of TFV-DP, the active moiety of tenofovir, in dried blood spot samples, which reflect longer-term cumulative drug exposure than tenofovir plasma levels.[81,92,93,123,126,127] In five observational studies of primarily men who have sex with men, based on presence of TFV-DP levels of 700 fmol/punch or greater (consistent with an average of ≥4 pills/week over the last 1 to 2 months, associated with an estimated reduction in risk of HIV acquisition of >95%[139-141] [see Key Question 4]), adherence rates ranged from 22 to more than 90 percent.[81,92,93,126,127] 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),[81] and another study (n=301) found that adherence was 83 percent at week 4 and 66 percent at week 48.[126] A smaller study (n=50) found that 90 percent (19/21) of patients met the drug level adherence threshold at a mean PrEP duration of 4.4 months.[127] In two studies, adherence rates based on self-report were similar to rates based on dried blood spot testing.[81,127] The adherence rates in these studies were higher than in the iPrEx open-label extension study (52% met the drug level adherence threshold at 4 weeks), which enrolled patients from the United States (<20% of study population), South Africa, Thailand, and South America.[142]

Two of the five observational studies (n=200 and n=72) that assessed adherence based on dried blood spot sample testing reported lower adherence rates.[92,93] Both focused on younger men who have sex with men (mean ages 20 and 16 years) than in the studies described above (mean age >30 years). The proportion of patients meeting the adherence threshold for 4 or more doses/week was around 50 percent at week 12, decreasing to 34 and 22 percent at week 48. The proportion of patients with 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. Other measures of adherence (e.g., self-report, pill counts, or medication electronic monitoring systems) were not reported.

An RCT of men who have sex with men and transgender women enrolled at a U.S. site compared adherence with daily, intermittent, and event-driven PrEP, based on TFV-DP 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%[141] [see Key Question 4][123]). 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).

An RCT of young men who have sex with men (n=20 randomized to PrEP) evaluated adherence based on plasma TFV levels.[94] Plasma levels measure free TFV and reflect more recent dosing (detectability consistent with dosing within the last week) than the intracellular levels measured with dried blood spot sample testing. Results were consistent with the observational studies of young men who have sex with men, with tenofovir detected in 63 percent of men randomized to PrEP at week 4, decreasing to 20 percent at week 24. Patients in this trial also received a group-based behavioral HIV prevention intervention.

For comparative purposes, the proportion of patients with detectable plasma TFV levels was approximately 80 percent in the Partners PrEP trial (persons at risk via heterosexual contact in Africa)[99] and 86 percent in the IPERGAY trial (men who have sex with men in Europe and Canada).[52] Both trials found PrEP to be effective. In Partners PrEP, the proportion of patients with plasma TDF levels greater than 40 ng/mL (consistent with dosing within the last 2 days) was about 70 percent,[99] and in the IPERGAY (event-driven dosing) trial,[52] TDF or FTC was detectable in plasma in 82 to 86 percent of participants. Although another trial (iPrEx) measured TFV-DP levels using dried blood spot samples in a subgroup of patients, the proportion meeting specified adherence thresholds was unclear.[141]

Three U.S.-based studies reported adherence using methods other than drug levels.[85,124,128] A U.S.-based RCT of men who have sex with men (n=373)[85] reported adherence based on medication event monitoring system data of 79 percent of doses taken and based on a pill count of 93 percent. 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).[128] An observational study of primarily men who have sex with men (n=267)[124] found that 92 percent of patients reported taking four or more pills in the last week at 3 and 6 months. Some U.S. and non-U.S. RCTs have shown lower levels of adherence based on drug levels than by self-report or pill counts,[76,94,95,143,144] although other RCTs have shown greater concordance.[78] Some discrepancies between drug levels and self-reported adherence or pill counts could be related to use of financial incentives for trial participation (patients in such a trial might have concerns about trial dismissal and loss of financial compensation 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).[145]

No study evaluated adherence to PrEP in U.S. persons who inject drugs or women and men at increased risk of HIV infection via heterosexual contact.

Key Question 4. What Is the Association Between Adherence to PrEP and Effectiveness for Preventing HIV Acquisition?

Summary

- Three randomized trials that performed subgroup analyses based on level of adherence found higher adherence to PrEP based on pill counts or daily diaries associated with greater effectiveness compared with placebo for reducing risk of HIV infection.
- Four of five randomized trials found that among participants randomized to PrEP, presence of tenofovir in plasma samples was associated with decreased likelihood of HIV infection compared with no detectable tenofovir (odds ratio [OR] ranged from 0.10 to 0.54).[70,76,97,99,109,119,120]
- One RCT and three observational studies found that all seroconverters on PrEP had undetectable levels of TDF or plasma levels consistent with low adherence, but the number of seroconverters in each study ranged from 1 to 4.

Evidence

This section focuses on within-study analyses on effects of adherence; analyses based on between-study estimates of adherence are reported in Key Question 1. Seven randomized trials[52,70,76,95,97,99,100,109,117,120] (**Appendix B Tables 1-3**) and five observational studies[81,92,93,125,126] (**Appendix B Tables 8–10**) evaluated the association between degree of adherence to PrEP using oral TDF or TDF-FTC and effectiveness for preventing HIV infection (**Table 6**). The number of patients on PrEP in the RCTs ranged from 199 to 3,136 (total N=9,473) and from 78 to 1,345 (total N=2,006) in the observational studies. Three of the observational studies were conducted in the United States;[81,92,93,146] the other studies were conducted in Asia or Africa or were international studies. One RCT focused on persons who inject drugs,[108] four RCTs on women and men at increased risk via heterosexual contact,[70,76,119,120] and three on men who have sex with men and transgender women.[52,78,100]

Three RCTs that performed subgroup analyses based on level of adherence found higher adherence to PrEP based on pill counts or daily diaries associated with greater effectiveness compared with placebo for reducing risk of HIV infection (**Table 6**).[70,97,99,100,109] All of the trials evaluated daily dosing. A trial of persons who inject drugs (the Bangkok Tenofovir Study), in which patients could choose between daily directly observed therapy or monthly visits without directly observed therapy, found an HR of 0.51 in patients with 60 percent or greater adherence and an HR of 0.16 in those with 97.5 percent or greater adherence.[97,109] Similarly, a trial of men who have sex with men and transgender women (iPrEx) found greater effectiveness at 90 percent or greater adherence based on pill counts (HR, 0.27 [95% CI, 0.12 to 0.59]) than with 50 percent or greater adherence (HR, 0.50 [95% CI, 0.30 to 0.82]).[100] There was a statistically significant interaction in iPrEx when patients were stratified according to greater or less than 90 percent pill use (HR, 0.27 [95% CI, 0.12 to 0.59] vs. HR, 0.79 [95% CI, 0.48 to 1.31]; p=0.02 for interaction). A third trial of heterosexual men and women (Partners PrEP) found adherence greater than 80 percent based on pill count associated with an OR for prevention of HIV infection of 0.08 (95% CI, 0.04 to 0.19).[70]

Five RCTs evaluated the association between plasma tenofovir levels among participants randomized to PrEP and likelihood of HIV seroconversion (**Table 6**).[70,76,97,99,109,119,120] All of the trials evaluated daily dosing. In four trials, higher TDF plasma levels were associated with decreased likelihood of HIV infection (ORs ranged from 0.10 to 0.54).[70,97,99,109,119,120] One of the trials was the FEM-PrEP trial, which failed to demonstrate a benefit overall from PrEP versus placebo in heterosexual women (HR, 0.94 [95% CI, 0.59 to 1.52]).[120] In this study, having a plasma TDF concentration greater than 10 ng/mL was associated with decreased risk of seroconversion (OR, 0.54 [95% CI, 0.17 to 1.76]). The fifth trial (VOICE) also failed to demonstrate an effect from PrEP in heterosexual women (RR, 0.87 [95% CI, 0.61 to 1.25] for TDF and RR, 1.02 [95% CI, 0.72 to 1.44] for TDF-FTC).[76] Unlike FEM-PrEP and the other three studies, it found no clear association between ever having a detectable TDF plasma level and risk of seroconversion (adjusted RR, 0.55 [95% CI, 0.26 to 1.14] for TDF and adjusted RR, 0.83 [95% CI, 0.39 to 1.76] for TDF-FTC), although there was a trend in that direction. One trial (Partners PrEP) reported PrEP to be highly effective across a range of tenofovir plasma levels (OR, 0.10 to 0.11 for tenofovir levels >0.3 to >40 ng/mL).[70,99]

The iPrEx RCT found reductions in risk of HIV acquisition of 50, 90, and 99 percent associated with TFV-DP concentrations of 3 (95% CI <1 to 7), 16 (95% CI, 3 to 28), and 33 (95% CI, 6 to 60) fmol/10^6 peripheral blood mononuclear cells, respectively.[141] A modeling analysis based on the iPrEx RCT and a dose-ranging study of directly observed PrEP (the STRAND dose-ranging study) estimated an efficacy of PrEP of 76 percent (95% CI, 56% to 96%) at two doses per week, 96 percent (95% CI, 90% to >99%) at four doses per week, and 99 percent (95% CI, 96 to >99%) at seven doses per week.[141]

The iPrEx Open Label Extension (iPrEx-OLE) study was an observational study of patients previously enrolled in three RCTs who did not seroconvert and were offered daily PrEP following completion of the RCTs.[125] It found that effectiveness of PrEP increased at higher concentrations of TFV-DP using dried blood spot samples. The HR for seroconversion, compared with no PrEP, was 0.56 (95% CI, 0.23 to 1.31) at less than 350 fmol/punch (equivalent to ≤2 tablets/week) and 0.16 (95% CI, 0.01 to 0.79) at 350 to 699 fmol/punch (equivalent to 2 to 3 tablets/week). There were no cases of seroconversion at 700 fmol/punch or greater (equivalent to ≥4 tablets/week).

One other RCT[52] and four observational studies[81,92,93,126] found that all seroconverters on PrEP had undetectable plasma levels of tenofovir or plasma levels consistent with low adherence (**Table 6**). However, the number of seroconverters in each study was small (1 to 4 patients per study).

Key Question 5. What Are the Harms of PrEP Versus Placebo or No PrEP When Used for the Prevention of HIV Infection?

Summary

- There was no difference between PrEP versus placebo or no PrEP in risk of serious adverse events (12 trials; RR, 0.93 [95% CI, 0.77 to 1.12]; I^2=56%).[52-54,70,76,78,85,97,100,117,119,120]
- PrEP 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; RR, 1.25 [95% CI, 0.99 to 1.59]; I^2=0%).[52,70,100,117,120]
- PrEP was associated with increased risk of renal adverse events (primarily ≥grade 1 creatinine elevation) (12 trials; 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.[52-54,70,76,78,85,97,100,117,119,120] Renal abnormalities generally resolved following PrEP cessation.
- PrEP was associated with increased risk of gastrointestinal adverse events (12 trials; 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;[52-54,70,76,78,85,97,100,117,119,120] gastrointestinal events were generally not serious and diminished over time.
- PrEP was associated with a trend toward increased risk of fracture that was not statistically significant (7 trials; RR, 1.23 [95% CI, 0.97 to 1.56]; I^2=0%).[52,70,76,85,97,100,119]
- There were no differences between PrEP versus placebo in risk of syphilis (4 trials; 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%).[70,78,100,119,120]
- There was no difference between PrEP versus placebo in risk of HSV (3 trials; RR, 0.86 [95% CI, 0.64 to 1.16]; I^2=48%) or hepatitis C virus infection (2 trials; RR, 0.73 [95% CI, 0.25 to 2.10]; I^2=0%).[52,78,80,107,119]
- Among women who became pregnant in PrEP trials, PrEP was not associated with increased risk of spontaneous abortion (3 trials; RR, 1.09 [95% CI, 0.79 to 1.50]; I^2=0%).[54,112,120] One trial found no differences between PrEP versus placebo in pregnancy rate, risk of preterm birth, birth anomalies, or postpartum infant mortality.[112]

Evidence

Serious Adverse Events

There was no difference between PrEP versus placebo in risk of serious adverse events (12 trials; RR, 0.93 [95% CI, 0.77 to 1.12]; I^2=56%) (**Table 7**; **Figure 11**).[52-54,70,76,78,85,97,100,117,119,120] 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;[53,54] 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%).[52] There were also no differences between 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%)[70,76,85,97,117] or TDF-FTC (9 trials; RR, 1.02 [95% CI, 0.81 to 1.30]; I^2=46%; p=0.23 for interaction) (**Figure 11**).[52-54,70,76,78,100,119,120] 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]).[78] 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 7**).[52,70,100,117,120] One trial[117] reported no withdrawals with either PrEP or placebo. In the other trials, PrEP was associated with a trend toward increased risk of withdrawal due to adverse events with PrEP versus placebo that was not statistically significant (4 trials; 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 12**). 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]).[120] 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,[104,114,119,147] which could result in increased fracture risk. PrEP was associated with a trend toward increased risk of fracture versus placebo that was not statistically significant (7 trials; RR, 1.23 [95% CI, 0.97 to 1.56]; I^2=0%; ARD, 0.21% [95% CI, -0.21% to 0.62%]) (**Table 7**; **Figure 13**).[52,70,76,85,97,100,119] The meta-analysis was heavily weighted (64%) by the Bangkok Tenofovir Study of persons who inject drugs, which reported a relatively high fracture rate (7.8% vs. 6.0%; RR, 1.29 [95% CI, 0.96 to 1.74]).[97] There was no statistically significant interaction between the PrEP regimen and fracture risk (p=0.50) (**Figure 13**). 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]).[52] 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.[89]

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,[85] iPrEx,[100] and Partners PrEP[70]) and the FDA review[89] 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 14**).

Renal Adverse Events

PrEP was associated with increased risk of renal adverse events (primarily ≥grade 1 serum creatinine elevation) versus placebo (12 trials; RR, 1.43 [95% CI, 1.18 to 1.75]; I^2=0%; ARD, 0.56% [95% CI, 0.09% to 1.04%]) (**Table 7**; **Figure 15**).[52-54,70,76,78,85,97,100,117,119,120] 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%).[52] 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[53,54,70,106,108,118] evaluated whether renal adverse events while on PrEP were persistent (**Appendix B Tables 1-3**). Three studies[70,106,118] reported a return to normal serum creatinine levels after cessation of PrEP and two others[53,54] reported normalization of creatinine level without PrEP cessation.[113] In one other trial, the Bangkok Tenofovir Study of persons who inject drugs, among 7 cases of grade 2 or worse creatinine elevation, all but 1 case resolved following PrEP cessation.[108]

Gastrointestinal Adverse Events

PrEP was associated with increased risk of gastrointestinal adverse events (primarily nausea) versus placebo (12 trials; RR, 1.63 [95% CI, 1.26 to 2.11]; I^2=43%; ARD, 1.95% [95% CI, 0.48% to 3.43%]) (**Table 7**; **Figure 16**).[52-54,70,76,78,85,97,100,117,119,120] 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 intermittent PrEP, but the estimate was imprecise (8.0% vs. 1.0%; RR, 8.08 [95% CI, 1.88 to 34.68]).[52] 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 intermittent PrEP (**Appendix B Tables 1-3**).[122] 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%)[70,76,85,97,117] and TDF-FTC (9 trials; RR, 1.84 [95% CI, 1.26 to 2.70]; I^2=49%),[52-54,70,76,78,100,119,120] with no statistically significant interaction (p=0.30) (**Figure 16**). Among studies that reported rates of diarrhea[52,70,76,78,85,119,120] or vomiting[76,120] 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.[97,100,119] Serious gastrointestinal events were rare in the trials that reported this outcome, with no differences between PrEP and placebo (**Appendix B Tables 1-3**).[76,78,100,117,119,120]

STIs

There were no differences between PrEP versus placebo or no PrEP in risk of syphilis (4 trials; RR, 1.08 [95% CI, 0.98 to 1.18]; I^2=0%) (**Figure 17**), gonorrhea (5 trials; RR, 1.07 [95% CI, 0.82 to 1.39]; I^2=49%) (**Figure 18**), chlamydia (5 trials; RR, 0.97 [95% CI, 0.80 to 1.18]; I^2=59%) (**Figure 19**), or combined bacterial STIs (2 trials; RR, 1.14 [95% CI, 0.97 to 1.34]; I^2=16%) (**Figure 20**; **Table 8**).[70,78,100,119,120] Combined STIs were defined as gonorrhea, chlamydia, or trichomoniasis in one trial[70] and gonorrhea, chlamydia, or syphilis in the other.[78] 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 if they are taking PrEP or placebo behave differently than those who know whether or not they are taking PrEP. The open-label PROUD trial, which enrolled men who have sex with men, found no statistically significant association 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 generally indicated trends toward 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%).[78] In the nonrandomized Demo Project (PrEP demonstration project in men who have sex with men), 26 percent of participants had an STI at baseline and approximately 50 percent had an STI while on PrEP.[81]

PrEP was not associated with increased risk of bacterial STIs when trials (open-label or blinded) were stratified according to whether they evaluated men who have sex with men or persons at risk of HIV infection via heterosexual contact (**Table 8**; **Figures 21–24**). The only trial conducted in persons who inject drugs did not report risk of STI.[97] Results for bacterial STIs were similar when data were pooled using the profile likelihood method.

There was no difference between PrEP versus placebo in risk of HSV infection (3 trials; RR, 0.85 [95% CI, 0.67 to 1.07]; I^2=19%) (**Figure 25**).[80,107,119] Two trials evaluated the risk of HSV infection based on serology in participants who were seronegative for HSV at baseline;[80,107] the other trial did not report the method for diagnosing HSV infection.[119] 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%)[70] but not in one trial of men who have sex with men (RR, 1.12 [95% CI, 0.80 to 1.56])[107] (**Table 8**). 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 of men who have sex with men, 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%; $p<0.05$).[107]

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 reported this outcome, and the estimate was imprecise (RR, 0.73 [95% CI, 0.25 to 2.10]; I^2=0%)[52,78] (**Figure 26**). Both trials (PROUD and IPERGAY) evaluated PrEP with TDF-FTC in men who have sex with men. There were 6 cases of hepatitis C virus infection in one trial[78] and 8 cases in the other.[52]

Pregnancy-Related Outcomes

No trial of PrEP enrolled pregnant women, and women who became pregnant during the course of the trial were withdrawn from participation. Three trials reported on pregnancy outcomes in women who were withdrawn from PrEP because of pregnancy.[54,112,120] In one trial, only one pregnancy occurred among women randomized to PrEP;[54] in the other two trials, 74 and 192 pregnancies occurred.[70,120] All of the trials were conducted in Africa and evaluated women at increased risk of HIV infection via heterosexual activity. Among women who became pregnant in the trials, PrEP was not associated with increased risk of spontaneous abortion (RR, 1.09 [95% CI, 0.79 to 1.50]; I^2=0%) (**Appendix B Tables 1-3**; **Figure 27**). When stratified according to the PrEP regimen used, TDF was not associated with increased risk, but was only evaluated in one trial (RR, 0.83 [95% CI, 0.50 to 1.37]).[112] 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%).[54,112,120] 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**).[112]

Contextual Question 1. What Factors Are Associated With Increased or Decreased Adherence to PrEP?

Data on factors associated with decreased or increased adherence to PrEP in U.S. primary care–applicable settings are limited. The only randomized trial conducted in the United States did not report factors associated with adherence.[85] Implementation studies conducted in U.S. populations indicate differences in adherence related to race/ethnicity, socioeconomic status, and presence of higher-risk behaviors, as well as some geographic/site differences in adherence not explained by these factors.

The largest (n=557) U.S. PrEP implementation study to date is the previously described Demo Project.[81] It enrolled men who have sex with men (98%) and transgender women (1.4%) in three cities (mean age, 34 to 35 years) and evaluated factors associated with adherence, defined by presence of protective TFV-DP levels in dried blood spot samples. In multivariate analysis, African American race was associated with lower adherence compared with white race (adjusted OR, 0.28 [95% CI, 0.12 to 0.64]). Although Latino, Asian, and “other” race/ethnicity were also associated with decreased likelihood of adherence, differences were not statistically significant. Factors associated with increased adherence were having stable housing (renting or owning housing) versus less stable housing (living with friends or family, public housing, or homeless) (adjusted OR, 2.02 [95% CI, 1.14 to 3.55]), or having condomless receptive anal sex with two or more partners (vs. 0 or 1 partner) in the past 3 months (adjusted OR, 1.82 [95% CI, 1.14 to 2.89]). There was no clear association between age, educational level, PrEP awareness, income level, health insurance status, depression, and alcohol or drug use and adherence to PrEP. Participants at the Miami site were less likely to be adherent to PrEP (vs. the San Francisco site; adjusted OR, 0.32 [95% CI, 0.17 to 0.60]), with no difference between the San Francisco and Washington, D.C., sites.

Another U.S.-based PrEP implementation study by Chan et al (n=267; mean age 32 years) evaluated factors associated with retention in care (a potential marker for adherence) after initiation of PrEP.[124] The population was primarily (~90%) men who have sex with men, with smaller proportions of heterosexual men and women (~10%) and transgender women (~1%). At 6 months, it 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.

A study of younger (ages 18 to 22 years) men who have sex with men (n=200), in whom overall adherence was lower than in studies of older men who have sex with men (see Key Question 3), 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).[93] 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). The study did not report the association between factors such as race/ethnicity, age, socioeconomic status, insurance status, or drug use behaviors and adherence.

A large (n=1,086) database study of veterans prescribed PrEP found older age (ages 50 to 64 vs. <35 years; adjusted OR, 2.00 [95% CI, 1.37 to 2.92]), male sex (vs. female sex; 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]) associated with increased adherence.[128] Other factors, including comorbid substance abuse or depression, low socioeconomic status, rural living, and region of the United States, were not significant predictors of adherence. This study used prescribing (refill) data to measure adherence and did not include information on HIV risk factors or indication for PrEP.

Data on factors associated with higher or lower adherence to PrEP in U.S populations of persons who inject drugs are lacking. In an open-label extension to the Bangkok Tenofovir Study RCT, which focused on persons who inject drugs who could elect to receive directly observed therapy, persons who injected midazolam or were in prison during open-label followup were more likely to be greater than 90 percent adherent than those who did not inject midazolam (OR, 2.2 [95% CI, 1.2 to 4.3]) or were not in prison (OR, 4.7 [95% CI, 3.1 to 7.2]). Persons who injected heroin or had been in prison were more likely to choose PrEP than persons without those characteristics (OR, 1.5 [95% CI, 1.1 to 2.1] and OR, 1.7 [95% CI, 1.3 to 2.1], respectively) and more likely to return for followup (OR, 3.0 [95% CI, 1.3 to 7.3] and OR, 2.3 [95% CI, 1.4 to 3.7], respectively).[148]

Data on factors associated with higher or lower adherence to PrEP in U.S. populations of women and men at increased risk of HIV infection via heterosexual contact are not available. In the Partners PrEP trial, which enrolled African men and women, factors associated with increased likelihood of low (<80%) adherence based on unannounced pill counts were younger age (adjusted OR, 1.4 per 10-year age increment [95% CI, 1.0 to 2.0]), no sex in the past month (adjusted OR, 4.2 [95% CI, 1.9 to 9.4] vs. having sex with condoms with a primary partner), and heavy alcohol use (adjusted OR, 2.8 [95% CI, 1.4 to 5.5]).[101] Male sex, HIV-infected partner CD4 count, education level, socioeconomic status, number of side effects, and time on PrEP were not associated with likelihood of low adherence. Women in the Partners PrEP trial who reported intimate partner violence were more likely to report low adherence based on pill count (adjusted RR, 1.49 [95% CI, 1.17 to 1.89])[149] or plasma tenofovir levels.[99,149] The VOICE trial, which enrolled heterosexual African women, reported low overall adherence based on plasma tenofovir levels.[76] Factors associated with presence of detectable plasma tenofovir in VOICE were being older than age 25 years (adjusted OR, 1.62 [95% CI, 1.12 to 2.34]), being married (adjusted OR, 2.24 [95% CI, 1.12 to 4.49]), having an independent income (adjusted OR, 1.42 [95% CI, 0.98 to 2.07), and being multiparous (adjusted OR, 1.84 [95% CI 1.26 to 2.69]).

Contextual Question 2. What Is the Risk of Infection With Antiretroviral Drug–Resistant HIV in Persons Treated With PrEP, and What Is the Effect of Infection With PrEP-Related, Antiretroviral Drug–Resistant HIV on Treatment Outcomes?

Ten RCTs reported rates of antiretroviral drug resistance in persons randomized to PrEP (N=8,661) (**Table 9**).[52,70,76,78,85,97,100,117,119,120] One trial evaluated event-driven PrEP[52] and the other nine trials evaluated daily PrEP. Five trials evaluated PrEP with TDF alone[70,76,85,97,117] and seven trials evaluated TDF-FTC;[52,70,100,120] two trials[70,76] evaluated both regimens. The most commonly reported mutations were the tenofovir resistance mutations K65R and K70E and the emtricitabine mutations M184I and M184V.

Resistance rates were low with either TDF or TDF-FTC, based on a denominator of the total number of patients randomized to PrEP. In four trials of TDF, two patients had resistance mutations (0.06% [2/3,149]).[70,76,85,97] In seven trials of TDF-FTC, 14 patients had resistance mutations (0.3% [14/5,085]).[52,70,76,78,100,119,120] Data were insufficient to determine how rates of antiretroviral resistance differed for daily versus event-driven PrEP. The only trial of event-driven PrEP reported 2 cases of HIV infection among patients randomized to PrEP, with no resistance mutation identified.[52]

The trials also reported the rate of resistance mutations, based on a denominator of patients randomized to PrEP with newly diagnosed HIV infection. In nine trials of patients randomized to TDF or TDF-FTC, 1.1 percent (3/282) of patients with newly diagnosed HIV infection on PrEP were diagnosed with tenofovir resistance mutations.[52,70,76,78,97,100,117,119,120] In seven of the trials, there were no cases of tenofovir resistance mutations (n=198),[52,76,78,97,100,120] and two trials reported 1 or 2 cases (n=10[119] and n=35[70]). Two of the 3 cases of tenofovir resistance were infected with HIV upon trial enrollment, presumably as a result of undiagnosed acute infection. Both involved the K65R mutation (including 1 case of multiple resistance mutations to K65R, M184V, and A62V).[70,119] No other case of multidrug resistance was identified in patients randomized to PrEP. The third case of tenofovir resistance, which was not infected with HIV upon trial enrollment, had the K65N mutation.[70]

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).[52,70,76,78,100,119,120] 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 were also available from the iPrEX-OLE observational study,[125] 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) (**Table 9**).[81,92,93,127] All of the observational 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.[125] Among the four U.S.-based studies, one of 10 patients diagnosed with HIV infection while on PrEP was found to have multiple antiretroviral drug mutations.[127]

No study was designed to evaluate the effects of antiretroviral drug resistance while receiving PrEP on clinical outcomes. However, the number of cases of HIV infections prevented by PrEP in clinical trials appears to greatly outnumber the cases of antiretroviral drug resistance. For example, based on data from the Partners PrEP trial, there were an estimated 123 cases of HIV infection averted, compared with 5 cases of drug resistance.[103] The Partners PrEP trial also found that PrEP-selected mutations were no longer detectable by 6 months after discontinuation of PrEP and remained undetectable through 12 and 24 months.[150] No study evaluated whether PrEP-selected mutations that become undetectable following cessation of PrEP reappear upon re-exposure to ART.

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; effects of adherence on effectiveness; estimates of adherence in U.S. populations on PrEP; and the diagnostic accuracy of instruments for identifying potential candidates for PrEP. **Table 10** summarizes the evidence reviewed for this report.

In randomized trials, PrEP 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%).[52-54,70,76,78,85,97,100,117,119,120] 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 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 men who have sex with men (HIV incidence, 4% to 8% with placebo or no PrEP), the pooled absolute difference was about 5 percent after 9 months to 2 years (range, 4% to 6%), for a number needed to treat of about 20.[52,78,85] In the United States, the only approved regimen for PrEP is daily TDF-FTC. However, 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%). Therefore, the overall pooled estimate includes both regimens. Statistical heterogeneity was present in the pooled estimate, but not related to use of TDF alone or TDF-FTC. Among individual trials, PrEP was least effective in two trials of African women at increased risk of HIV infection because of heterosexual activity characterized by low rates of PrEP adherence.[76,120] 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.[52,53,70,78,85,119]

Additional analyses also support an association between higher PrEP adherence and greater effectiveness, including subgroup analyses of trial participants stratified according to level of PrEP adherence and analyses on the association between tenofovir levels and risk of HIV infection in persons using PrEP.[70,76,97,99,100,109,119,120] Modeling based on trial data indicates that PrEP is highly effective in men who have sex with men taking four doses per week (estimated reduction in risk, 96%), and reduction in risk is high even at two doses per week (reduction in risk, 76%),[141] suggesting important benefits of PrEP even with 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. In fact, one trial (IPERGAY) found event-driven PrEP in men who have sex with men associated with substantially reduced risk of HIV infection versus no PrEP (RR, 0.14 [95% CI, 0.03 to 0.63]).[52] IPERGAY evaluated a population of men who have sex with men with relatively frequent sexual intercourse (median, 10 episodes per month) and dosing of PrEP (median, 15 doses per month), potentially limiting applicability to populations in which dosing is less frequent. However, a post hoc subgroup analysis of IPERGAY found that event-driven PrEP was also effective in men who used 15 or fewer doses per month (HIV incidence, 0 vs. 9.3/100 person-years; relative reduction in risk of HIV infection, 100% [95% CI, 20 to 100]).[151]

The applicability of evidence on effects of adherence and event-driven or intermittent dosing from studies of men who have sex with men 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.[152] On the other hand, simian studies have shown protective effects of tenofovir alafenamide from rectal simian HIV challenge despite low rectal mucosal concentrations, suggesting that the correlation between rectal or genital mucosal concentrations of tenofovir and protection from HIV infection may be limited.[153] No study evaluated effectiveness of intermittent or event-driven dosing in women or persons who inject drugs.

Findings regarding effectiveness of PrEP were robust in subgroup and stratified analyses based on HIV risk category (men who have sex with men, persons who inject drugs, or persons at risk of HIV infection via heterosexual contact), study duration, study quality, age, and sex. However, evidence in persons who inject drugs was limited to one Thai-based trial in which most patients received directly observed therapy and sterile syringes were not provided (RR, 0.52 [95% CI, 0.29 to 0.92]),[97] and all trials of persons at risk via heterosexual contact were conducted in Africa, which might limit 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 HIV-infected partners treated with ART). No study evaluated effectiveness of PrEP according to an HIV-infected sexual partner's use of ART or viral load,[52,78,85] and no randomized trial enrolled adolescents. However, in 2018 the FDA approved TDF-FTC for PrEP in adolescents weighing at least 35 kg. This decision was informed by a demonstration study of PrEP in men who have sex with men ages 15 to 17 years that found a similar safety profile for TDF-FTC compared with the safety profile observed in adults.[92]

Evidence on beneficial effects of PrEP on clinical outcomes other than HIV infection was sparse. PrEP was associated with a statistically nonsignificant trend toward reduced risk of mortality 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.[52,53,70,76,78,85,97,100,117,119,120] No trial reported effects of PrEP on quality of life, although limited qualitative research suggests that PrEP may reduce anxiety or worry about getting HIV.[154]

Although PrEP was associated with some harms, most appeared relatively mild and reversible with discontinuation of PrEP. PrEP was not associated with an increased risk of serious adverse events,[52-54,70,76,78,85,97,100,117,119,120] and there was a statistically nonsignificant trend toward increased risk of withdrawal due to adverse events (RR, 1.25 [95% CI, 0.99 to 1.59]).[52,70,100,117,120] PrEP was associated with increased risk of gastrointestinal events (RR, 1.63 [95% CI, 1.26 to 2.11]; ARD, 1.95%),[52-54,70,76,78,85,97,100,117,119,120] that generally improved with longer duration of therapy. Consistent with renal effects of tenofovir, PrEP was also associated with an increased risk of renal insufficiency (RR, 1.43 [95% CI, 1.18 to 1.75]; ARD, 0.56%),[52-54,70,76,78,85,97,100,117,119,120] which generally appeared to be mild and resolved with cessation of PrEP. Consistent with effects of tenofovir on bone loss, PrEP was associated with a statistically nonsignificant trend toward increased risk of fracture (RR, 1.23 [95% CI, 0.97 to 1.56]);[52,70,76,85,97,100,119] results of the fracture meta-analysis were heavily weighted by the Bangkok Tenofovir Study.[97] 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, any effects of PrEP on fracture risk appear small (ARD, 0.21%). For all harms, low adherence could attenuate risk estimates.

The rate of resistance mutations to tenofovir or emtricitabine appears low. Most cases of antiretroviral resistance occurred in persons who were HIV-infected at baseline, underscoring the importance of clinical history and HIV testing to rule out acute or chronic HIV infection before initiation of PrEP. There was insufficient evidence to determine the effects of antiretroviral resistance on clinical outcomes, which is likely to depend on the specific resistance mutation, persistence of antiretroviral resistance following cessation of PrEP, the propensity for resistance to return with re-exposure, and the selection and effectiveness of alternative therapy, if needed.[155] In U.S. settings, alternative antiretroviral regimens are generally available for the common (K65R, M184I, M184V) resistance mutations observed in trials of PrEP. Furthermore, the number of HIV cases averted by PrEP appears to be substantially higher than the number of cases of antiretroviral resistance caused.[103]

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.[70,78,100,119,120] However, in most trials, patients were blinded to whether they were randomized to PrEP or placebo, which might affect sexual behaviors differently than when patients know they are on PrEP, such as in clinical practice. One open-label trial (PROUD) found no statistically significant association between PrEP and STIs in men who have sex with men, but there was a trend toward increased risk, consistent with the higher prevalence of risky sexual behaviors among men randomized to PrEP that was observed in this trial.[78] In addition, participants in randomized trials may differ from the general population of PrEP users with regard to STI risk behaviors. Although a U.S. demonstration project found a high rate of STIs in men who have sex with men on PrEP, it was not possible to determine if PrEP increased the risk of STIs, since it did not include a no-PrEP comparison group.[81] A recent 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]).[156] Methodological shortcomings of the nonrandomized studies included 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),[81,93,97] which might offset negative effects related to any increase in risky behaviors. There was no association between PrEP and risk of HSV infection,[80,107,119] although some trials[80,119] found decreased risk or a trend toward decreased risk, consistent with antiviral effects of tenofovir on HSV.[79,80] Cases of acute hepatitis C virus infection have been reported in U.S. men who have sex with men using PrEP,[157] but data from randomized trials are too limited to determine effects on risk of hepatitis C virus infection.[52,78]

Our findings are generally consistent with other recent meta-analyses that found PrEP to be effective at reducing risk of HIV infection and greater estimates of effectiveness in trials reporting higher adherence.[90,158,159] For example, a review by Fonner et al also found a roughly linear relationship between adherence and PrEP effectiveness (based on the log RR).[90] Our findings were strengthened with the addition of recent, large trials that were published subsequent to the previous reviews, including the only trial of event-driven PrEP (IPERGAY)[52] and an open-label pragmatic trial (PROUD).[78] A sigmoid-shaped association between mean tenofovir plasma levels in trials of PrEP and effectiveness for preventing HIV infection has been proposed, but the analysis included data from trials of nonoral PrEP, was based on relatively few studies reporting plasma levels, and did not include some recently published trials.[160] Previous reviews also reported similar findings of no increased risk of serious adverse events or any adverse event, although most reviews did not focus on individual harms.[90,158,159] Our finding of an increased risk of renal adverse events was consistent with a recent review that found PrEP associated with increased risk of grade 1 creatinine elevation or worse (OR, 1.39 [95% CI, 1.09 to 1.71]).[161]

Data on effects of PrEP in pregnancy were very limited. Trials that enrolled women excluded pregnant women and discontinued PrEP in women who became pregnant. However, among women who became pregnant in the trials, PrEP was not associated with increased risk of spontaneous abortion (RR, 1.09 [95% CI, 0.79 to 1.50])[54,112,120] or other adverse pregnancy outcomes. A systematic review of women 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.[162] Although FDA labeling information and perinatal antiretroviral treatment guidelines permit use of TDF-FTC during pregnancy, guidelines note that data on safety of PrEP use during pregnancy and lactation are limited.[47] A recent African randomized trail found combination ART with tenofovir associated with increased risk of early infant death compared with combination ART with zidovudine,[163] although methodological issues in the trial have been noted,[164] and applicability to U.S. practice is uncertain. TDF-FTC is a FDA pregnancy category B drug, and the FDA-approved label recommends that nursing mothers not breastfeed if they are taking TDF-FTC.

Understanding adherence to PrEP in U.S. primary care and primary care–applicable settings could help to inform applicability of RCTs, which were primarily conducted in low-income settings. Two implementation studies of U.S. men who have sex with men (mean age, 34 to 35 years) found high levels of adherence (80% to 90%) based on documentation of highly protective drug levels.[81,127] Studies of younger (mean age, 16 to 20 years) U.S. men who have sex with men found lower levels of adherence that declined over time, highlighting the need for additional PrEP adherence support strategies in this population.[92,93] One RCT of U.S. men who have sex with men found higher adherence with daily than intermittent or event-driven PrEP.[123] Data on adherence to PrEP in U.S. persons who inject drugs and persons at risk via heterosexual contact are needed.

Instruments that are accurate for predicting risk of incident HIV infection could help inform decisions regarding eligibility for PrEP. Several instruments for predicting incident HIV infection in men who have sex with men found moderate discrimination (AUROC estimates ranged from 0.66 to 0.72), but require further validation.[129-132] 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. One instrument for predicting incidence of HIV infection in persons who inject drugs also reported moderate discrimination, but has not been validated.[133] Several studies evaluated instruments for predicting risk of HIV infection in women but were developed using data from African cohorts, with limited applicability to U.S. settings. CDC guidelines include criteria for determining eligibility for PrEP in men who have sex with men, persons who inject drugs, and persons at risk via heterosexual activity, but more validation is needed.[47] No study evaluated an instrument for predicting incident HIV infection in persons not already identified as belonging to a risk category. This is relevant because patients who are at risk of acquiring HIV infection may not be recognized as belonging to an HIV risk category.

Limitations

Our review had some 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.[88] Therefore, we repeated analyses in which statistical heterogeneity was present using the profile likelihood method, which 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 topics other than complementary medicine, and we did not identify large non-English trials of PrEP versus placebo in other systematic reviews.[165,166] 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.[91] 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.[89] 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.[100] 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 for the iPrEx, Partners PrEP, and CDC Safety Study trials, a sensitivity analysis based on 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. Regimens under investigation include an alternative form of tenofovir with fewer adverse effects, long-acting injectable formulations, vaginal gels or rings, and implants.

The specific prodrug of tenofovir currently approved by the FDA for PrEP is TDF. A different prodrug, tenofovir alafenamide phosphate, appears to be associated with fewer renal adverse effects and fractures than TDF,[167] and is undergoing evaluation in combination with FTC for PrEP.[168] Tenofovir could also be delivered as a biodegradable, long-acting implant.[169]

Maraviroc is a cysteine-cysteine chemokine receptor 5 antagonist HIV entry inhibitor that achieves high concentrations in cervicovaginal fluid, vaginal tissues, and rectal tissues; does not interact with commonly used oral contraceptives; does not select for drug resistance to recommended first-line antiretroviral drugs; and is associated with less bone loss than TDF and has been investigated for PrEP. A recent randomized trial of 188 women who reported recent condomless vaginal intercourse with at least one man with HIV infection or of unknown serostatus was not designed to assess efficacy, but reported no cases of HIV infection in women randomized to daily maraviroc only, maraviroc with TDF, maraviroc with FTC, or TDF-FTC, with no difference in risk of adverse events.[170] A similarly designed trial of 406 men who have sex with men and transgender women was also not powered to assess efficacy, but reported 5 cases of HIV infection with maraviroc alone, 1 with maraviroc with TDF, and none with maraviroc with FTC or TDF-FTC (p=0.32 for differences by regimen).[171]

Long-acting injectable formulations of antiretroviral drugs that provide sustained drug delivery can be dosed as infrequently as once every 2 or 3 months.[172] Two long-acting injectable agents are cabotegravir and rilpivirine, although data on effects on HIV infection versus placebo or standard PrEP are not yet available. A potential drawback of long-acting injectable agents is the extremely long half-life following administration. Missed or delayed doses would result in a prolonged pharmacological tail period with subtherapeutic drug levels that could increase the likelihood of resistance mutations if HIV infection is acquired. This differs from implants, which could be removed if needed without a prolonged pharmacological tail period.

In women, PrEP could be delivered vaginally via gel or a ring. Although one trial found pericoital 1 percent tenofovir gel associated with a reduction in risk of HIV transmission of nearly 40 percent,[75] other trials found no effect,[76,77] with some evidence of an association between higher adherence and greater effectiveness. Two trials found that the dapivirine vaginal ring, inserted monthly, was associated with a reduction in risk of HIV infection of about 30 percent versus placebo,[73,74] or lower than the efficacy reported in most trials of daily oral PrEP. As in trials of other PrEP formulations, effectiveness was higher in women who were more adherent. The vaginal ring was not effective in younger (age <21 years) women, a subgroup with lower adherence.

Relevance for Priority Populations, Particularly Racial/Ethnic Minorities

In the United States, 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,[100] and trials found PrEP to be effective in diverse racial/ethnic populations worldwide. However, one study found that the proportion of PrEP initiators who are black (10%) or Hispanic (12%) is low relative to the rate of new HIV infections in these groups (44% and 23%, respectively),[173] suggesting disparities in provision of PrEP. Nearly three-quarters of new PrEP initiators are white, despite accounting for about one-quarter of new infections.

Although PrEP was associated with decreased risk of HIV infection in women at high risk of acquisition via heterosexual contact, all trials were conducted in Africa. Some data suggest disparities in the United States with regard to implementation of PrEP in women. In one study, women comprised about 20 percent of PrEP initiators,[173] despite accounting for about 40 percent of PrEP-eligible persons.[64] Another study found that only 2.5 percent of persons with commercial insurance prescribed PrEP were women.[174] Data on the number of pregnant or lactating women on PrEP are not available, but use in these populations is likely to be low.

Evidence also suggested ongoing barriers to implementation of PrEP in men who have sex with men. In U.S. men who have sex with men who met CDC criteria for PrEP, more than half were unwilling to take it or believed they were inappropriate candidates.[175] Less than 10 percent of persons who were appropriate candidates were using and adherent to PrEP. A study of young (ages 16 to 29 years) men who have sex with men found that about 12 percent reported ever taking PrEP; among black participants, the proportion was even lower, at 4.7 percent.[176] A study

of young (ages 16 to 29 years) black men who have sex with men found that more than half of those who were eligible for and interested in starting PrEP did not follow up for initiation, even though the study was designed to cover clinic, laboratory, and prescription costs.[177]
Data on uptake and effectiveness of PrEP in transgender women is limited. A study of transgender women in San Francisco found that by the end of 2013, 14 percent knew about PrEP, despite a high HIV prevalence in this population.[178] Although it is unlikely that there are significant drug interactions between hormone treatments and PrEP, pharmacological interaction studies in transgender women are lacking,[179] although several studies are underway.[180-182] Randomized trials that included transgender women have not been powered to evaluate effectiveness in this subgroup. A post hoc analysis of iPrEx[100] found that PrEP was effective in men who have sex with men (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),[98] precluding reliable conclusions about a subgroup difference. In the iPrEx trial, adherence was lower in transgender women than in men who have sex with men, 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 this population. No PrEP trial enrolled transgender men and data on the prevalence of HIV infection in this population are lacking.[183]

One Asian trial found PrEP to be effective in persons who inject drugs.[97] Uptake of PrEP in persons who inject drugs appears relatively low. A 2012 study of persons who inject drugs in Washington, D.C., found that only 13 percent had ever heard of PrEP and none had ever used PrEP or knew someone who had.[184] About 50 percent were very likely and one-quarter somewhat likely to take PrEP if it was available without cost. Factors associated with willingness to use PrEP included younger age, sharing injection equipment, and believing they would no longer need to use clean needles. A 2012 to 2013 study of persons who inject drugs in Vancouver, Canada, found that approximately one third expressed willingness to use PrEP.[185] Factors associated with willingness to use PrEP included younger age, engaging in sex work, and reporting multiple recent sexual partners. Further PrEP studies in persons who inject drugs are indicated.

The FDA recently approved daily oral TDF-FTC in adolescents weighing at least 35 kg. Data indicate increasing incidence of HIV infection among adolescents and young adults. Persons younger than age 25 years represent about 7.5 percent of PrEP initiators.[173] A recent implementation study of men who have sex with men ages 15 to 17 years in which patients were permitted to autonomously consent found low adherence that decreased over time, with a high incidence of STIs and HIV infection.[92]

Future Research

A number of trials of PrEP are ongoing. These include trials on the safety and efficacy of injectable cabotegravir compared with daily oral TDF-FTC for PrEP in HIV-uninfected women, men who have sex with men, and transgender women;[186,187] a trial on safety and efficacy of emtricitabine and tenofovir alafenamide fixed-dose combination once daily for PrEP in men and transgender women who have sex with men and are at risk of HIV-1 infection;[168] a trial of injectable rilpivirine in HIV-uninfected women;[188] and a trial of an enhanced versus standard PrEP adherence intervention in young, black men who have sex with men.[189] Trials that compare daily versus event-driven or intermittent dosing and are sufficiently powered to evaluate effects on risk of HIV acquisition would be helpful for clarifying effective and efficient dosing strategies in different populations. A recent trial conducted in Africa (n=622) of daily, intermittent (twice weekly with an additional dose after sexual intercourse) or event-driven (24 to 48 hours before and within 2 hours after sexual intercourse) TDF-FTC for PrEP in men who have sex with men and women at risk of HIV infection via heterosexual contact was not designed to assess comparative efficacy for preventing HIV infection, and reported only 5 cases of seroconversion following randomization, although adherence was highest with the daily regimen.[122,123] Research is needed to better understand the adherence implications of different dosing regimens in U.S. populations and effect on PrEP effectiveness.

Randomized trials or demonstration projects of PrEP in U.S. populations of women at high risk via heterosexual contact and persons who inject drugs are needed 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. Research is needed to determine the safety and effectiveness of PrEP during pregnancy or lactation and in transgender women, the effectiveness and long-term safety (e.g., bone effects) of PrEP in adolescents, and to understand effects of PrEP on quality of life. Studies on factors associated with adherence and methods for increasing uptake and adherence to PrEP would be very helpful for guiding strategies to increase uptake and adherence to PrEP, particularly in populations with low adherence, such as adolescents and racial/ethnic minorities.

Additional research would help clarify effects of PrEP related to behavioral risk compensation. Open-label studies, including observational studies that include a concurrent no-PrEP comparison group and account for differential STI 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. Research is also needed on effects of PrEP on hepatitis C virus infection, particularly in populations at high risk of hepatitis C virus (e.g., persons who inject drugs, men who have sex with men).

Research is also needed to develop and validate instruments for identifying persons at high risk of acquiring HIV infection. Existing instruments in men who have sex with men and persons who inject drugs require further validation in independent cohorts, ideally with prospective application of risk assessment instruments and assessment of HIV incidence, and should be applicable to racial/ethnic minorities. Initial instruments of men who have sex with men were developed using cohorts in which racial/ethnic minorities were underrepresented, with some studies showing poor predictive utility of existing instruments in black men who have sex with men.[134,135] A study of a new risk instrument (Sex Pro) specifically designed for black men who have sex with men has been conducted, but only published as a conference abstract.[190] Instruments are also needed for assessing risk of HIV infection in heterosexually active U.S. women.

Conclusions

In adults at increased risk of HIV infection, PrEP with oral TDF or TDF-FTC is associated with decreased risk of HIV infection compared with placebo or no PrEP, although effectiveness decreases with inadequate adherence. PrEP is associated with increased risk of renal and gastrointestinal events, but the incidence of nongastrointestinal adverse events is low and most adverse events appear mild and reversible with discontinuation of PrEP. Evidence on the accuracy of instruments for identifying persons at high risk of HIV infection is limited, with further validation required.

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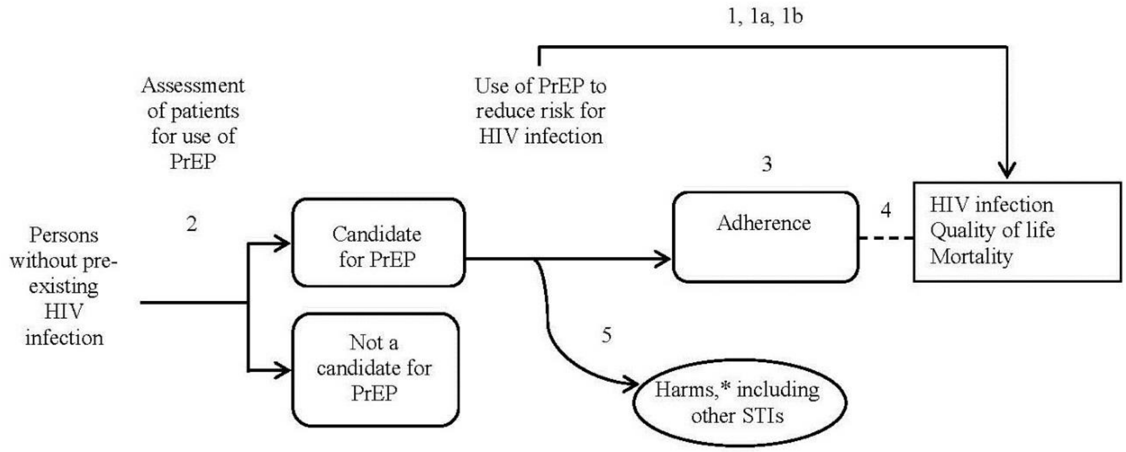
Figure 1. Analytic Framework



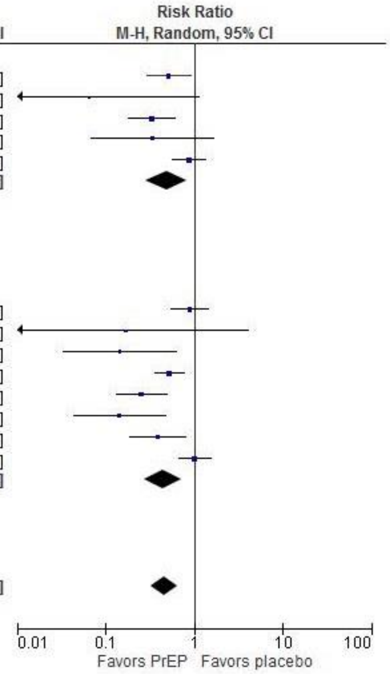
Note: The numbers on the analytic framework correspond to the numbers of the key questions.

*Harms also include renal insufficiency, fractures, pregnancy-related outcomes, infection with antiretroviral drug–resistant HIV, gastrointestinal harms, headaches, and discontinuation due to adverse events.

Abbreviations: PrEP=pre-exposure prophylaxis; STI=sexually transmitted infection.

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

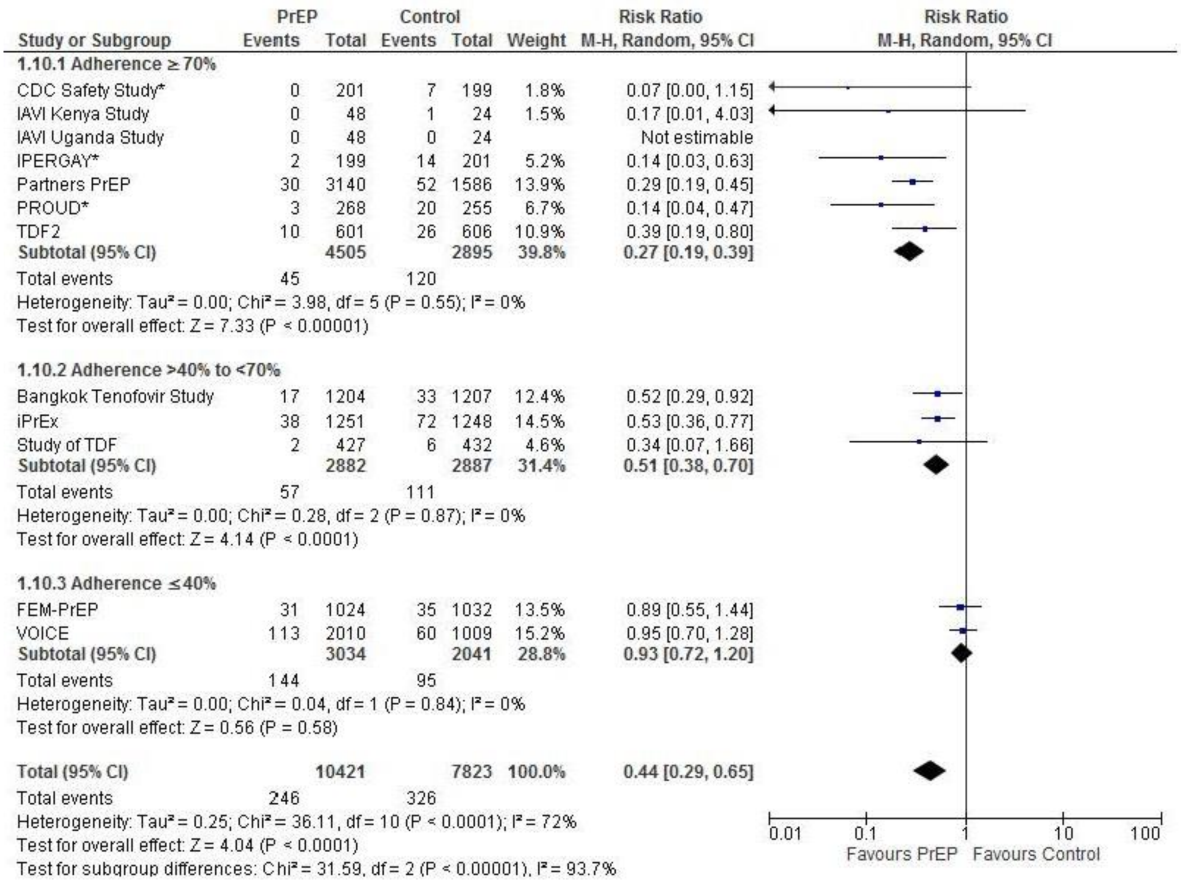
Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 TDF						
Bangkok Tenofovir Study	17	1204	33	1207	10.2%	0.52 [0.29, 0.92]
CDC Safety Study*	0	201	7	199	1.3%	0.07 [0.00, 1.15]
Partners PrEP - TDF arm	17	1572	26	793	9.9%	0.33 [0.18, 0.60]
Study of TDF	2	427	6	432	3.5%	0.34 [0.07, 1.66]
VOICE - TDF arm	52	1007	30	504	11.6%	0.87 [0.56, 1.34]
Subtotal (95% CI)		**4411**		**3135**	**36.5%**	**0.49 [0.28, 0.84]**
Total events	88		102			
Heterogeneity: Tau² = 0.19; Chi² = 9.50, df = 4 (P = 0.05); I² = 58%						
Test for overall effect: Z = 2.60 (P = 0.009)						
1.2.2 FTC-TDF						
FEM-PrEP	31	1024	35	1032	11.2%	0.89 [0.55, 1.44]
IAVI Kenya Study	0	48	1	24	1.1%	0.17 [0.01, 4.03]
IPERGAY*	2	199	14	201	4.0%	0.14 [0.03, 0.63]
iPrEx	38	1251	72	1248	12.1%	0.53 [0.36, 0.77]
Partners PrEP - FTC-TDF arm	13	1568	26	793	9.4%	0.25 [0.13, 0.49]
PROUD*	3	268	20	255	5.2%	0.14 [0.04, 0.47]
TDF2	10	601	26	606	8.8%	0.39 [0.19, 0.80]
VOICE - FTC-TDF arm	61	1003	30	505	11.7%	1.02 [0.67, 1.56]
Subtotal (95% CI)		**5962**		**4664**	**63.5%**	**0.44 [0.27, 0.72]**
Total events	158		224			
Heterogeneity: Tau² = 0.30; Chi² = 27.08, df = 7 (P = 0.0003); I² = 74%						
Test for overall effect: Z = 3.31 (P = 0.0009)						
Total (95% CI)		**10373**		**7799**	**100.0%**	**0.46 [0.33, 0.66]**
Total events	246		326			
Heterogeneity: Tau² = 0.22; Chi² = 36.59, df = 12 (P = 0.0003); I² = 67%						
Test for overall effect: Z = 4.34 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%						



*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

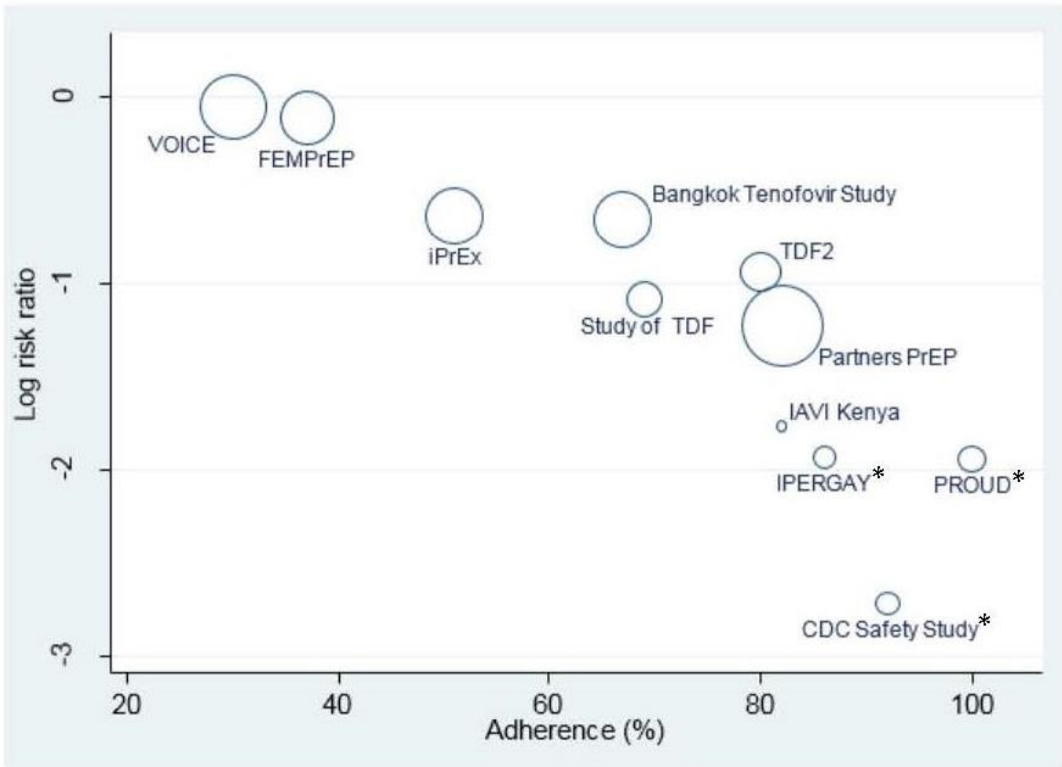


Note: Based on plasma testing, unless otherwise noted**.**

*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.

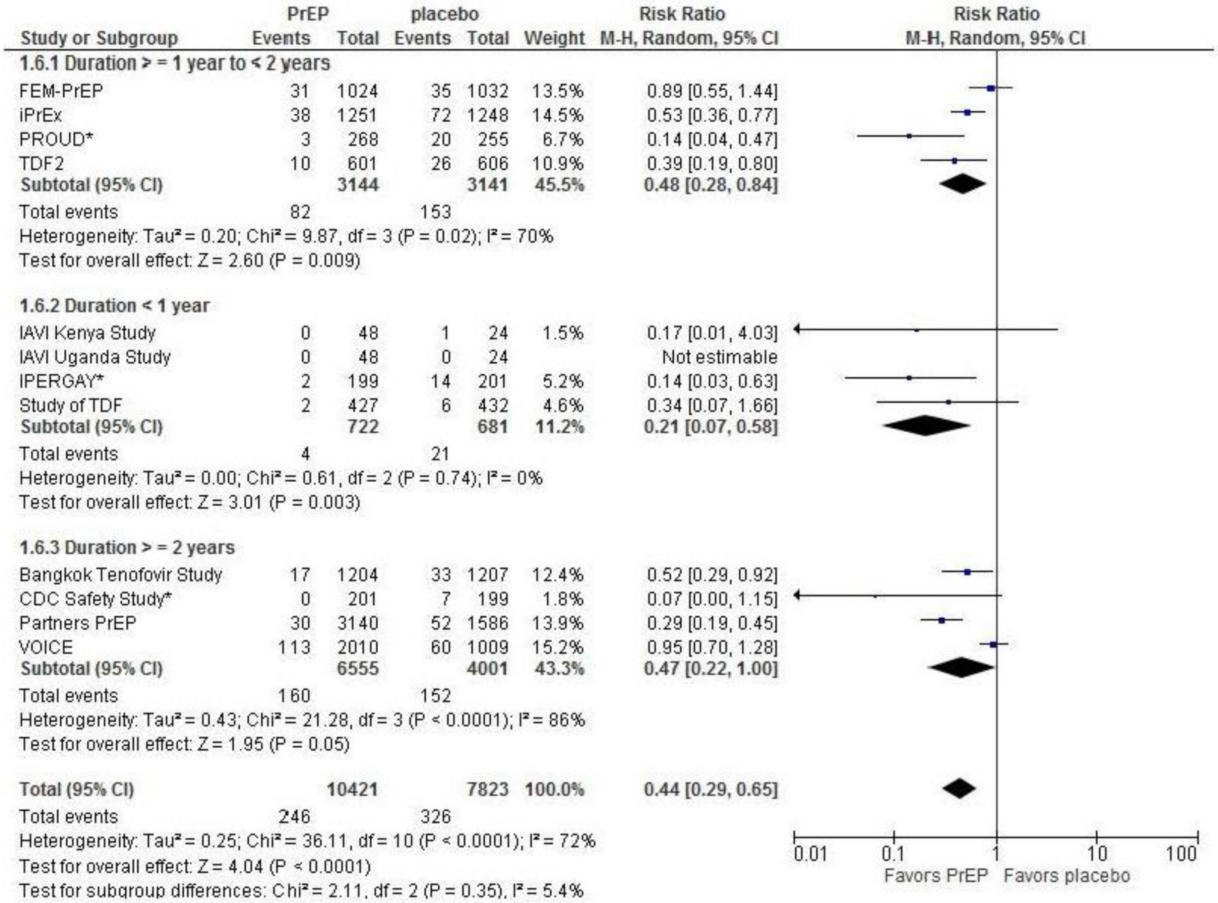
Figure 4. Meta-Regression: PrEP Efficacy Versus Adherence



*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.

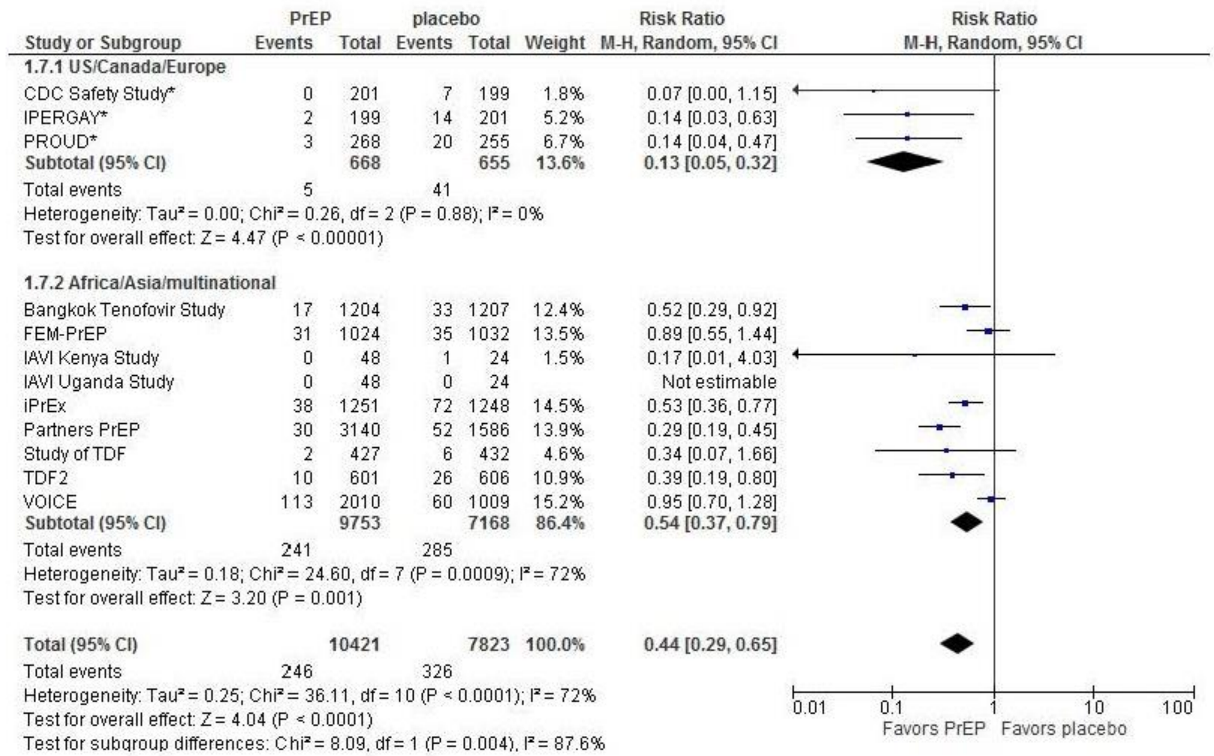
Figure 5. Meta-Analysis: HIV Infection Stratified by Study Duration



*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



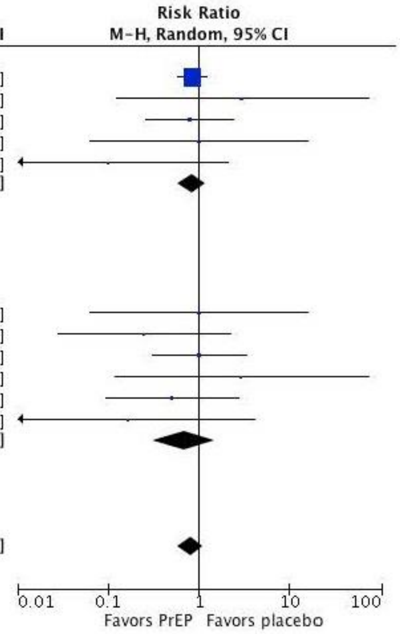
Study or Subgroup	PrEP Events	PrEP Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 US/Canada/Europe						
CDC Safety Study*	0	201	7	199	1.8%	0.07 [0.00, 1.15]
IPERGAY*	2	199	14	201	5.2%	0.14 [0.03, 0.63]
PROUD*	3	268	20	255	6.7%	0.14 [0.04, 0.47]
Subtotal (95% CI)		**668**		**655**	**13.6%**	**0.13 [0.05, 0.32]**
Total events	5		41			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 4.47 (P < 0.00001)						
1.7.2 Africa/Asia/multinational						
Bangkok Tenofovir Study	17	1204	33	1207	12.4%	0.52 [0.29, 0.92]
FEM-PrEP	31	1024	35	1032	13.5%	0.89 [0.55, 1.44]
IAVI Kenya Study	0	48	1	24	1.5%	0.17 [0.01, 4.03]
IAVI Uganda Study	0	48	0	24		Not estimable
iPrEx	38	1251	72	1248	14.5%	0.53 [0.36, 0.77]
Partners PrEP	30	3140	52	1586	13.9%	0.29 [0.19, 0.45]
Study of TDF	2	427	6	432	4.6%	0.34 [0.07, 1.66]
TDF2	10	601	26	606	10.9%	0.39 [0.19, 0.80]
VOICE	113	2010	60	1009	15.2%	0.95 [0.70, 1.28]
Subtotal (95% CI)		**9753**		**7168**	**86.4%**	**0.54 [0.37, 0.79]**
Total events	241		285			
Heterogeneity: Tau² = 0.18; Chi² = 24.60, df = 7 (P = 0.0009); I² = 72%						
Test for overall effect: Z = 3.20 (P = 0.001)						
Total (95% CI)		**10421**		**7823**	**100.0%**	**0.44 [0.29, 0.65]**
Total events	246		326			
Heterogeneity: Tau² = 0.25; Chi² = 36.11, df = 10 (P < 0.0001); I² = 72%						
Test for overall effect: Z = 4.04 (P < 0.0001)						
Test for subgroup differences: Chi² = 8.09, df = 1 (P = 0.004), I² = 87.6%						

*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

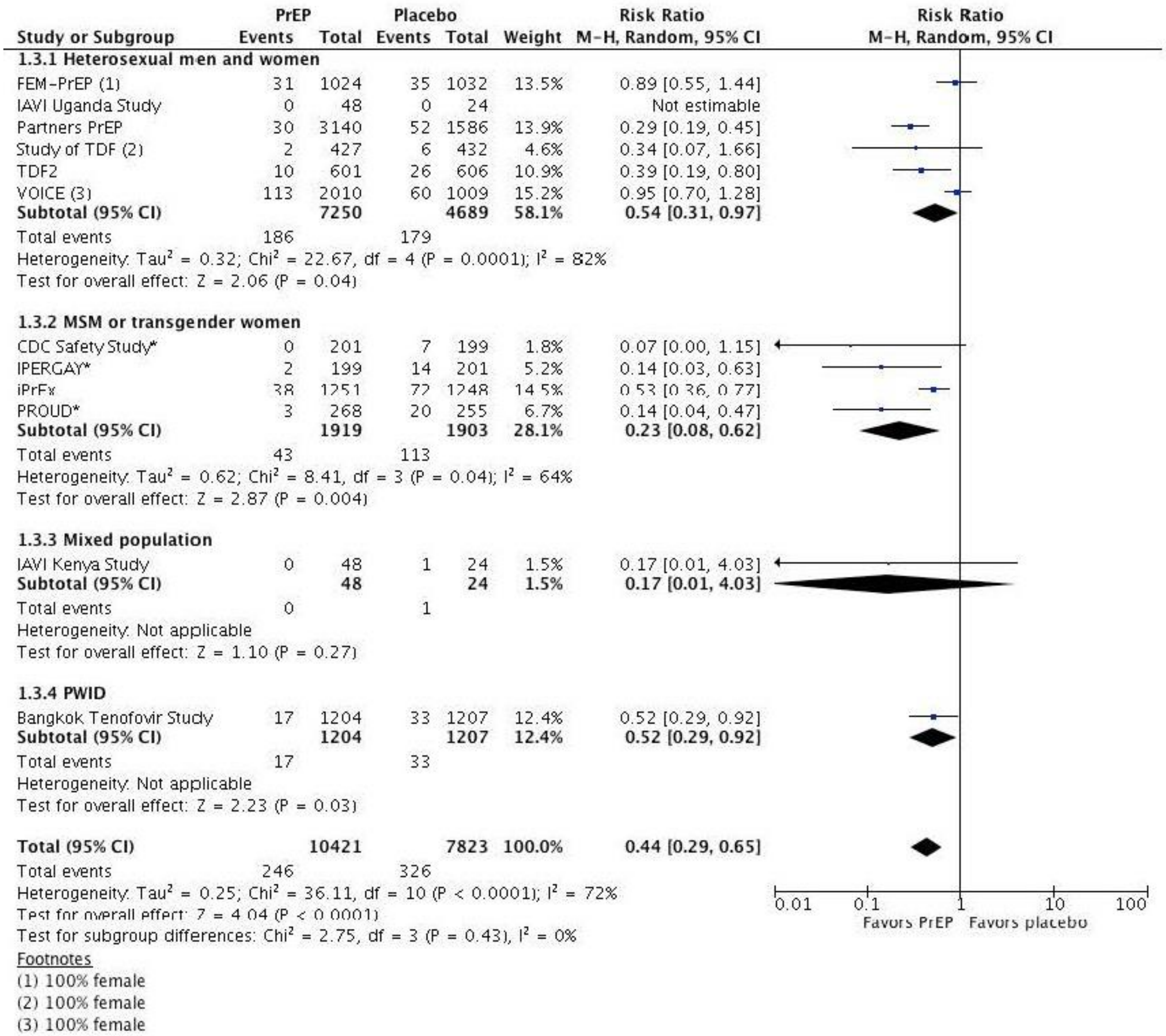
Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 TDF						
Bangkok Tenofovir Study	49	1204	58	1209	72.6%	0.85 [0.58, 1.23]
CDC Safety Study*	1	201	0	199	1.0%	2.97 [0.12, 72.48]
Partners PrEP - TDF arm	8	1584	5	792	8.1%	0.80 [0.26, 2.44]
Study of TDF	1	427	1	432	1.3%	1.01 [0.06, 16.12]
VOICE - TDF arm	0	1007	2	504	1.1%	0.10 [0.00, 2.08]
Subtotal (95% CI)		**4423**		**3136**	**84.1%**	**0.83 [0.59, 1.18]**
Total events	59		66			
Heterogeneity: Tau² = 0.00; Chi² = 2.52, df = 4 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
1.9.2 FTC-TDF						
FEM-PrEP	1	1024	1	1032	1.3%	1.01 [0.06, 16.09]
iPrEx	1	1251	4	1248	2.1%	0.25 [0.03, 2.23]
Partners PrEP - FTC-TDF arm	8	1579	4	792	7.0%	1.00 [0.30, 3.32]
PROUD*	1	275	0	269	1.0%	2.93 [0.12, 71.73]
TDF2	2	601	4	606	3.5%	0.50 [0.09, 2.74]
VOICE - FTC-TDF arm	0	1003	1	505	1.0%	0.17 [0.01, 4.12]
Subtotal (95% CI)		**5733**		**4452**	**15.9%**	**0.69 [0.31, 1.52]**
Total events	13		14			
Heterogeneity: Tau² = 0.00; Chi² = 2.95, df = 5 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
Total (95% CI)		**10156**		**7588**	**100.0%**	**0.81 [0.59, 1.11]**
Total events	72		80			
Heterogeneity: Tau² = 0.00; Chi² = 5.67, df = 10 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%						



*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.

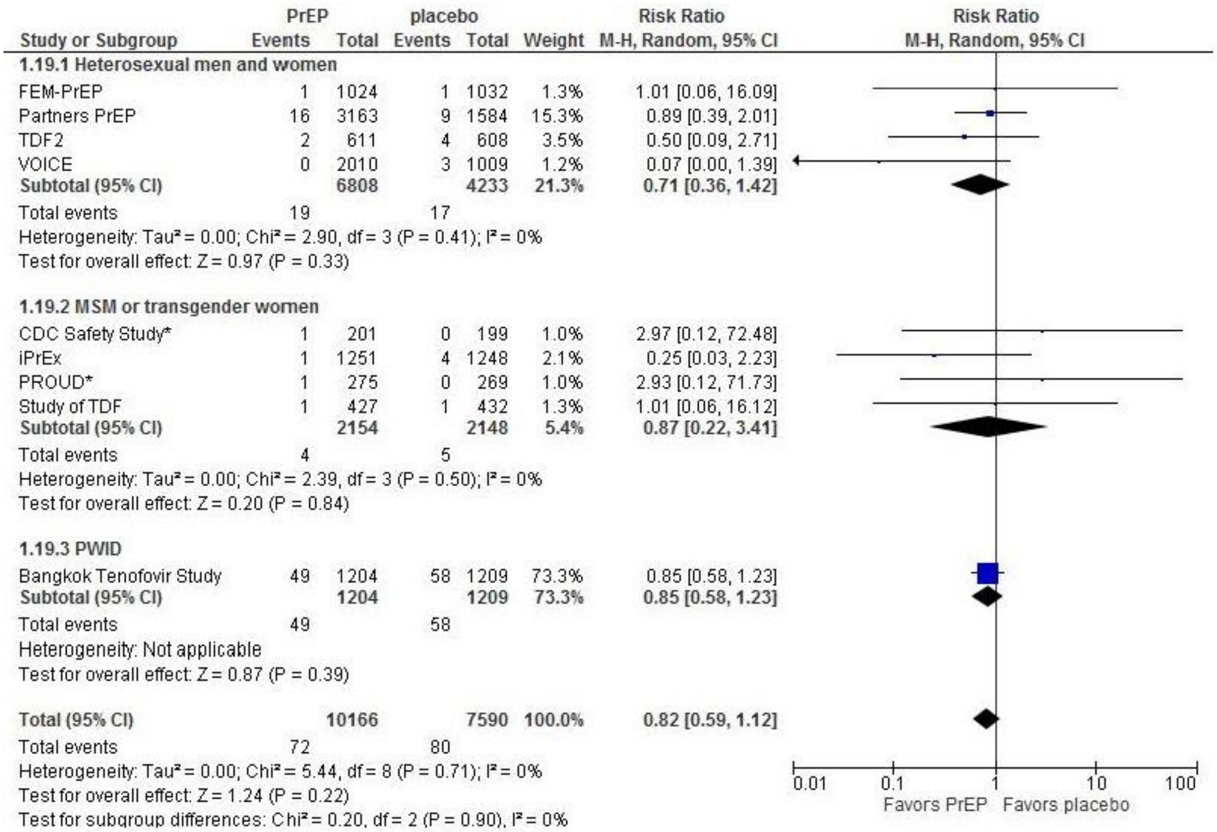
Figure 8. Meta-Analysis: HIV Infection Stratified by HIV Risk Category



*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 9. Meta-Analysis: Mortality Stratified by HIV Risk Category



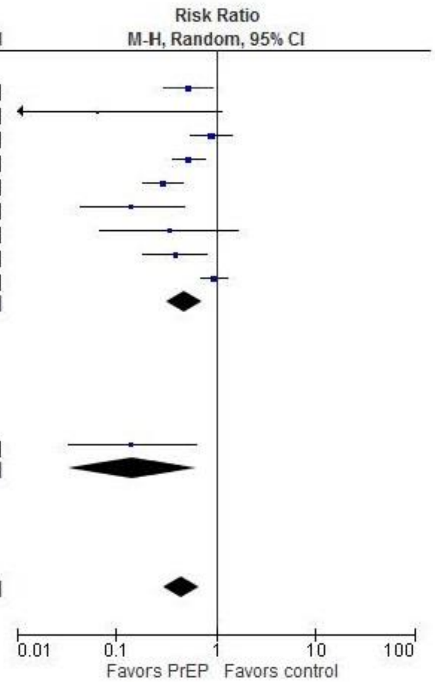
Study or Subgroup	PrEP Events	PrEP Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.19.1 Heterosexual men and women						
FEM-PrEP	1	1024	1	1032	1.3%	1.01 [0.06, 16.09]
Partners PrEP	16	3163	9	1584	15.3%	0.89 [0.39, 2.01]
TDF2	2	611	4	608	3.5%	0.50 [0.09, 2.71]
VOICE	0	2010	3	1009	1.2%	0.07 [0.00, 1.39]
Subtotal (95% CI)		**6808**		**4233**	**21.3%**	**0.71 [0.36, 1.42]**
Total events	19		17			
Heterogeneity: Tau² = 0.00; Chi² = 2.90, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
1.19.2 MSM or transgender women						
CDC Safety Study*	1	201	0	199	1.0%	2.97 [0.12, 72.48]
iPrEx	1	1251	4	1248	2.1%	0.25 [0.03, 2.23]
PROUD*	1	275	0	269	1.0%	2.93 [0.12, 71.73]
Study of TDF	1	427	1	432	1.3%	1.01 [0.06, 16.12]
Subtotal (95% CI)		**2154**		**2148**	**5.4%**	**0.87 [0.22, 3.41]**
Total events	4		5			
Heterogeneity: Tau² = 0.00; Chi² = 2.39, df = 3 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
1.19.3 PWID						
Bangkok Tenofovir Study	49	1204	58	1209	73.3%	0.85 [0.58, 1.23]
Subtotal (95% CI)		**1204**		**1209**	**73.3%**	**0.85 [0.58, 1.23]**
Total events	49		58			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.39)						
Total (95% CI)		**10166**		**7590**	**100.0%**	**0.82 [0.59, 1.12]**
Total events	72		80			
Heterogeneity: Tau² = 0.00; Chi² = 5.44, df = 8 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.22)						
Test for subgroup differences: Chi² = 0.20, df = 2 (P = 0.90), I² = 0%						

*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 10. Meta-Analysis: HIV Infection Stratified by Dosing Strategy

Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Daily dosing						
Bangkok Tenofovir Study	17	1204	33	1207	12.6%	0.52 [0.29, 0.92]
CDC Safety Study*	0	201	7	199	1.8%	0.07 [0.00, 1.15]
FEM-PrEP	31	1024	35	1032	13.7%	0.89 [0.55, 1.44]
iPrEx	38	1251	72	1248	14.6%	0.53 [0.36, 0.77]
Partners PrEP	30	3140	52	1586	14.0%	0.29 [0.19, 0.45]
PROUD*	3	268	20	255	6.8%	0.14 [0.04, 0.47]
Study of TDF	2	427	6	432	4.7%	0.34 [0.07, 1.66]
TDF2	10	601	26	606	11.0%	0.39 [0.19, 0.80]
VOICE	113	2010	60	1009	15.4%	0.95 [0.70, 1.28]
Subtotal (95% CI)		**10126**		**7574**	**94.7%**	**0.47 [0.32, 0.71]**
Total events	244		311			
Heterogeneity: Tau² = 0.24; Chi² = 31.95, df = 8 (P < 0.0001); I² = 75%						
Test for overall effect: Z = 3.60 (P = 0.0003)						
1.5.2 Intermittent/on-demand dosing						
IPERGAY*	2	199	14	201	5.3%	0.14 [0.03, 0.63]
Subtotal (95% CI)		**199**		**201**	**5.3%**	**0.14 [0.03, 0.63]**
Total events	2		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.58 (P = 0.010)						
Total (95% CI)		**10325**		**7775**	**100.0%**	**0.44 [0.29, 0.67]**
Total events	246		325			
Heterogeneity: Tau² = 0.26; Chi² = 35.54, df = 9 (P < 0.0001); I² = 75%						
Test for overall effect: Z = 3.92 (P < 0.0001)						
Test for subgroup differences: Chi² = 2.35, df = 1 (P = 0.13), I² = 57.4%						

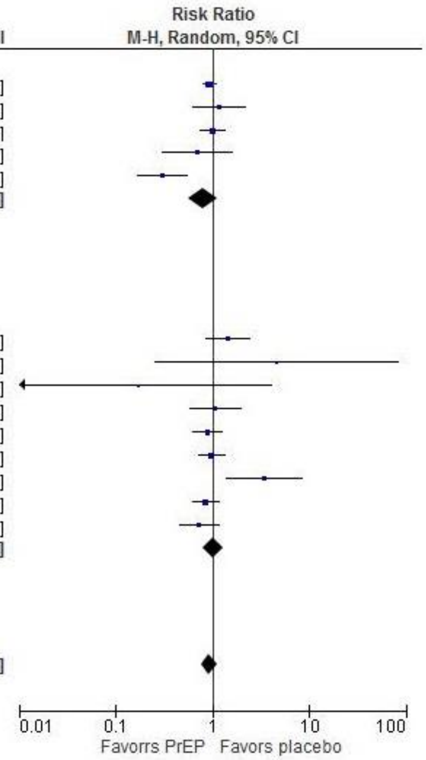


*U.S, Canada, or Europe.

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

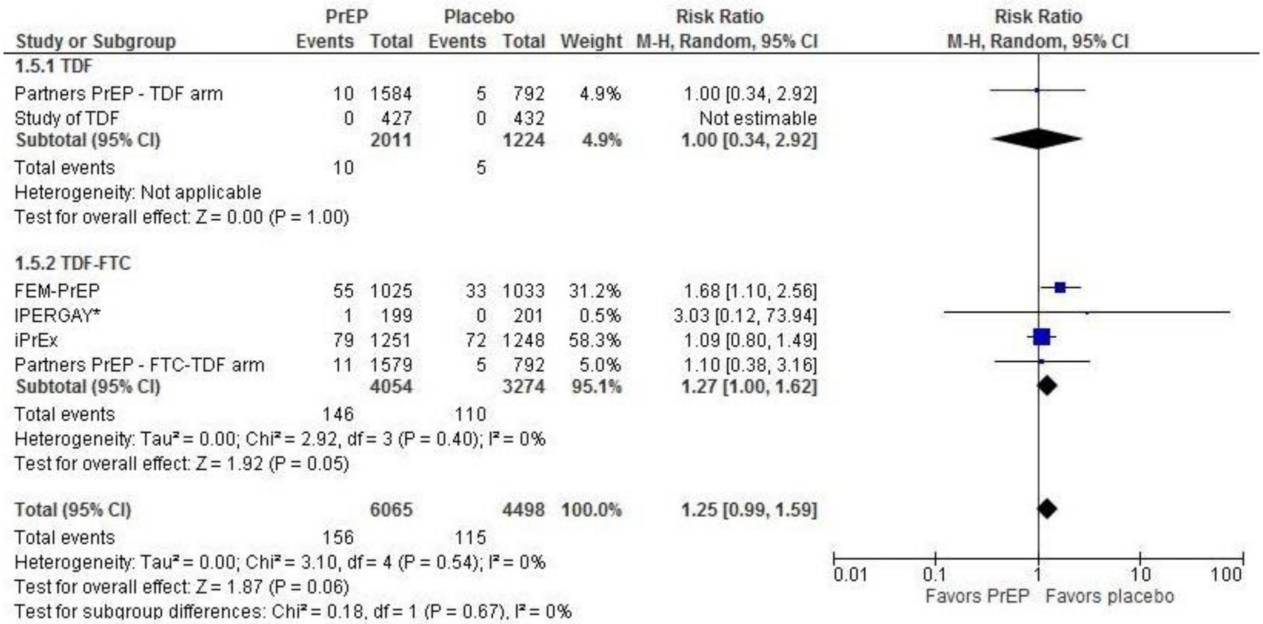
Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 TDF						
Bangkok Tenofovir Study	227	1204	246	1209	14.5%	0.93 [0.79, 1.09]
CDC Safety Study*	20	201	17	199	5.8%	1.16 [0.63, 2.16]
Partners PrEP - TDF arm	118	1584	59	792	11.4%	1.00 [0.74, 1.35]
Study of TDF	9	427	13	432	3.8%	0.70 [0.30, 1.62]
VOICE - TDF arm	17	1007	28	504	6.1%	0.30 [0.17, 0.55]
Subtotal (95% CI)		**4423**		**3136**	**41.6%**	**0.79 [0.56, 1.12]**
Total events	391		363			
Heterogeneity: Tau² = 0.10; Chi² = 14.49, df = 4 (P = 0.006); I² = 72%						
Test for overall effect: Z = 1.33 (P = 0.18)						
1.2.2 FTC-TDF						
FEM-PrEP	33	1025	23	1033	7.1%	1.45 [0.86, 2.45]
IAVI Kenya Study	4	48	0	24	0.4%	4.59 [0.26, 81.94]
IAVI Uganda Study	0	48	1	24	0.3%	0.17 [0.01, 4.03]
IPERGAY*	20	199	17	181	5.8%	1.07 [0.58, 1.98]
iPrEx	60	1251	67	1248	10.5%	0.89 [0.64, 1.25]
Partners PrEP - FTC-TDF arm	115	1579	59	792	11.4%	0.98 [0.72, 1.32]
PROUD*	21	275	6	269	3.4%	3.42 [1.40, 8.35]
TDF2	68	611	79	608	11.3%	0.86 [0.63, 1.16]
VOICE - FTC-TDF arm	42	1003	29	505	8.1%	0.73 [0.46, 1.16]
Subtotal (95% CI)		**6039**		**4684**	**58.4%**	**1.02 [0.81, 1.30]**
Total events	363		281			
Heterogeneity: Tau² = 0.05; Chi² = 14.68, df = 8 (P = 0.07); I² = 46%						
Test for overall effect: Z = 0.18 (P = 0.86)						
Total (95% CI)		**10462**		**7820**	**100.0%**	**0.93 [0.77, 1.12]**
Total events	754		644			
Heterogeneity: Tau² = 0.05; Chi² = 29.76, df = 13 (P = 0.005); I² = 56%						
Test for overall effect: Z = 0.78 (P = 0.44)						
Test for subgroup differences: Chi² = 1.45, df = 1 (P = 0.23), I² = 30.9%						



*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 12. Meta-Analysis: Withdrawals Due to Adverse Events Stratified by Study Drug



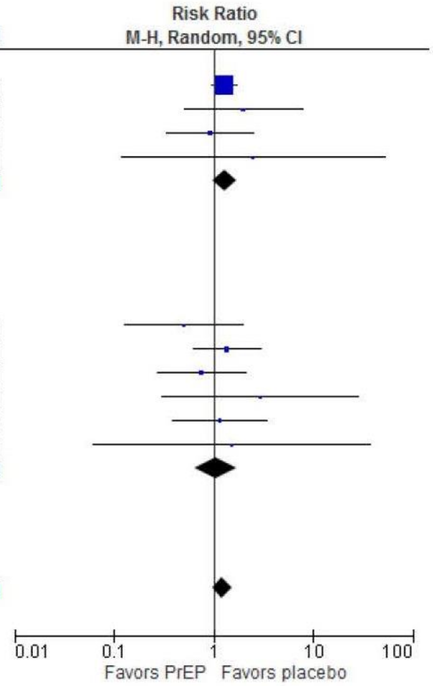
Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 TDF						
Partners PrEP - TDF arm	10	1584	5	792	4.9%	1.00 [0.34, 2.92]
Study of TDF	0	427	0	432		Not estimable
Subtotal (95% CI)		**2011**		**1224**	**4.9%**	**1.00 [0.34, 2.92]**
Total events	10		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.5.2 TDF-FTC						
FEM-PrEP	55	1025	33	1033	31.2%	1.68 [1.10, 2.56]
IPERGAY*	1	199	0	201	0.5%	3.03 [0.12, 73.94]
iPrEx	79	1251	72	1248	58.3%	1.09 [0.80, 1.49]
Partners PrEP - FTC-TDF arm	11	1579	5	792	5.0%	1.10 [0.38, 3.16]
Subtotal (95% CI)		**4054**		**3274**	**95.1%**	**1.27 [1.00, 1.62]**
Total events	146		110			
Heterogeneity: Tau² = 0.00; Chi² = 2.92, df = 3 (P = 0.40); I² = 0%						
Test for overall effect: Z = 1.92 (P = 0.05)						
Total (95% CI)		**6065**		**4498**	**100.0%**	**1.25 [0.99, 1.59]**
Total events	156		115			
Heterogeneity: Tau² = 0.00; Chi² = 3.10, df = 4 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.87 (P = 0.06)						
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%						

*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 13. Meta-Analysis: Fracture Stratified by Study Drug

Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 TDF						
Bangkok Tenofovir Study	94	1204	73	1209	65.9%	1.29 [0.96, 1.74]
CDC Safety Study*	6	201	3	199	3.0%	1.98 [0.50, 7.81]
Partners PrEP - TDF arm	11	1584	6	792	5.8%	0.92 [0.34, 2.47]
VOICE - TDF arm	2	1007	0	505	0.6%	2.51 [0.12, 52.18]
Subtotal (95% CI)		**3996**		**2705**	**75.4%**	**1.29 [0.98, 1.70]**
Total events	113		82			
Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 3 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						
1.8.2 FTC-TDF						
IPERGAY*	3	199	6	201	3.0%	0.51 [0.13, 1.99]
iPrEx	15	1251	11	1248	9.6%	1.36 [0.63, 2.95]
Partners PrEP - FTC-TDF arm	9	1579	6	792	5.4%	0.75 [0.27, 2.11]
PROUD*	3	275	1	269	1.1%	2.93 [0.31, 28.04]
TDF2	7	611	6	608	4.9%	1.16 [0.39, 3.43]
VOICE - FTC-TDF arm (1)	1	1003	0	504	0.6%	1.51 [0.06, 36.98]
Subtotal (95% CI)		**4918**		**3622**	**24.6%**	**1.06 [0.66, 1.72]**
Total events	38		30			
Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 5 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.81)						
Total (95% CI)		**8914**		**6327**	**100.0%**	**1.23 [0.97, 1.56]**
Total events	151		112			
Heterogeneity: Tau² = 0.00; Chi² = 4.28, df = 9 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%						



Footnotes
(1) Lower limb fracture

*U.S, Canada, or Europe.

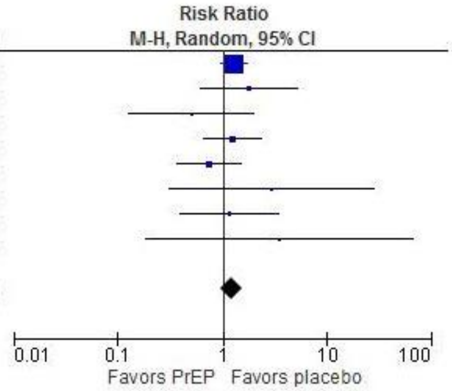
Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; df=degrees of freedom; FTC=emtricitabine; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; M-H=Mantel-Haenszel test; PrEP=pre-exposure prophylaxis; 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 14. Meta-Analysis: Fracture Using FDA Data (iPrEx, Partners PrEP, CDC Safety Study)

Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bangkok Tenofovir Study	94	1204	73	1209	61.9%	1.29 [0.96, 1.74]
CDC Safety Study*	9	201	5	199	4.7%	1.78 [0.61, 5.22]
IPERGAY*	3	199	6	201	2.9%	0.51 [0.13, 1.99]
iPrEx	21	1251	17	1248	13.4%	1.23 [0.65, 2.32]
Partners PrEP	19	3163	13	1584	10.9%	0.73 [0.36, 1.48]
PROUD*	3	275	1	269	1.1%	2.93 [0.31, 28.04]
TDF2	7	611	6	608	4.6%	1.16 [0.39, 3.43]
VOICE	3	2010	0	1009	0.6%	3.52 [0.18, 68.00]
Total (95% CI)		**8914**		**6327**	**100.0%**	**1.20 [0.96, 1.52]**
Total events	159		121			

Heterogeneity: Tau² = 0.00; Chi² = 5.31, df = 7 (P = 0.62); I² = 0%

Test for overall effect: Z = 1.57 (P = 0.12)

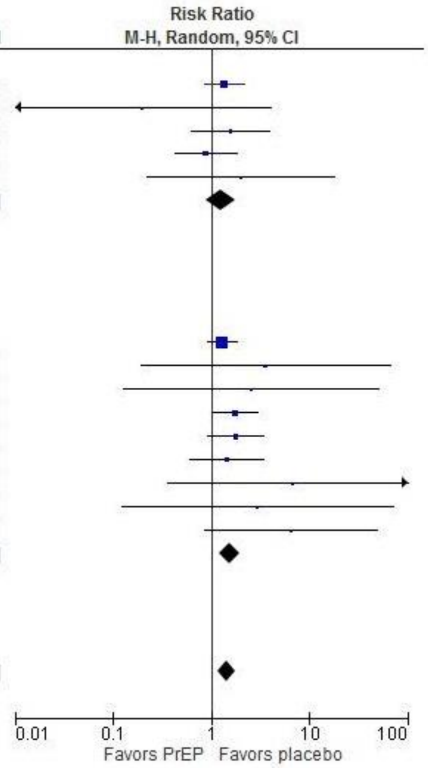


*U.S, Canada, or Europe.

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

Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 TDF						
Bangkok Tenofovir Study	42	1204	31	1209	19.0%	1.36 [0.86, 2.15]
CDC Safety Study* (1)	0	201	2	199	0.4%	0.20 [0.01, 4.10]
Partners PrEP - TDF arm	19	1584	6	792	4.8%	1.58 [0.63, 3.96]
Study of TDF	13	363	15	368	7.5%	0.88 [0.42, 1.82]
VOICE - TDF arm (2)	4	1007	1	505	0.8%	2.01 [0.22, 17.90]
Subtotal (95% CI)		**4359**		**3073**	**32.6%**	**1.24 [0.87, 1.76]**
Total events	78		55			
Heterogeneity: Tau² = 0.00; Chi² = 2.89, df = 4 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
1.11.2 FTC-TDF						
FEM-PrEP	72	1025	56	1033	34.8%	1.30 [0.92, 1.82]
IAVI Kenya Study	3	48	0	24	0.5%	3.57 [0.19, 66.47]
IAVI Uganda Study	2	48	0	24	0.4%	2.55 [0.13, 51.13]
IPERGAY*	35	199	20	201	15.1%	1.77 [1.06, 2.95]
iPrEx	25	1251	14	1248	9.4%	1.78 [0.93, 3.41]
Partners PrEP - FTC-TDF arm	20	1579	7	792	5.4%	1.43 [0.61, 3.37]
PROUD* (3)	3	273	0	267	0.5%	6.85 [0.36, 131.92]
TDF2	1	611	0	608	0.4%	2.99 [0.12, 73.14]
VOICE - FTC-TDF arm (4)	13	1003	1	504	1.0%	6.53 [0.86, 49.79]
Subtotal (95% CI)		**6037**		**4701**	**67.4%**	**1.54 [1.21, 1.96]**
Total events	174		98			
Heterogeneity: Tau² = 0.00; Chi² = 5.08, df = 8 (P = 0.75); I² = 0%						
Test for overall effect: Z = 3.48 (P = 0.0005)						
Total (95% CI)		**10396**		**7774**	**100.0%**	**1.43 [1.18, 1.75]**
Total events	252		153			
Heterogeneity: Tau² = 0.00; Chi² = 8.94, df = 13 (P = 0.78); I² = 0%						
Test for overall effect: Z = 3.55 (P = 0.0004)						
Test for subgroup differences: Chi² = 1.01, df = 1 (P = 0.31), I² = 1.0%						



Footnotes
(1) Creatinine elevation leading to study withdrawal
(2) Any creatinine event
(3) Study drug interruption due to high creatinine concentration
(4) Any creatinine event

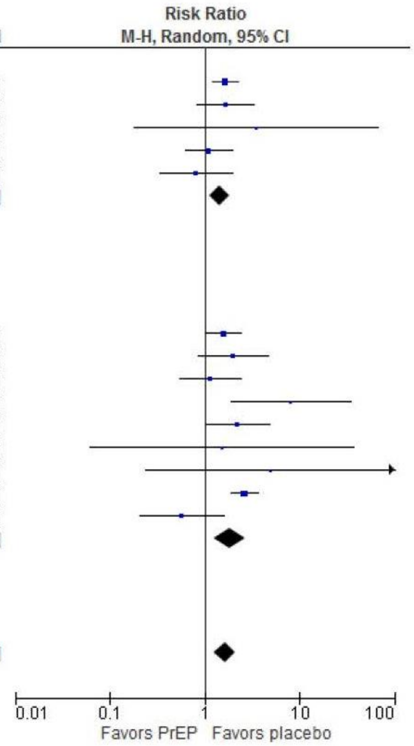
Note: Defined as ≥grade 1 serum creatinine elevation unless otherwise noted.

*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 16. Meta-Analysis: Gastrointestinal Adverse Events Stratified by Study Drug

Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 TDF						
Bangkok Tenofovir Study (1)	96	1204	59	1209	15.9%	1.63 [1.19, 2.24]
CDC Safety Study*	20	201	12	199	8.3%	1.65 [0.83, 3.28]
Partners PrEP - TDF arm (2)	3	1584	0	792	0.7%	3.50 [0.18, 67.72]
Study of TDF (3)	24	427	22	432	10.4%	1.10 [0.63, 1.94]
VOICE - TDF arm (4)	13	1007	8	505	6.1%	0.81 [0.34, 1.95]
Subtotal (95% CI)		**4423**		**3137**	**41.5%**	**1.45 [1.13, 1.85]**
Total events	156		101			
Heterogeneity: Tau² = 0.00; Chi² = 3.60, df = 4 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.97 (P = 0.003)						
1.14.2 FTC-TDF						
FEM-PrEP (5)	50	1024	32	1032	13.0%	1.57 [1.02, 2.43]
IAVI Kenya Study (6)	20	48	5	24	6.4%	2.00 [0.86, 4.67]
IAVI Uganda Study (7)	16	48	7	24	7.6%	1.14 [0.54, 2.40]
IPERGAY* (8)	16	199	2	201	2.7%	8.08 [1.88, 34.68]
iPrEx	20	1251	9	1248	7.1%	2.22 [1.01, 4.85]
Partners PrEP - FTC-TDF arm (9)	1	1579	0	792	0.6%	1.51 [0.06, 36.92]
PROUD* (10)	2	275	0	269	0.7%	4.89 [0.24, 101.41]
TDF2 (11)	113	611	43	608	15.4%	2.62 [1.87, 3.65]
VOICE - FTC-TDF arm (12)	8	1003	7	504	4.9%	0.57 [0.21, 1.57]
Subtotal (95% CI)		**6038**		**4702**	**58.5%**	**1.84 [1.26, 2.70]**
Total events	246		105			
Heterogeneity: Tau² = 0.13; Chi² = 15.80, df = 8 (P = 0.05); I² = 49%						
Test for overall effect: Z = 3.14 (P = 0.002)						
Total (95% CI)		**10461**		**7839**	**100.0%**	**1.63 [1.26, 2.11]**
Total events	402		206			
Heterogeneity: Tau² = 0.08; Chi² = 22.91, df = 13 (P = 0.04); I² = 43%						
Test for overall effect: Z = 3.72 (P = 0.0002)						
Test for subgroup differences: Chi² = 1.09, df = 1 (P = 0.30), I² = 8.5%						



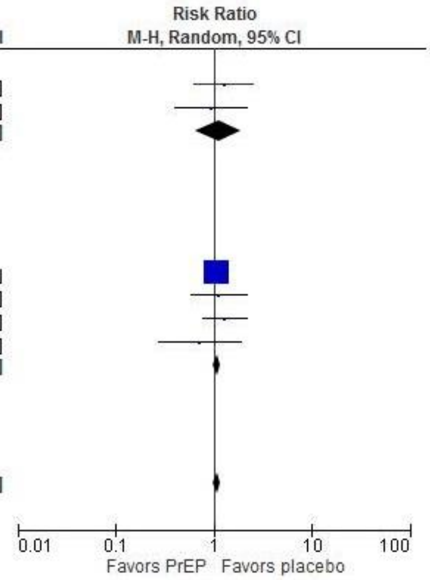
Footnotes
(1) Nausea or vomiting
(2) Nausea
(3) Abdominal pain
(4) Grade 2 or higher nausea
(5) Nausea
(6) Any gastrointestinal adverse event
(7) Any gastrointestinal adverse event
(8) Nausea
(9) Nausea
(10) Serious vomiting
(11) Nausea
(12) Grade 2 or higher nausea

*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: Syphilis Stratified by Study Drug

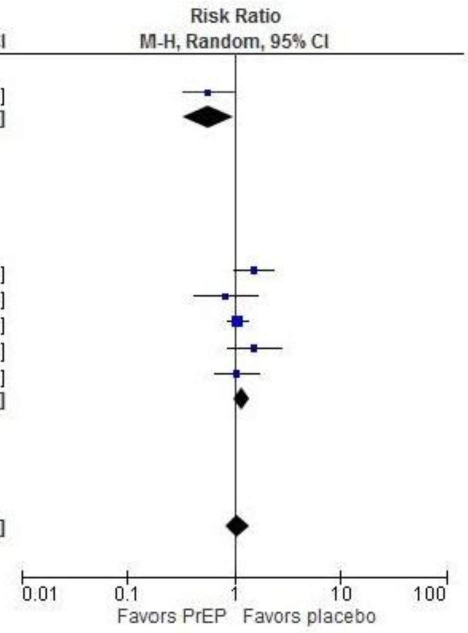
Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 TDF						
Partners PrEP - TDF arm	28	1584	11	792	1.7%	1.27 [0.64, 2.54]
VOICE - TDF arm	15	1007	8	505	1.1%	0.94 [0.40, 2.20]
Subtotal (95% CI)		**2591**		**1297**	**2.8%**	**1.13 [0.66, 1.93]**
Total events	43		19			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
1.17.2 FTC-TDF						
iPrEx	527	1251	491	1248	91.5%	1.07 [0.97, 1.18]
Partners PrEP - FTC-TDF arm	27	1579	12	792	1.8%	1.13 [0.57, 2.22]
PROUD*	30	263	22	247	3.0%	1.28 [0.76, 2.16]
VOICE - FTC-TDF arm	10	1003	7	504	0.9%	0.72 [0.27, 1.87]
Subtotal (95% CI)		**4096**		**2791**	**97.2%**	**1.07 [0.98, 1.18]**
Total events	594		532			
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 3 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.52 (P = 0.13)						
Total (95% CI)		**6687**		**4088**	**100.0%**	**1.08 [0.98, 1.18]**
Total events	637		551			
Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 5 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.57 (P = 0.12)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%						



*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 18. Meta-Analysis: Gonorrhea Stratified by Study Drug



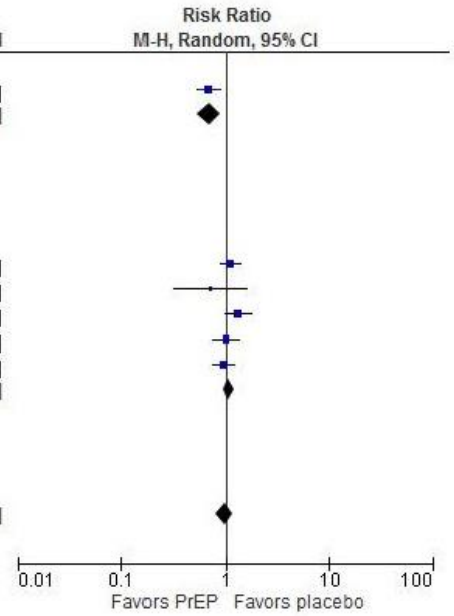
Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.20.1 TDF						
VOICE - TDF arm	26	1007	23	505	14.0%	0.57 [0.33, 0.98]
Subtotal (95% CI)		**1007**		**505**	**14.0%**	**0.57 [0.33, 0.98]**
Total events	26		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.02 (P = 0.04)						
1.20.2 FTC-TDF						
FEM-PrEP	50	1024	33	1032	18.3%	1.53 [0.99, 2.35]
iPrEx	14	1248	17	1251	10.1%	0.83 [0.41, 1.67]
PROUD*	103	261	89	242	28.8%	1.07 [0.86, 1.34]
TDF2	28	611	18	608	13.1%	1.55 [0.87, 2.77]
VOICE - FTC-TDF arm	46	1003	22	504	15.8%	1.05 [0.64, 1.73]
Subtotal (95% CI)		**4147**		**3637**	**86.0%**	**1.15 [0.97, 1.37]**
Total events	241		179			
Heterogeneity: Tau² = 0.00; Chi² = 4.06, df = 4 (P = 0.40); I² = 2%						
Test for overall effect: Z = 1.59 (P = 0.11)						
Total (95% CI)		**5154**		**4142**	**100.0%**	**1.07 [0.82, 1.39]**
Total events	267		202			
Heterogeneity: Tau² = 0.05; Chi² = 9.80, df = 5 (P = 0.08); I² = 49%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 5.78, df = 1 (P = 0.02), I² = 82.7%						

*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 19. Meta-Analysis: Chlamydia Stratified by Study Drug

Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.23.1 TDF						
VOICE - TDF arm	105	1007	77	505	18.9%	0.68 [0.52, 0.90]
Subtotal (95% CI)		**1007**		**505**	**18.9%**	**0.68 [0.52, 0.90]**
Total events	105		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.72 (P = 0.007)						
1.23.2 FTC-TDF						
FEM-PrEP	136	1024	124	1032	21.3%	1.11 [0.88, 1.39]
iPrEx	10	1251	14	1248	4.9%	0.71 [0.32, 1.60]
PROUD*	77	261	54	242	17.5%	1.32 [0.98, 1.79]
TDF2	76	611	75	608	17.6%	1.01 [0.75, 1.36]
VOICE - FTC-TDF arm	144	1003	76	504	19.8%	0.95 [0.74, 1.23]
Subtotal (95% CI)		**4150**		**3634**	**81.1%**	**1.07 [0.94, 1.22]**
Total events	443		343			
Heterogeneity: Tau² = 0.00; Chi² = 3.91, df = 4 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Total (95% CI)		**5157**		**4139**	**100.0%**	**0.97 [0.80, 1.18]**
Total events	548		420			
Heterogeneity: Tau² = 0.03; Chi² = 12.19, df = 5 (P = 0.03); I² = 59%						
Test for overall effect: Z = 0.26 (P = 0.79)						
Test for subgroup differences: Chi² = 8.29, df = 1 (P = 0.004), I² = 87.9%						

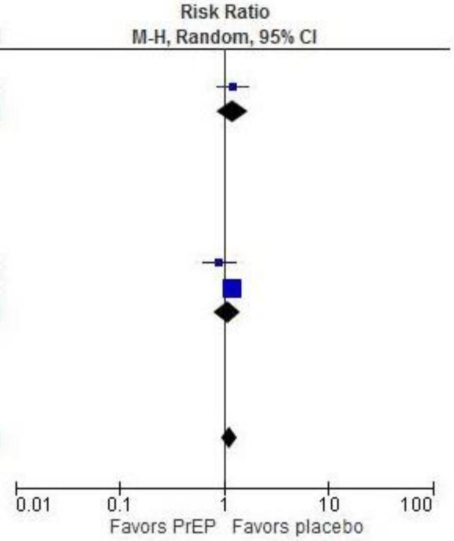


*U.S, Canada, or Europe.

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: Combined Bacterial STIs Stratified by Study Drug

Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.26.1 TDF						
Partners PrEP - TDF arm	102	1584	42	792	19.6%	1.21 [0.86, 1.72]
Subtotal (95% CI)		**1584**		**792**	**19.6%**	**1.21 [0.86, 1.72]**
Total events	102		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.28)						
1.26.2 FTC-TDF						
Partners PrEP - TDF arm	76	1579	43	792	18.2%	0.89 [0.62, 1.28]
PROUD*	152	275	124	269	62.2%	1.20 [1.01, 1.42]
Subtotal (95% CI)		**1854**		**1061**	**80.4%**	**1.07 [0.80, 1.44]**
Total events	228		167			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.36$, df = 1 (P = 0.12); $I^2 = 58\%$						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**3438**		**1853**	**100.0%**	**1.14 [0.97, 1.34]**
Total events	330		209			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.37$, df = 2 (P = 0.31); $I^2 = 16\%$						
Test for overall effect: Z = 1.54 (P = 0.12)						
Test for subgroup differences: $Chi^2 = 0.27$, df = 1 (P = 0.60), $I^2 = 0\%$						

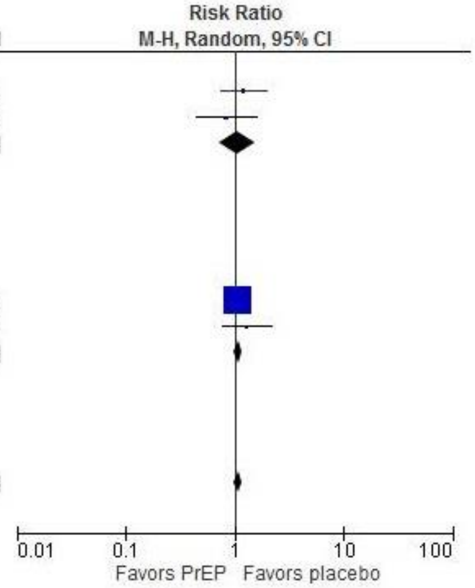


*U.S, Canada, or Europe.

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 21. Meta-Analysis: Syphilis Stratified by HIV Risk Category

Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Heterosexual men and women						
Partners PrEP	55	3163	23	1584	3.5%	1.20 [0.74, 1.94]
VOICE	25	2010	15	1009	2.0%	0.84 [0.44, 1.58]
Subtotal (95% CI)		**5173**		**2593**	**5.5%**	**1.05 [0.71, 1.54]**
Total events	80		38			
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.80)						
1.18.2 MSM						
iPrEx	527	1251	491	1248	91.4%	1.07 [0.97, 1.18]
PROUD*	30	263	22	247	3.0%	1.28 [0.76, 2.16]
Subtotal (95% CI)		**1514**		**1495**	**94.5%**	**1.08 [0.98, 1.18]**
Total events	557		513			
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 1.56 (P = 0.12)						
Total (95% CI)		**6687**		**4088**	**100.0%**	**1.08 [0.98, 1.18]**
Total events	637		551			
Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 3 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.57 (P = 0.12)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%						

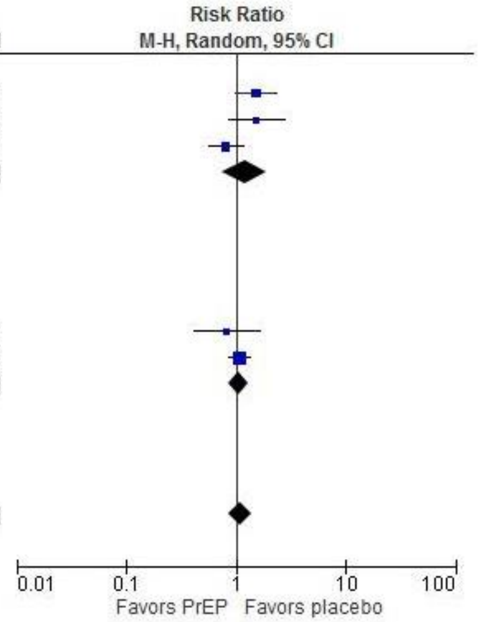


*U.S, Canada, or Europe.

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 22. Meta-Analysis: Gonorrhea Stratified by HIV Risk Category

Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.21.1 Heterosexual						
FEM-PrEP	50	1024	33	1032	19.4%	1.53 [0.99, 2.35]
TDF2	28	611	18	608	13.0%	1.55 [0.87, 2.77]
VOICE	72	2010	45	1009	23.4%	0.80 [0.56, 1.16]
Subtotal (95% CI)		**3645**		**2649**	**55.8%**	**1.20 [0.76, 1.92]**
Total events	150		96			
Heterogeneity: Tau² = 0.11; Chi² = 6.37, df = 2 (P = 0.04); I² = 69%						
Test for overall effect: Z = 0.78 (P = 0.44)						
1.21.2 MSM						
iPrEx	14	1251	17	1248	9.7%	0.82 [0.41, 1.66]
PROUD*	103	261	89	242	34.5%	1.07 [0.86, 1.34]
Subtotal (95% CI)		**1512**		**1490**	**44.2%**	**1.05 [0.85, 1.30]**
Total events	117		106			
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						
Total (95% CI)		**5157**		**4139**	**100.0%**	**1.10 [0.86, 1.40]**
Total events	267		202			
Heterogeneity: Tau² = 0.03; Chi² = 7.08, df = 4 (P = 0.13); I² = 43%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.59), I² = 0%						

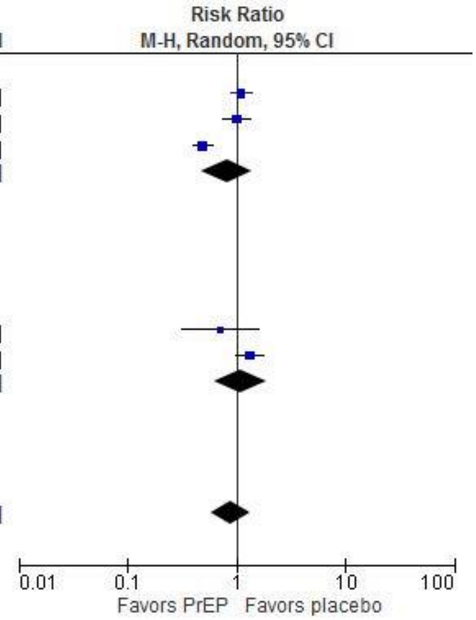


*U.S, Canada, or Europe.

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 23. Meta-Analysis: Chlamydia Stratified by HIV Risk Category

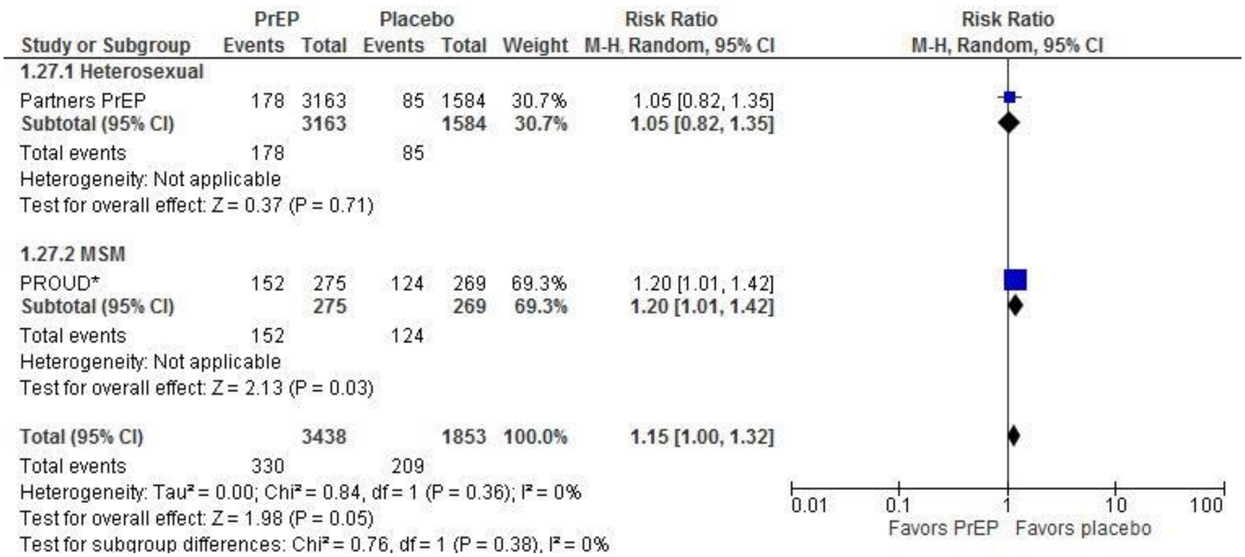
Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.24.1 Heterosexual						
FEM-PrEP	136	1024	124	1032	22.2%	1.11 [0.88, 1.39]
TDF2	76	611	75	608	21.3%	1.01 [0.75, 1.36]
VOICE	149	2010	153	1009	22.4%	0.49 [0.40, 0.60]
Subtotal (95% CI)		**3645**		**2649**	**65.9%**	**0.81 [0.47, 1.41]**
Total events	361		352			
Heterogeneity: Tau² = 0.22; Chi² = 30.40, df = 2 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 0.74 (P = 0.46)						
1.24.2 MSM						
iPrEx	10	1251	14	1248	12.8%	0.71 [0.32, 1.60]
PROUD*	77	261	54	242	21.2%	1.32 [0.98, 1.79]
Subtotal (95% CI)		**1512**		**1490**	**34.1%**	**1.09 [0.62, 1.92]**
Total events	87		68			
Heterogeneity: Tau² = 0.10; Chi² = 2.00, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Total (95% CI)		**5157**		**4139**	**100.0%**	**0.89 [0.58, 1.36]**
Total events	448		420			
Heterogeneity: Tau² = 0.20; Chi² = 40.85, df = 4 (P < 0.00001); I² = 90%						
Test for overall effect: Z = 0.55 (P = 0.58)						
Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0%						



*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 24. Meta-Analysis – Any STI Stratified by HIV Risk Category

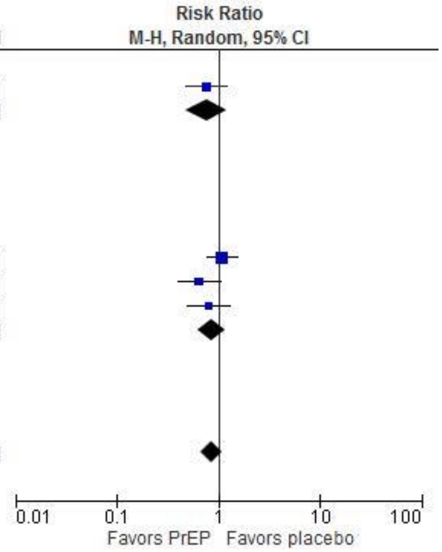


*U.S, Canada, or Europe.

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

Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.33.1 TDF						
Partners PrEP - TDF arm	42	513	26	241	21.9%	0.76 [0.48, 1.21]
Subtotal (95% CI)		**513**		**241**	**21.9%**	**0.76 [0.48, 1.21]**
Total events	42		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.16 (P = 0.24)						
1.33.2 FTC-TDF						
iPrEx	65	671	60	676	36.7%	1.09 [0.78, 1.52]
Partners PrEP - FTC-TDF arm	37	528	26	240	20.9%	0.65 [0.40, 1.04]
TDF2	28	611	35	608	20.5%	0.80 [0.49, 1.29]
Subtotal (95% CI)		**1810**		**1524**	**78.1%**	**0.86 [0.62, 1.18]**
Total events	130		121			
Heterogeneity: Tau² = 0.03; Chi² = 3.35, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Total (95% CI)		**2323**		**1765**	**100.0%**	**0.85 [0.67, 1.07]**
Total events	172		147			
Heterogeneity: Tau² = 0.01; Chi² = 3.69, df = 3 (P = 0.30); I² = 19%						
Test for overall effect: Z = 1.37 (P = 0.17)						
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.67), I² = 0%						



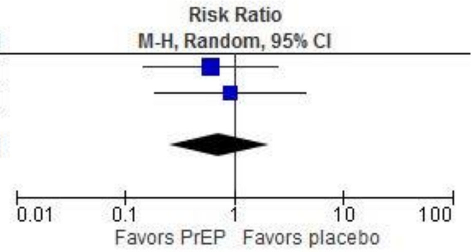
*U.S, Canada, or Europe.

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 26. Meta-Analysis: Hepatitis C Virus Infection

Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
IPERGAY*	3	199	5	201	55.7%	0.61 [0.15, 2.50]
PROUD*	3	258	3	238	44.3%	0.92 [0.19, 4.53]
Total (95% CI)		**457**		**439**	**100.0%**	**0.73 [0.25, 2.10]**
Total events	6		8			

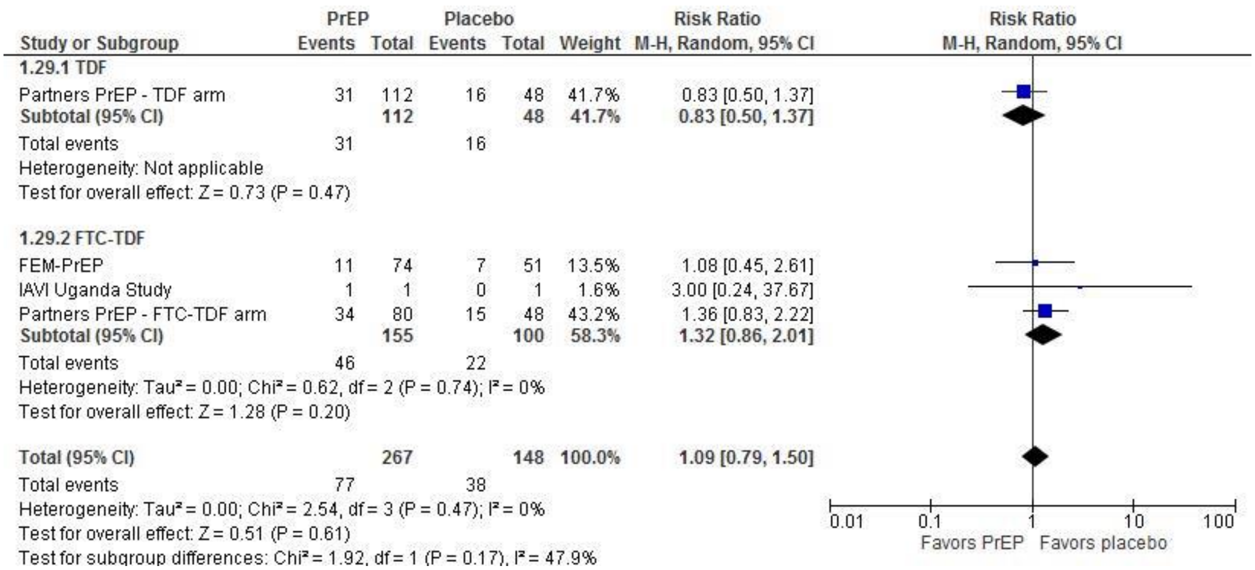
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)



*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 27. Meta-Analysis: Spontaneous Abortion Stratified by Study Drug



Study or Subgroup	PrEP Events	PrEP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.29.1 TDF						
Partners PrEP - TDF arm	31	112	16	48	41.7%	0.83 [0.50, 1.37]
Subtotal (95% CI)		**112**		**48**	**41.7%**	**0.83 [0.50, 1.37]**
Total events	31		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
1.29.2 FTC-TDF						
FEM-PrEP	11	74	7	51	13.5%	1.08 [0.45, 2.61]
IAVI Uganda Study	1	1	0	1	1.6%	3.00 [0.24, 37.67]
Partners PrEP - FTC-TDF arm	34	80	15	48	43.2%	1.36 [0.83, 2.22]
Subtotal (95% CI)		**155**		**100**	**58.3%**	**1.32 [0.86, 2.01]**
Total events	46		22			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
Total (95% CI)		**267**		**148**	**100.0%**	**1.09 [0.79, 1.50]**
Total events	77		38			
Heterogeneity: Tau² = 0.00; Chi² = 2.54, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Chi² = 1.92, df = 1 (P = 0.17), I² = 47.9%						

*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.

Table 1. Summary of U.S. Public Health Service Guidance on Use of PrEP

Guidance for	Details
Detecting substantial risk of acquiring HIV infection	**Men who have sex with men:** • HIV-infected sexual partner • Recent bacterial STI* • High number of sexual partners • History of inconsistent or no condom use • Commercial sex work **Heterosexual women and men:** • HIV-infected sexual partner • Recent bacterial STI† • High number of sexual partners • History of inconsistent or no condom use • Commercial sex work • In high-prevalence area or network **Persons who inject drugs:** • HIV-positive drug injection partner • Sharing injection equipment
Clinically eligible	• Documented negative HIV test result before prescribing PrEP • No signs/symptoms of acute HIV infection • Normal renal function; no contraindicated medications • Documented hepatitis B virus infection and vaccination status
Prescription	Daily, continuing, oral doses of TDF-FTC (Truvada®), ≤90-day supply
Other services	• Followup visits at least every 3 months to provide the following: HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, and STI symptom assessment • At 3 months and every 6 months thereafter, assess renal function • Every 3 to 6 months, test for bacterial STIs **Men who have sex with men:** Oral/rectal STI testing **Heterosexual women and men:** For women, assess pregnancy intent; pregnancy test every 3 months **Persons who inject drugs:** Access to clean needles/syringes and drug treatment services

Source: U.S. Public Health Service, Centers for Disease Control and Prevention, 2017.[60]
*Gonorrhea, chlamydia, and syphilis for men who have sex with men, including those who inject drugs.
†Gonorrhea and syphilis for heterosexual women and men, including those who inject drugs.

Abbreviations: PrEP=pre-exposure prophylaxis; STI=sexually transmitted infection; TDF-FTC=tenofovir disoproxil fumarate-emtricitabine.

Table 2. Study Characteristics of RCTs 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)
Bangkok Tenofovir Study Choopanya, 2013[97] 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)
FEM PrEP Van Damme 2012[120] 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)
CDC Safety Study Grohskopf 2013 U.S.[85] 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%	92% (pill count)
IAVI Uganda Study Kibengo 2013[54] 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)
IAVI Kenya Study Mutua 2012[53] 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)
IPERGAY Molina 2015[52] 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)

Table 2. Study Characteristics of RCTs 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)
iPrEx Grant 2010[100] 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%	51% (plasma)
Partners PrEP Baeten 2012[70] 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)
PROUD McCormack 2016[78] 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)‡
Study of TDF Peterson 2007[117] 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[119] 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)

Table 2. Study Characteristics of RCTs 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)
VOICE Marrazzo 2015[76] 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)

*Primary publication; details on all included publications appear in **Appendix B Table 1.**
†Daily, oral dose unless specified.
‡Sample of patients who reported that they were taking PrEP.

Abbreviations: ART=antiretroviral therapy; FTC=emtricitabine; iPrEx=Pre-Exposure Prophylaxis Initiative; 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 RCTs of PrEP Versus Placebo/No PrEP

Study characteristics	Subgroups	Number of trials	RR (95% CI)	I^2
All trials	-	11[52,53,70,76,78,85,97,100,117,119,120]	0.46 (0.33 to 0.66)	67%
Study quality	Restricted to good-quality trials	10[52,53,70,76,85,97,100,117,119,120]	0.48 (0.33 to 0.71)	71%
PrEP drug regimen *(p=0.79 for interaction)*	TDF	5[70,76,85,97,117]	0.49 (0.28 to 0.84)	58%
	TDF-FTC	8[52,53,70,76,78,100,117,120]	0.44 (0.27 to 0.72)	67%
Adherence *(p<0.00001 for interaction)*	Adherence ≥70%	6[52,53,70,78,85,119]	0.27 (0.19 to 0.39)	0%
	Adherence >40% to <70%	3[97,100,117]	0.51 (0.38 to 0.70)	0%
	Adherence ≤40%	2[76,120]	0.93 (0.72 to 1.20)	0%
HIV risk category *(p=0.43 for interaction)*	Heterosexual men and women	5[70,76,117,119,120]	0.54 (0.31 to 0.97)	82%
	Men who have sex with men	4[52,78,85,100]	0.23 (0.08 to 0.62)	64%
	Persons who inject drugs	1[97]	0.52 (0.29 to 0.92)	Not applicable
Dosing schedule *(p=0.13 for interaction)*	Daily dosing	9[53,70,76,78,85,97,100,117,119,120]	0.47 (0.32 to 0.71)	75%
	On-demand dosing	1[52]	0.14 (0.03 to 0.63)	Not applicable
Followup duration *(p=0.35 for interaction)*	Duration of followup <1 year	3[52,53,117]	0.21 (0.07 to 0.58)	0%
	Duration of followup ≥1 to 2 years	4[78,100,119,120]	0.48 (0.28 to 0.84)	70%
	Duration of followup ≥2 years	4[70,76,85,97]	0.47 (0.22 to 1.00)	86%
Industry support *(p=0.38 for interaction)*	Study reported industry support	3[53,119,120]	0.58 (0.27 to 1.22)	54%
	Study reported government or nonprofit funding only	8[52,70,76,78,85,97,100,117]	0.39 (0.23 to 0.64)	77%
Country setting *(p=0.004 for interaction)*	U.S. or other high-income countries	3[52,78,85]	0.13 (0.05 to 0.32)	0%
	Africa, Asia, or international trial	8[53,70,76,97,100,117,119,120]	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 Versus Placebo on HIV Infection in Population Subgroups

Study	Age	Sex/Gender	Race/Ethnicity	Risk behaviors
Bangkok Tenofovir Study Choopanya, 2013[97]	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[120]	≥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[100]	<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[70]	*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[119]	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

Abbreviations: CI=confidence interval; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; HR=hazard ratio; iPrEx=Pre-Exposure Prophylaxis Initiative; MSM=men who have sex with men; NR=not reported; PrEP=pre-exposure prophylaxis; RR=relative risk; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study.

Table 5. Rates of Adherence to PrEP in U.S. Primary Care Settings

Study, year	Study design	N	Population	Years PrEP administered	Drug levels	Self report	Other method of assessing adherence
Chan, 2016[124]	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 Latino: 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
CDC Safety Study Grohskopf, 2013[85]	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%)
Grant 2018[123]	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%

Table 5. Rates of Adherence to PrEP in U.S. Primary Care Settings

Study, year	Study design	N	Population	Years PrEP administered	Drug levels	Self report	Other method of assessing adherence
Hosek, 2017[93] Project PrEPare, ATN 110	Treatment series	200	MSM Mean age: 20 years Latino: 26% Non-Latino black/African American: 66% Non-Latino white: 29% Non-Latino 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
Hosek, 2017[92] Project PrEPare, ATN 113	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

Table 5. Rates of Adherence to PrEP in U.S. Primary Care Settings

Study, year	Study design	N	Population	Years PrEP administered	Drug levels	Self report	Other method of assessing adherence
Hosek, 2013[94] Project PrEPare, ATN 082	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
Landovitz, 2017[126] PATH-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
Liu, 2016[81] The Demo Project	Treatment series	557	MSM (98%) and transgender women (1.4%) Mean age: 35 years White: 48% Latino: 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%

Table 5. Rates of Adherence to PrEP in U.S. Primary Care Settings

Study, year	Study design	N	Population	Years PrEP administered	Drug levels	Self report	Other method of assessing adherence
Montgomery, 2016[127]	Treatment series	50	MSM (95%) Mean age: 34 years Non-Hispanic white: 58% Non-Hispanic black: 26% Hispanic or Latino: 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
Van Epps 2018[128]	Retrospective cohort	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%)

Abbreviations: CDC=Centers for Disease Control and Prevention; FSM=females who have sex with males; IQR=interquartile range; MSM=men who have sex with men; MSF=men who have sex with females; NR=not reported; PrEP=pre-exposure prophylaxis; RCT=randomized, controlled trial; TVF-DP=tenofovir disoproxil fumarate-diphosphate; TDF-FTC=tenofovir disoproxil fumarate-emtricitabine; U.S.=United States.

Table 6. Association Between Adherence to PrEP and Effectiveness for Preventing HIV Acquisition

Study name Author, year Study design	Number of patients on PrEP	Overall effectiveness, PrEP vs. placebo	Effectiveness, PrEP vs. placebo, according to level of adherence	On PrEP, seroconverters vs. non-seroconverters, according to PrEP drug levels
Bangkok Tenofovir Study Choopanya, 2013[97]* and Martin 2015[109] RCT	1,204	RR, 0.52 (95% CI, 0.29 to 0.92)	"Adherent" (drug taken 71% of days and no more than 2 consecutive days missed, based on daily diary): HR, 0.44 (95% CI, 0.14 to 1.19) ≥60% adherence: HR, 0.51 ≥75% adherence: HR, 0.42 ≥97.5% adherence: HR, 0.16	Quantifiable tenofovir plasma concentration: 39% (5/13) of cases and 67% (93/138) of controls; OR, 0.30 (95% CI, 0.09 to 0.98)
FEM-PrEP Van Damme, 2012[120]* and Agot 2015[95] RCT	1,062	HR, 0.94 (95% CI, 0.59 to 1.52)	NR	Plasma TDF >10 ng/mL: 15% (4/27) of cases and 24% (19/78) of controls; OR, 0.54 (95% CI, 0.17 to 1.76)
IPERGAY Molina 2015[52] RCT	199	RR, 0.14 (95% CI, 0.03 to 0.63)	NR	Study drugs not detected in plasma of 2 seroconverters
iPrEx Grant 2010[100]* RCT	1,251	HR, 0.53 (95% CI, 0.36 to 0.78)	≥50% pill use: HR, 0.50 (95% CI, 0.30 to 0.82) <50% pill use: HR, 0.68 (95% CI, 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	NR
Partners PrEP Baeten 2012a[70]* and Donnell 2014[99] RCT	3,136	RR, 0.29 (95% CI, 0.19 to 0.45)	>80% pill count coverage: OR, 0.08 (95% CI, 0.04 to 0.19)	Tenofovir >0.3 ng/mL in plasma: 41% (9/29) of cases vs. 83% (772/945 samples) of controls; OR, 0.10 (95% CI, 0.05 to 0.23) Tenofovir >10 ng/mL in plasma: 41% (9/29) of cases vs. 79% (730/945 samples) of controls; OR, 0.13 (95% CI, 0.06 to 0.30) Tenofovir >40 ng/mL in plasma: 24% (6/29) of cases vs. 72% (670/945 samples) of controls; OR, 0.11 (95% CI, 0.04 to 0.27) Tenofovir detected in plasma: 41% (9/29) of cases vs. 83% (772/945) of controls; OR, 0.10 (95% CI, 0.05 to 0.23)
TDF2 Thigpen, 2012[119]* RCT	611	RR, 0.39 (95% CI, 0.19 to 0.81)	NR	Detectable tenofovir plasma level: 50% (2/4) of cases vs. 80% (55/69) of controls; OR, 0.25 (95% CI, 0.03 to 1.97) Detectable FTC plasma level: 50% (2/4) of cases vs. 81% (56/69) of controls; OR, 0.23 (95% CI, 0.03 to 1.80)

Table 6. Association Between Adherence to PrEP and Effectiveness for Preventing HIV Acquisition

Study name Author, year Study design	Number of patients on PrEP	Overall effectiveness, PrEP vs. placebo	Effectiveness, PrEP vs. placebo, according to level of adherence	On PrEP, seroconverters vs. non-seroconverters, according to PrEP drug levels
VOICE Marrazzo 2015[76]* RCT	2,010	RR, 0.87 (95% CI, 0.61 to 1.25) for TDF and RR, 1.02 (95% CI, 0.72 to 1.44) for TDF- FTC	NR	Tenofovir ever detected in plasma TDF: 26% (14/54) of cases and 44% (68/156) of controls; aRR, 0.55 (95% CI, 0.26 to 1.14) TDF-FTC: 39% (24/61) of cases and 52% (77/148) of controls; aRR, 0.83 (95% CI, 0.39 to 1.76)
Hosek, 2017[93] Project PrEPare, ATN 110 Observational	200	--	NR	TDF plasma level not detectable in 4 seroconverters
Hosek 2017[92] *Project PrEPare, ATN 113* Observational	78	--	NR	TDF plasma levels consistent with <2 doses of PrEP/week in 3 seroconverters
iPrEx-OLE Grant, 2014[125] Observational	1,345	--	NR	TDF level quantifiable on dried blood spot testing: HR, 0.80 (95% CI, 0.38 to 1.67) <350 fmol/punch (~<2 tablets/week): HR, 0.56 (95% CI, 0.23 to 1.31) 350–699 fmol/punch (~2 to 3 tablets/week): HR, 0.16 (95% CI, 0.01 to 0.79) 700–1,249 fmol/punch (~4 to 6 tablets/week): HR, 0.00 (95% CI, 0.00 to 0.21)
PATH-PrEP Landovitz, 2017[126] Observational	278	--	NR	TDF plasma level consistent with <2 doses of PrEP/week in 1 seroconverter
U.S. PrEP Demonstration Project Liu, 2016[81] and Cohen, 2015[146] Observational	383	--	NR	TDF plasma levels consistent with poor adherence in 2 seroconverters

*Main study publication.

Abbreviations: aRR=adjusted relative risk; CI=confidence interval; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; HR=hazard ratio; IPERGAY=Intervention Préventive de l'Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; NR=not reported; OR=odds ratio; PrEP=pre-exposure prophylaxis; RCT=randomized, controlled trial; RR=relative risk; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; U.S.=United States; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

Table 7. Adverse Events in Trials of PrEP Versus Placebo/No PrEP

Outcome	Number of trials*	RR (95% CI)	I^2
Serious adverse events *PrEP drug regimen (p=0.23 for interaction)*	12[52-54,70,76,78,85,97,100,117,119,120]	0.93 (0.77 to 1.12)	56%
TDF	5[70,76,85,97,117]	0.79 (0.56 to 1.12)	72%
TDF-FTC	9[52-54,70,76,78,100,119,120]	1.02 (0.81 to 1.30)	46%
Withdrawal due to adverse events *PrEP drug regimen (p=0.67 for interaction)*	4[52,70,100,120]	1.25 (0.99 to 1.59)	0%
TDF	1[70]	1.00 (0.34 to 2.92)	Not applicable
TDF-FTC	4[52,70,100,120]	1.27 (1.00 to 1.59)	0%
Fracture *PrEP drug regimen (p=0.50 for interaction)*	8[52,70,76,78,85,97,100,119]	1.23 (0.97 to 1.56)	0%
TDF	4[70,76,85,97]	1.29 (0.98 to 1.70)	0%
TDF-FTC	6[52,70,76,78,100,119]	1.06 (0.66 to 1.72)	0%
Renal adverse events *PrEP drug regimen (p=0.31 for interaction)*	12[52-54,70,76,78,85,97,100,117, 119,120]	1.43 (1.18 to 1.75)	0%
TDF	5[70,76,85,97,117]	1.24 (0.87 to 1.76)	0%
TDF-FTC	9[52-54,70,76,78,100,119,120]	1.54 (1.21 to 1.96)	0%
Gastrointestinal adverse events *PrEP drug regimen (p=0.30 for interaction)*	12[52-54,70,76,78,85,97,100,117,119,120]	1.63 (1.26 to 2.11)	43%
TDF	5[70,76,85,97,117]	1.45 (1.13 to 1.85)	0%
TDF-FTC	9[52-54,70,76,78,100,119,120]	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 8. Risk of STI in Trials and PrEP Versus Placebo/No 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[70,78]	1.14 (0.97 to 1.34)	16%
TDF	1[70]	1.21 (0.86 to 1.72)	Not applicable
TDF-FTC	2[70,78]	1.07 (0.80 to 1.44)	58%
Heterosexual men and women	1[70]	1.05 (0.82 to 1.35)	Not applicable
MSM	1[78]	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[70,76,78,100]	1.08 (0.98 to 1.18)	0%
TDF	2[70,76]	1.13 (0.66 to 1.93)	0%
TDF-FTC	4[70,76,78,100]	1.07 (0.98 to 1.18)	0%
Heterosexual men and women	2[70,76]	1.05 (0.71 to 1.54)	0%
MSM	2[78,100]	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[76,78,100,119,120]	1.07 (0.82 to 1.39)	49%
TDF	1[76]	0.57 (0.33 to 0.98)	Not applicable
TDF-FTC	5[76,78,100,119,120]	1.15 (0.97 to 1.37)	2%
Heterosexual men and women	3[76,119,120]	1.20 (0.76 to 1.92)	69%
MSM	2[78,100]	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[76,78,100,119,120]	0.97 (0.80 to 1.18)	59%
TDF	1[76]	0.68 (0.52 to 0.90)	Not applicable
TDF-FTC	5[76,78,100,119,120]	1.07 (0.94 to 1.22)	0%
Heterosexual men and women	3[76,119,120]	0.81 (0.47 to 1.41)	93%
MSM	2[78,100]	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[80,107,119]	0.85 (0.67 to 1.07)	19%
TDF	1[80]	0.76 (0.48 to 1.21)	Not applicable
TDF-FTC	3[80,107,119]	0.86 (0.62 to 1.18)	40%
Heterosexual men and women	2 [80,119]	0.73 (0.56 to 0.96)	0%
MSM	1[107]	1.12 (0.80 to 1.56)	Not applicable
Hepatitis C virus infection†	2[52,78]	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 9. Rates of Antiretroviral Drug Resistance in Patients Taking PrEP

Study Author, year Study design	PrEP regimen	Resistance mutations among persons with newly diagnosed HIV infection	Resistance mutations among persons randomized to PrEP
Bangkok Tenofovir Study Choopanya 2013[97] RCT	A: 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[120] RCT	A: 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[85] RCT	A: TDF daily (n=201)	TDF vs. placebo K65R: 0% (0/0) vs.0% (0/7)	0% (0/201)
IPERGAY Molina 2015[52] RCT	A: TDF-FTC on demand (n=199)	TDF-FTC (n=2) vs. placebo (n=14) No resistance mutations identified	0% (0/199)
iPrEx Grant 2010[100] RCT	A: 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[70] RCT	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[78] RCT	A: 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[117] RCT	A: 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[119] RCT	A: 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[76] RCT	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
iPrEx-OLE Grant 2014[125] Observational	A: TDF-FTC daily (n=1225)	M184V: 3.6% (1/28)	0.1% (1/1,225)

Table 9. Rates of Antiretroviral Drug Resistance in Patients Taking PrEP

Study Author, year Study design	PrEP regimen	Resistance mutations among persons with newly diagnosed HIV infection	Resistance mutations among persons randomized to PrEP
Hosek 2017[93] Project PrEPare, ATN 110 Observational	A: TDF-FTC daily (n=200)	Antiretroviral drug resistance (not specified): 0% (0/4)	0% (0/200)
Hosek 2017[92] Project PrEPare, ATN 113 Observational	A: TDF-FTC daily (n=78)	Antiretroviral drug resistance to TDF or FTC: 0% (0/3)	0% (0/78)
Liu 2016[81] Observational	A: TDF-FTC daily (n=383)	Antiretroviral drug resistance to TDF or FTC: 0% (0/2)	0% (0/383)
Montgomery 2016[127] Observational	A: TDF-FTC daily (n=35)	M184V, D67N, T215S, and K219Q: 100% (1/1)	2.0% (1/50)

*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; iPrEx=Pre-Exposure Prophylaxis Initiative; iPrEx-OLE=Pre-Exposure Prophylaxis Initiative–Open Label Extension; 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.

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 vs. placebo or no PrEP	HIV infection: k=12 RCTs (n=18,244)	11 trials; RR, 0.46 (95% CI, 0.33 to 0.66); I^2=67%; ARR, -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	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=17,756)	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.	Moderate	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
KQ1a. Benefits of PrEP by population subgroups	HIV infection: k=12 RCTs (n=18,244)	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	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.
KQ1b. Benefits of 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 on-demand PrEP (n=535)	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, but not powered to assess effects on HIV infection	Some inconsistency in stratified analyses (may be explained by level of adherence); precise No reporting bias detected	Good	See Body of Evidence Limitations for KQ1, HIV infection.	High for TDF vs. TDF-FTC, moderate for daily dosing vs. on-demand dosing	Five trials evaluated TDF alone, which is not approved for PrEP in the U.S. 1 trial evaluated on-demand dosing of PrEP vs. placebo in MSM; no studies on intermittent or on-demand dosing in women or PWID.

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. Diagnostic accuracy of instruments for identifying persons at risk of incident HIV infection	k=7 studies of risk prediction or diagnostic accuracy (n=32,311)	MSM: AUROC, 0.66 to 0.72 for different instruments in 3 studies; a fourth study reported better goodness of fit than with instruments evaluated in other studies (AUROC NR). AUROC, 0.49 to 0.63 for different instruments in 2 studies of black MSM. PWID: AUROC, 0.72 in 1 study.	Consistent; precise No reporting bias detected	Fair	Retrospective design; each instrument validated in 1 study or not validated in a cohort independent from the one used to develop the instrument; cutoffs not predefined in any study.	Low	All studies conducted in the U.S.; 3 studies used cohorts that included persons who underwent HIV testing prior to the year 2000; no study evaluated a U.S.-applicable instrument for risk prediction in women.
KQ3. Adherence to PrEP in U.S. primary care–applicable settings	k=10 (3 RCTs and 7 observational studies) (n=3,177)	In 5 studies of U.S. MSM, adherence to PrEP (based on dried blood spot sampling levels consistent with ≥4 doses/weeks) ranged from 22% to 90%; adherence rates were lower in studies of younger (mean age, 16 to 20 years) MSM. One RCT of U.S. MSM found higher adherence with daily than intermittent or event-driven PrEP.	Inconsistent; precise No reporting bias detected	Fair	Observational data from implementation studies; variability in duration of PrEP use; high attrition; variability in methods for measuring adherence.	Moderate	Most studies evaluated U.S. MSM; no direct evidence on adherence in U.S. PWID or women and men at increased risk of HIV infection via heterosexual contact; adherence rates were higher in some studies that evaluated a lower threshold for adherence.
KQ4. Association between adherence to PrEP and effectiveness for preventing HIV acquisition	k=12 (7 RCTs and 5 observational studies) (n=11,479)	Three RCTs found higher adherence to PrEP associated with greater effectiveness for reducing risk of HIV infection than lower adherence. Four of 5 RCTs found presence of tenofovir in plasma samples associated with decreased likelihood of HIV infection compared with no detectable tenofovir (ORs ranged from 0.10 to 0.54).	Consistent; precise No reporting bias detected; however, not all RCTs of PrEP reported on the association between adherence and PrEP effectiveness	Good	Findings based on within-study subgroup analyses from RCTs and case-control analyses of patients randomized to PrEP; some studies reported small numbers of seroconverters on PrEP.	High	Studies performed in diverse geographic settings; only 1 study evaluated PWID.

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	Serious adverse events: k=12 (n=18,282)	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	See Applicability for KQ1, HIV infection.
	Withdrawals due to adverse events: k=4 (n=10,563)	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	See Applicability for KQ1, HIV infection.
	Renal adverse events: k=12 (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%)	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	See Applicability for KQ1, HIV infection.
	Gastrointestinal adverse events: k=12 (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%)	Some inconsistency; precise No reporting bias detected	Good	Composite outcome, with no difference for specific gastrointestinal adverse events.	High	See Applicability for KQ1, HIV infection.
	Fracture: k=7 (n=15,241)	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	See Applicability for KQ1, HIV infection.

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, cont.	Syphilis: k=4 (n=10,775)	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	See Applicability for KQ1, HIV infection.
	Gonorrhea: k=5 (n=9,296)	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	See Applicability for KQ1, HIV infection.
	Chlamydia: k=5 (n=9,296)	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	See Applicability for KQ1, HIV infection.
	Combined bacterial STIs: k=2 (n=5,291)	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	See Applicability for KQ1, HIV infection.

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, cont.	Herpes simplex virus infection: k=3 (n=4,103)	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	See Applicability fo KQ1, HIV infection
	Hepatitis C virus infection: k=2 (n=896)	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	See Applicability fo KQ1, HIV infection
	Spontaneous abortion†: k=3 (n=485)	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	Analyses of women at high risk of HIV infection via heterosexual contact who were taken off PrEP at time of pregnancy

*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; KQ=key question; NR=not reported; OR=odds ratio; PrEP=pre-exposure prophylaxis; RCT=randomized, controlled trial; RR=relative risk; STI=sexually transmitted infection; U.S.=United States.

Key Questions 1, 3-5

Database: Ovid MEDLINE(R) without Revisions
1 exp Pre-Exposure Prophylaxis/
2 (preexposure prophylaxis or prep).ti,ab.
3 Anti-HIV Agents/
4 (hiv or "human immunodeficiency virus").ti,ab.
5 (1 or 2) and (3 or 4)
6 limit 5 to english language

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp Pre-Exposure Prophylaxis/
2 (preexposure prophylaxis or prep).ti,ab.
3 Anti-HIV Agents/
4 (hiv or "human immunodeficiency virus").ti,ab.
5 (1 or 2) and (3 or 4)
6 limit 5 to english language

Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 (preexposure prophylaxis or prep).mp.
2 (hiv or "human immunodeficiency virus").mp.
3 1 and 2

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)

Key Question 2

Database: Ovid MEDLINE(R) without Revisions
1 exp HIV Infections/
2 (hiv or "human immunodeficiency virus").mp.
3 exp Risk/
4 ("risk assessment" or "risk factors").mp.
5 exp "Sensitivity and Specificity"/
6 (sensitivity or specificity or "diagnostic accuracy").mp.
7 (1 or 2) and (3 or 4) and (5 or 6)
8 limit 7 to yr="2005 - 2018"

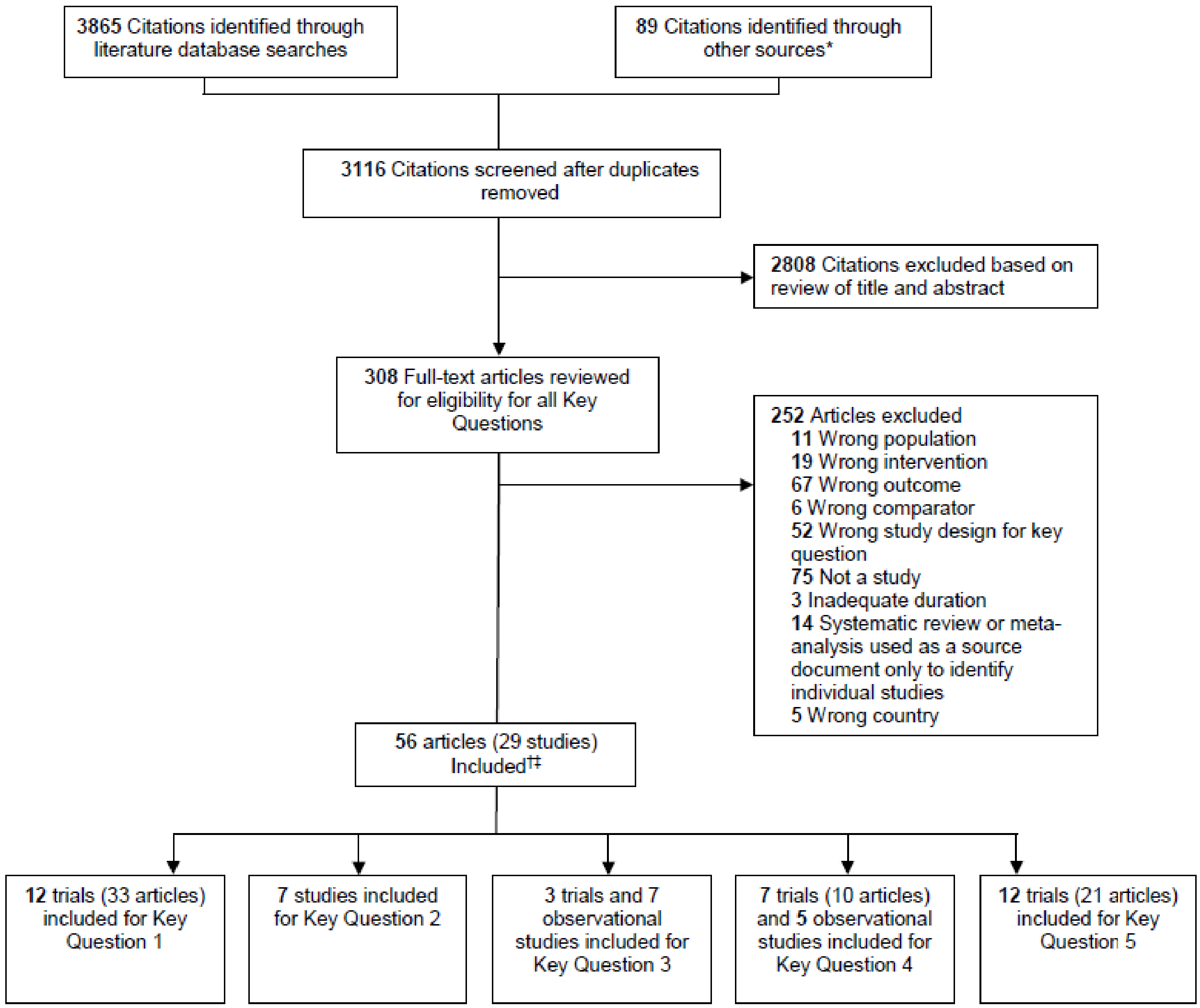
Appendix A2. Inclusion and Exclusion Criteria

	Included	Excluded
Populations	Adolescents (ages 13 to <18 years) and adults (age ≥18 years) without pre-existing HIV infection at increased risk of HIV acquisition*	Persons living with HIV, children
Interventions	Daily or on-demand/intermittent oral antiretroviral therapy with TDF-FTC or TDF	Other PrEP regimens
Comparisons	Placebo or no PrEP (including deferred PrEP)	One PrEP regimen vs. another
Outcomes	Risk of HIV acquisition, quality of life, risk of other sexually transmitted infections, risk of hepatitis C virus infection, renal insufficiency, fracture, pregnancy-related outcomes, and adherence† to PrEP regimen	Outcomes not listed, including condom use
Setting	**All KQs:** Settings in which PrEP is delivered in ways applicable to U.S. primary care settings **KQ 3:** United States or U.S.-relevant countries	Inpatient settings
Study design	Randomized, controlled trials for effectiveness and harms; controlled observational studies for harms‡ if randomized, controlled trials are not available; diagnostic accuracy studies for risk assessment; and longitudinal studies (randomized, controlled trials and controlled or uncontrolled cohort studies) for adherence	

* Including pregnant women.
† Measures of adherence include patient diaries or self-report, pill counts, adherence monitoring devices, biochemical measures (e.g., serum drug levels), and prescription fill data.
‡ Study must perform statistical adjustment for potential confounders to be included.

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

Appendix A3. Literature Flow Diagram



*Other sources include reference lists of relevant articles, studies, and systematic reviews; suggestions from reviewers; and includes background articles.
†Some papers are included in multiple Key Questions.
‡22 articles also addressed the Contextual Questions, of which 19 overlap with the articles that addressed Key Questions.

Appendix A4. Included Studies List

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;19(5):743-51. doi: 10.1007/s10461-014-0859-z. PMID: 25100053.

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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;5(2):e68-e78. doi: 10.1016/S2352-3018(17)30156-X. PMID: 28986029.

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;44(1):48-56. doi: 10.1097/olq.0000000000000535. PMID: 27898570.

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;161(1):11-9. doi: 10.7326/M13-2471. PMID: 24979446.

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.

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;28(2):223-6. doi: 10.1097/QAD.0000000000000102. PMID: 24361682.

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;381(9883):2083-90. doi: 10.1016/S0140-6736(13)61127-7. PMID: 23769234.

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;68(4):439-48. doi: 10.1097/QAI.0000000000000479. PMID: 25501614.

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;2(12):e512-9. doi: 10.1016/S2352-3018(15)00206-4. PMID: 26614965.

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;66(3):340-8. doi: 10.1097/QAI.0000000000000172. PMID: 24784763.

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;14(9):820-9. doi: 10.1016/S1473-3099(14)70847-3. PMID: 25065857.

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Appendix A4. Included Studies List

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Appendix A5. Excluded Studies List

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Anonymous. The safety of tenofovir-emtricitabine for HIV pre-exposure prophylaxis (PrEP) in individuals with active hepatitis B. J Acquir Immune Defic Syndr. 2016 Jul 1;72(3):e82. doi: 10.1097/QAI.0000000000001100. PMID: 27309968. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

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Auerbach JD, Kinsky S, Brown G, et al. Knowledge, attitudes, and likelihood of pre-exposure prophylaxis (PrEP) use among US women at risk of acquiring HIV. AIDS Patient Care STDS. 2015 Feb;29(2):102-10. doi: 10.1089/apc.2014.0142. PMID: 25513954. Excluded: wrong outcome.

Baeten J, Donnell D, Ndase P, et al. Single-agent TDF versus combination FTC/TDF PrEP among heterosexual men and women. Top Antivir Med. START: 2014 Mar 3 CONFERENCE END: 2014 Mar 6, 21st Conference on Retroviruses and Opportunistic Infections, CROI 2014 (21)United States;22(e-1):23. doi: 10.1371/journal.pone.0090111. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

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Baeten JM, Donnell D, Mugo NR, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. Lancet Infect Dis. 2014 Nov;14(11):1055-64. doi: 10.1016/S1473-3099(14)70937-5. PMID: 25300863. Excluded: wrong comparator.

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. Excluded: wrong intervention.

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Baker J, O'Hara KM. Oral preexposure prophylaxis to prevent HIV infection: clinical and public health implications. JAAPA. 2014 Dec;27(12):10-7. doi: 10.1097/01.JAA.0000456567.37724.e0. PMID: 25390822. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

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Baxi SM, Liu A, Bacchetti P, et al. Measuring intermittent and daily PrEP adherence by hair levels, self-report and MEMS caps openings. Top Antivir Med. START: 2014 Mar 3 CONFERENCE END: 2014 Mar 6, 21st Conference on Retroviruses and Opportunistic Infections, CROI 2014 (21)United States;22(e-1):499-500. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Baxi SM, Vittinghoff E, Bacchetti P, et al. Comparing pharmacologic measures of tenofovir exposure in a U.S. pre-exposure prophylaxis randomized trial. PLoS One. 2018;13(1):e0190118. doi: 10.1371/journal.pone.0190118. PMID: 29315307. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

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Bekker LG, Gill K, Wallace M. Pre-exposure prophylaxis for South African adolescents: What evidence? S Afr Med J. 2015 Nov;105(11):907-11. doi: 10.7196/SAMJ.2015.v105i11.10222. PMID: 26632316. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

Bekker LG, Hughes J, Amico R, et al. HPTN 067/ADAPT cape town: A comparison of daily and nondaily PrEP dosing in African women. Top Antivir Med. 2015;23:449-50. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Bekker LG, Johnson L, Cowan F, et al. Combination HIV prevention for female sex workers: what is the evidence? Lancet. 2015 Jan 3;385(9962):72-87. doi: 10.1016/S0140-6736(14)60974-0. PMID: 25059942. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

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Bipath P, Levay P, Olorunju S, et al. A non-specific biomarker of disease activity in HIV/AIDS patients from resource-limited environments. Afr Health Sci. 2015 Jun;15(2):334-43. doi: 10.4314/ahs.v15i2.5. PMID: 26124777. Excluded: wrong outcome.

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Bristow CC, Konda KA, Wong J, et al. Choosing a metric for measurement of pre-exposure prophylaxis. Lancet Infect Dis. 2014 Dec;14(12):1177-8. doi: 10.1016/S1473-3099(14)70989-2. PMID: 25455980. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Brooks RA, Landovitz RJ, Kaplan RL, et al. Sexual risk behaviors and acceptability of HIV pre-exposure prophylaxis among HIV-negative gay and bisexual men in serodiscordant relationships: a mixed methods study. AIDS Patient Care STDS. 2012 Feb;26(2):87-94. doi: 10.1089/apc.2011.0283. PMID: 22149764. Excluded: wrong outcome.

Brooks RA, Landovitz RJ, Regan R, et al. Perceptions of and intentions to adopt HIV pre-exposure prophylaxis among black men who have sex with men in Los Angeles. Int J STD AIDS. 2015 Dec;26(14):1040-8. doi: 10.1177/0956462415570159. PMID: 25638214. Excluded: wrong outcome.

Broz D, Wejnert C, Pham HT, et al. HIV infection and risk, prevention, and testing behaviors among injecting drug users -- National HIV Behavioral Surveillance System, 20 U.S. cities, 2009. MMWR Surveill Summ. 2014 Jul 04;63(6):1-51. PMID: 24990587. Excluded: wrong outcome.

Buchbinder SP, Glidden DV, Liu AY, et al. HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial. Lancet Infect Dis. 2014 Jun;14(6):468-75. doi: 10.1016/S1473-3099(14)70025-8. PMID: 24613084. Excluded: wrong outcome.

Appendix A5. Excluded Studies List

Burns DN, Grossman C, Turpin J, et al. Role of oral pre-exposure prophylaxis (PrEP) in current and future HIV prevention strategies. Curr HIV/AIDS Rep. 2014 Dec;11(4):393-403. doi: 10.1007/s11904-014-0234-8. PMID: 25283184. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Cabral A, J MB, Ngure K, et al. Intimate partner violence and self-reported pre-exposure prophylaxis interruptions among HIV-negative partners in HIV serodiscordant couples in Kenya and Uganda. J Acquir Immune Defic Syndr. 2018 Feb 01;77(2):154-9. doi: 10.1097/QAI.0000000000001574. PMID: 29076883. Excluded: wrong outcome.

Cailhol J, Rouyer C, Alloui C, et al. Dolutegravir and neuropsychiatric adverse events: a continuing debate. AIDS. 2017 Sep 10;31(14):2023-4. doi: 10.1097/qad.0000000000001596. PMID: 28857781. Excluded: inadequate duration.

Calabrese SK, Magnus M, Mayer KH, et al. Putting PrEP into practice: Lessons learned from early-adopting U.S. providers' firsthand experiences providing HIV pre-exposure prophylaxis and associated care. PLoS One. 2016;11(6):e0157324. doi: 10.1371/journal.pone.0157324. PMID: 27304883. Excluded: wrong outcome.

Calabrese SK, Underhill K, Earnshaw VA, et al. Framing HIV pre-exposure prophylaxis (PrEP) for the general public: How inclusive messaging may prevent prejudice from diminishing public support. AIDS Behav. 2016 Jul;20(7):1499-513. doi: 10.1007/s10461-016-1318-9. PMID: 26891840. Excluded: wrong outcome.

Callahan R, Nanda K, Kapiga S, et al. Pregnancy and contraceptive use among women participating in the FEM-PrEP trial. J Acquir Immune Defic Syndr. 2015 Feb 1;68(2):196-203. doi: 10.1097/QAI.0000000000000413. PMID: 25590272. Excluded: wrong outcome.

Cambiano V, Miners A, Dunn D, et al. Cost-effectiveness of pre-exposure prophylaxis for HIV prevention in men who have sex with men in the UK: a modelling study and health economic evaluation. Lancet Infect Dis. 2018 Jan;18(1):85-94. doi: 10.1016/S1473-3099(17)30540-6. PMID: 29054789. Excluded: wrong study design for Key Question.

Carballo-Dieguez A, Balan IC, Brown W, 3rd, et al. High levels of adherence to a rectal microbicide gel and to oral Pre-Exposure Prophylaxis (PrEP) achieved in MTN-017 among men who have sex with men (MSM) and transgender women. PLoS One. 2017;12(7):e0181607. doi: 10.1371/journal.pone.0181607. PMID: 28750059. Excluded: wrong population.

Carballo-Dieguez A, Giguere R, Dolezal C, et al. Preference of oral tenofovir disoproxil fumarate/emtricitabine versus rectal tenofovir reduced-glycerin 1% gel regimens for HIV prevention among cisgender men and transgender women who engage in receptive anal intercourse with men. AIDS Behav. 2017 Dec;21(12):3336-45. doi: 10.1007/s10461-017-1969-1. PMID: 29119473. Excluded: wrong comparator.

Carnegie NB, Goodreau SM, Liu A, et al. Targeting pre-exposure prophylaxis among men who have sex with men in the United States and Peru: partnership types, contact rates, and sexual role. J Acquir Immune Defic Syndr. 2015 May 1;69(1):119-25. doi: 10.1097/QAI.0000000000000555. PMID: 25942463. Excluded: wrong study design for Key Question.

Carney EF. Clinical trials. Renal safety of TDF as pre-exposure prophylaxis for HIV-1 infection. Nat Rev Nephrol. 2015 Mar;11(3):127. doi: 10.1038/nrneph.2015.1. PMID: 25599622. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

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. Excluded: wrong population.

CDC. HIV testing and risk behaviors among gay, bisexual, and other men who have sex with men - United States. MMWR Morb Mortal Wkly Rep. 2013 Nov 29;62(47):958-62. PMID: 24280915. Excluded: wrong outcome.

Celum C, Baeten JM. Tenofovir-based pre-exposure prophylaxis for HIV prevention: evolving evidence. Curr Opin Infect Dis. 2012 Feb;25(1):51-7. doi: 10.1097/QCO.0b013e32834ef5ef. PMID: 22156901. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Celum C, Baeten JM. Antiretroviral-based HIV-1 prevention: antiretroviral treatment and pre-exposure prophylaxis. Antivir Ther. 2012;17(8):1483-93. doi: 10.3851/IMP2492. PMID: 23221365. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Celum CL. HIV preexposure prophylaxis: new data and potential use. Top Antivir Med. 2011 Dec;19(5):181-5. PMID: 22298887. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Celum CL, Delany-Moretlwe S, McConnell M, et al. Rethinking HIV prevention to prepare for oral PrEP implementation for young African women. J Int AIDS Soc. 2015;18(4 Suppl 3):20227. doi: 10.7448/IAS.18.4.20227. PMID: 26198350. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Centers for Disease Control and Prevention. Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. MMWR Morb Mortal Wkly Rep. 2011 Jan 28;60(3):65-8. PMID: 21270743. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Centers for Disease Control and Prevention. Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults. MMWR Morb Mortal Wkly Rep. 2012 Aug 10;61(31):586-9. PMID: 22874836. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Chakrapani V, Newman PA, Shunmugam M, et al. Acceptability of HIV pre-exposure prophylaxis (PrEP) and implementation challenges among men who have sex with men in India: a qualitative investigation. AIDS Patient Care STDS. 2015 Oct;29(10):569-77. doi: 10.1089/apc.2015.0143. PMID: 26348459. Excluded: wrong outcome.

Chan L, Asriel B, Eaton EF, et al. Potential kidney toxicity from the antiviral drug tenofovir: new indications, new formulations, and a new prodrug. Curr Opin Nephrol Hypertens. 2018 03;27(2):102-12. doi: 10.1097/MNH.0000000000000392. PMID: 29278542. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Chan PA, Rose J, Maher J, et al. A latent class analysis of risk factors for acquiring HIV among men who have sex with men: Implications for implementing pre-exposure prophylaxis programs. AIDS Patient Care STDS. 2015 Nov;29(11):597-605. doi: 10.1089/apc.2015.0113. PMID: 26389735. Excluded: wrong intervention.

Chan R. Biomedical strategies for human immunodeficiency virus (HIV) prevention? A new paradigm. Ann Acad Med Singapore. 2012 Dec;41(12):595-601. PMID: 23303118. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Chen A, Dowdy DW. Clinical effectiveness and cost-effectiveness of HIV pre-exposure prophylaxis in men who have sex with men: risk calculators for real-world decision-making. PLoS One. 2014;9(10):e108742. doi: 10.1371/journal.pone.0108742. PMID: 25285793. Excluded: wrong study design for Key Question.

Chua A, Ford N, Wilson D, et al. The tenofovir pre-exposure prophylaxis trial in Thailand: Researchers should show more openness in their engagement with the community [1] (multiple letters). PLoS Med. 2005;2(10):1044-6. doi: 10.1371/journal.pmed.0020346. PMID: 16231979. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Cid-Silva P, Llibre JM, Fernandez-Bargiela N, et al. Clinical experience with the integrase inhibitors dolutegravir and elvitegravir in HIV-infected patients: Efficacy, safety and tolerance. Basic Clin Pharmacol Toxicol. 2017 Nov;121(5):442-6. doi: 10.1111/bcpt.12828. PMID: 28627771. Excluded: inadequate duration.

Clutter DS, Jordan MR, Bertagnolio S, et al. HIV-1 drug resistance and resistance testing. Infect Genet Evol. 2016 1;46:292-307. PMID: 27587334. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 Transmission. N Engl J Med. 2016 Jul 18doi: 10.1056/NEJMoa1600693. PMID: 27424812. Excluded: wrong intervention.

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. Excluded: wrong population.

Cohen MS, Muessig KE, Smith MK, et al. Antiviral agents and HIV prevention: controversies, conflicts, and consensus. AIDS. 2012 Aug 24;26(13):1585-98. doi: 10.1097/QAD.0b013e3283543e83. PMID: 22507927. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Colby D, Srithanaviboonchai K, Vanichseni S, et al. HIV pre-exposure prophylaxis and health and community systems in the global south: Thailand case study. J Int AIDS Soc. 2015;18(4 Suppl 3):19953. doi: 10.7448/IAS.18.4.19953. PMID: 26198342. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Collier KL, Colarossi LG, Sanders K. A PrEP information and self-screening tool for women. AIDS Educ Prev. 2018 Feb;30(1):13-25. doi: 10.1521/aeap.2018.30.1.13. PMID: 29481302. Excluded: wrong study design for Key Question.

Conniff J, Evensen A. Preexposure prophylaxis (PrEP) for HIV prevention: The primary care perspective. J Am Board Fam Med. 2016 Jan-Feb;29(1):143-51. doi: 10.3122/jabfm.2016.01.150223. PMID: 26769887. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Coovadia H, Moodley D. Improving HIV pre-exposure prophylaxis for infants. Lancet. 2016 Feb 6;387(10018):513-4. doi: 10.1016/S0140-6736(15)00983-6. PMID: 26603916. Excluded: wrong population.

Corneli A, Field S, Namey E, et al. Preparing for the rollout of pre-exposure prophylaxis (PrEP): A vignette survey to identify intended sexual behaviors among women in Kenya and South Africa if using PrEP. PLoS One. 2015;10(6):e0129177. doi: 10.1371/journal.pone.0129177. PMID: 26056842. Excluded: wrong study design for Key Question.

Corneli A, Namey E, Ahmed K, et al. Motivations for reducing other HIV risk-reduction practices if taking pre-exposure prophylaxis: Findings from a qualitative study among women in Kenya and South Africa. AIDS Patient Care STDS. 2015 Sep;29(9):503-9. doi: 10.1089/apc.2015.0038. PMID: 26196411. Excluded: wrong outcome.

Appendix A5. Excluded Studies List

Corneli A, Perry B, Agot K, et al. Facilitators of adherence to the study pill in the FEM-PrEP clinical trial. PLoS One. 2015;10(4):e0125458. doi: 10.1371/journal.pone.0125458. PMID: 25867624. Excluded: wrong outcome.

Corneli A, Wang M, Agot K, et al. Perception of HIV risk and adherence to a daily, investigational pill for HIV prevention in FEM-PrEP. J Acquir Immune Defic Syndr. 2014 Dec 15;67(5):555-63. doi: 10.1097/QAI.0000000000000362. PMID: 25393942. Excluded: wrong outcome.

Corneli AL, McKenna K, Headley J, et al. A descriptive analysis of perceptions of HIV risk and worry about acquiring HIV among FEM-PrEP participants who seroconverted in Bondo, Kenya, and Pretoria, South Africa. J Int AIDS Soc. 2014;17(3 Suppl 2):19152. doi: 10.7448/IAS.17.3.19152. PMID: 25224613. Excluded: wrong outcome.

Cremin I, Morales F, Jewell BL, et al. Seasonal PrEP for partners of migrant miners in southern Mozambique: a highly focused PrEP intervention.[Erratum appears in J Int AIDS Soc. 2016;19(1):20948; PMID: 26905056]. J Int AIDS Soc. 2015;18(4 Suppl 3):19946. doi: 10.7448/IAS.18.4.19946. PMID: 26198340. Excluded: wrong study design for Key Question.

Curlin ME, Martin MT, Wasinrapee P, et al. Effect of TDF monotherapy PrEP on immune function in seroconverting individuals. Top Antivir Med. 2015;23(453). Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Dai JY, Gilbert PB, Hughes JP, et al. Estimating the efficacy of preexposure prophylaxis for HIV prevention among participants with a threshold level of drug concentration. Am J Epidemiol. 2013 Feb 1;177(3):256-63. doi: 10.1093/aje/kws324. PMID: 23302152. Excluded: wrong outcome.

Damery S, Nichols L, Holder R, et al. Assessing the predictive value of HIV indicator conditions in general practice: a case-control study using the THIN database. Br J Gen Pract. 2013 Jun;63(611):e370-7. doi: 10.3399/bjgp13X668159. PMID: 23735407. Excluded: wrong intervention.

Daughtridge GW, Conyngham SC, Ramirez N, et al. I am men's health: Generating adherence to HIV pre-exposure prophylaxis (PrEP) in young men of color who have sex with men. J Int Assoc Provid AIDS Care. 2015 Mar-Apr;14(2):103-7. doi: 10.1177/2325957414555230. PMID: 25331226. Excluded: wrong outcome.

de Lastours V, Fonsart J, Burlacu R, et al. Concentrations of tenofovir and emtricitabine in saliva: implications for preexposure prophylaxis of oral HIV acquisition. Antimicrob Agents Chemother. 2011 Oct;55(10):4905-7. doi: 10.1128/AAC.00120-11. PMID: 21788466. Excluded: wrong outcome.

Defechereux PA, Mehrotra M, Liu AY, et al. Depression and oral FTC/TDF pre-exposure prophylaxis (PrEP) among men and transgender women who have sex with men (MSM/TGW). AIDS Behav. 2016 Jul;20(7):1478-88. doi: 10.1007/s10461-015-1082-2. PMID: 26078115. Excluded: wrong outcome.

Dijkstra M, de Bree GJ, Stolte IG, et al. Development and validation of a risk score to assist screening for acute HIV-1 infection among men who have sex with men. BMC Infect Dis. 2017 Jun 14;17(1):425. doi: 10.1186/s12879-017-2508-4. PMID: 28615005. Excluded: wrong population.

Dimitrov DT, Masse BR, Donnell D. PrEP adherence patterns strongly affect individual HIV risk and observed efficacy in randomized clinical trials. J Acquir Immune Defic Syndr. 2016 Aug 1;72(4):444-51. doi: 10.1097/QAI.0000000000000993. PMID: 26990823. Excluded: wrong study design for Key Question.

Dolezal C, Frasca T, Giguere R, et al. Awareness of post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) is low but interest is high among men engaging in condomless anal sex with men in Boston, Pittsburgh, and San Juan. AIDS Educ Prev. 2015 Aug;27(4):289-97. doi: 10.1521/aeap.2015.27.4.289. PMID: 26241380. Excluded: wrong outcome.

Dolling DI, Desai M, McOwan A, et al. An analysis of baseline data from the PROUD study: an open-label randomised trial of pre-exposure prophylaxis. Trials. 2016;17(1):163. doi: 10.1186/s13063-016-1286-4. PMID: 27013513. Excluded: wrong outcome.

Donnell D, Hughes JP, Wang L, et al. Study design considerations for evaluating efficacy of systemic preexposure prophylaxis interventions. J Acquir Immune Defic Syndr. 2013 Jul;63 Suppl 2:S130-4. doi: 10.1097/QAI.0b013e3182986fac. PMID: 23764624. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Donnell D, Ramos E, Celum C, et al. The effect of oral preexposure prophylaxis on the progression of HIV-1 seroconversion. AIDS. 2017 Sep 10;31(14):2007-16. doi: 10.1097/QAD.0000000000001577. PMID: 28692542. Excluded: wrong outcome.

Dumond JB, Yeh RF, Patterson KB, et al. Antiretroviral drug exposure in the female genital tract: implications for oral pre- and post-exposure prophylaxis. AIDS. 2007 Sep 12;21(14):1899-907. PMID: 17721097. Excluded: wrong outcome.

Appendix A5. Excluded Studies List

Eaton LA, Driffin DD, Smith H, et al. Psychosocial factors related to willingness to use pre-exposure prophylaxis for HIV prevention among Black men who have sex with men attending a community event. Sex Health. 2014 Jul;11(3):244-51. doi: 10.1071/SH14022. PMID: 25001553. Excluded: wrong outcome.

Eccles-Radtke C, Henry K. Turning the tide against AIDS by preventing new HIV infections initial experience with Minnesota's first PrEP clinic. Minn Med. 2015 Jan;98(1):45-8. PMID: 25665269. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

Eisingerich AB, Wheelock A, Gomez GB, et al. Attitudes and acceptance of oral and parenteral HIV preexposure prophylaxis among potential user groups: a multinational study. PLoS One. 2012;7(1):e28238. doi: 10.1371/journal.pone.0028238. PMID: 22247757. Excluded: wrong outcome.

Elion R, Coleman M. The preexposure prophylaxis revolution: from clinical trials to routine practice: implementation view from the USA. Curr Opin HIV AIDS. 2016 Jan;11(1):67-73. doi: 10.1097/COH.0000000000000222. PMID: 26599165. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Elsesser SA, Oldenburg CE, Biello KB, et al. Seasons of risk: Anticipated behavior on vacation and interest in episodic antiretroviral pre-exposure prophylaxis (PrEP) among a large national sample of U.S. men who have sex with men (MSM). AIDS Behav. 2016 Jul;20(7):1400-7. doi: 10.1007/s10461-015-1238-0. PMID: 26538056. Excluded: wrong outcome.

Escudero DJ, Kerr T, Operario D, et al. Inclusion of trans women in pre-exposure prophylaxis trials: a review. AIDS Care. 2015;27(5):637-41. doi: 10.1080/09540121.2014.986051. PMID: 25430940. Excluded: wrong outcome.

Escudero DJ, Lurie MN, Kerr T, et al. HIV pre-exposure prophylaxis for people who inject drugs: a review of current results and an agenda for future research. J Int AIDS Soc. 2014;17:18899. doi: 10.7448/IAS.17.1.18899. PMID: 24679634. Excluded: wrong study design for Key Question.

Excler JL, Rida W, Priddy F, et al. AIDS vaccines and preexposure prophylaxis: is synergy possible? AIDS Res Hum Retroviruses. 2011 Jun;27(6):669-80. doi: 10.1089/AID.2010.0206. PMID: 21043994. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Farcasanu M, Kwon DS. The influence of cervicovaginal microbiota on mucosal immunity and prophylaxis in the battle against HIV. Curr HIV/AIDS Rep. 2018 Feb;15(1):30-8. doi: 10.1007/s11904-018-0380-5. PMID: 29516267. Excluded: wrong study design for Key Question.

Fernandez-Montero JV, Barreiro P, Del Romero J, et al. Antiretroviral drugs for pre-exposure prophylaxis of HIV infection. AIDS Rev. 2012 Jan-Mar;14(1):54-61. PMID: 22297504. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

Flash C, Landovitz R, Giler RM, et al. Two years of Truvada for pre-exposure prophylaxis utilization in the US. J Int AIDS Soc. 2014;17(4 Suppl 3):19730. doi: 10.7448/IAS.17.4.19730. PMID: 25397476. Excluded: wrong study design for Key Question.

Flash CA, Stone VE, Mitty JA, et al. Perspectives on HIV prevention among urban black women: a potential role for HIV pre-exposure prophylaxis. AIDS Patient Care STDS. 2014 Dec;28(12):635-42. doi: 10.1089/apc.2014.0003. PMID: 25295393. Excluded: wrong outcome.

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. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

Ford N, Shubber Z, Calmy A, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: a systematic review. Clin Infect Dis. 2015 Jun 1;60 Suppl 3:S170-6. doi: 10.1093/cid/civ092. PMID: 25972499. Excluded: wrong intervention.

Franks J, Hirsch-Moverman Y, Loquere AS, Jr., et al. Sex, PrEP, and stigma: Experiences with HIV pre-exposure prophylaxis among New York City MSM participating in the HPTN 067/ADAPT study. Aids Behav. 2018 Apr;22(4):1139-49. doi: 10.1007/s10461-017-1964-6. PMID: 29143163. Excluded: wrong outcome.

Fransen K, de Baetselier I, Rammutla E, et al. Detection of new HIV infections in a multicentre HIV antiretroviral pre-exposure prophylaxis trial. J Clin Virol. 2017 Aug;93:76-80. doi: 10.1016/j.jcv.2017.03.013. PMID: 28351689. Excluded: wrong study design for Key Question.

Fu R, Owens DK, Brandeau ML. Cost-effectiveness of alternative strategies for provision of HIV preexposure prophylaxis for people who inject drugs. AIDS. 2018 Mar 13;32(5):663-72. doi: 10.1097/QAD.0000000000001747. PMID: 29334549. Excluded: wrong outcome.

Appendix A5. Excluded Studies List

Gandhi M, Glidden DV, Mayer K, et al. Association of age, baseline kidney function, and medication exposure with declines in creatinine clearance on pre-exposure prophylaxis: an observational cohort study. Lancet HIV. 2016 Nov;3(11):e521-e8. doi: 10.1016/s2352-3018(16)30153-9. PMID: 27658870. Excluded: wrong study design for Key Question.

Gatey C, Pintado C, Chas J, et al. [Pre-exposure prophylaxis of HIV infection]. Rev Prat. 2014 Oct;64(8):1073-5. PMID: 25510128. Excluded: not English language but possibly relevant.

Glidden DV, Mulligan K, McMahan V, et al. Brief report: Recovery of bone mineral density after discontinuation of tenofovir-based HIV pre-exposure prophylaxis. J Acquir Immune Defic Syndr. 2017 Oct 01;76(2):177-82. doi: 10.1097/QAI.0000000000001475. PMID: 28639995. Excluded: wrong outcome.

Goodreau SM, Hamilton DT, Jenness SM, et al. Targeting human immunodeficiency virus pre-exposure prophylaxis to adolescent sexual minority males in higher prevalence areas of the United States: A modeling study. J Adolesc Health. 2018 Mar;62(3):311-9. doi: 10.1016/j.jadohealth.2017.09.023. PMID: 29248392. Excluded: wrong study design for Key Question.

Grant RM, Liegler T. Weighing the risk of drug resistance with the benefits of HIV preexposure prophylaxis. J Infect Dis. 2015 Apr 15;211(8):1202-4. doi: 10.1093/infdis/jiu678. PMID: 25587019. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Grinsztejn B, Hoagland B, Moreira RI, et al. Retention, engagement, and adherence to pre-exposure prophylaxis for men who have sex with men and transgender women in PrEP Brasil: 48 week results of a demonstration study. Lancet HIV. 2018 03;5(3):e136-e45. doi: 10.1016/S2352-3018(18)30008-0. PMID: 29467098. Excluded: wrong country.

Guest G, Shattuck D, Johnson L, et al. Changes in sexual risk behavior among participants in a PrEP HIV prevention trial. Sex Transm Dis. 2008 Dec;35(12):1002-8. PMID: 19051397. Excluded: wrong study design for Key Question.

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. Excluded: wrong comparator.

Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel. JAMA. 2016 Jul 12;316(2):191-210. doi: 10.1001/jama.2016.8900. PMID: 27404187. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

Haberer JE, Bangsberg DR, Baeten JM, et al. Defining success with HIV pre-exposure prophylaxis: a prevention-effective adherence paradigm. AIDS. 2015 Jul 17;29(11):1277-85. doi: 10.1097/QAD.0000000000000647. PMID: 26103095. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Haberer JE, Kidoguchi L, Heffron R, et al. Alignment of adherence and risk for HIV acquisition in a demonstration project of pre-exposure prophylaxis among HIV serodiscordant couples in Kenya and Uganda: a prospective analysis of prevention-effective adherence. J Int AIDS Soc. 2017 07 25;20(1):21842. doi: 10.7448/IAS.20.1.21842. PMID: 28741331. Excluded: wrong outcome.

Hankins C, Macklin R, Warren M. Translating PrEP effectiveness into public health impact: key considerations for decision-makers on cost-effectiveness, price, regulatory issues, distributive justice and advocacy for access. J Int AIDS Soc. 2015;18(4 Suppl 3):19973. doi: 10.7448/IAS.18.4.19973. PMID: 26198343. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Hannaford A, Lipshie-Williams M, Starrels JL, et al. The use of online posts to identify barriers to and facilitators of HIV pre-exposure prophylaxis (PrEP) among men who have sex with men: A comparison to a systematic review of the peer-reviewed literature. Aids Behav. 2018 Apr;22(4):1080-95. doi: 10.1007/s10461-017-2011-3. PMID: 29285638. Excluded: wrong outcome.

Haukoos JS, Hopkins E, Bender B, et al. Comparison of enhanced targeted rapid HIV screening using the Denver HIV risk score to nontargeted rapid HIV screening in the emergency department. Ann Emerg Med. 2013 Mar;61(3):353-61. doi: 10.1016/j.annemergmed.2012.10.031. PMID: 23290527. Excluded: wrong population.

Haukoos JS, Hopkins E, Bucossi MM, et al. Brief report: Validation of a quantitative HIV risk prediction tool using a national HIV testing cohort. J Acquir Immune Defic Syndr. 2015 Apr 15;68(5):599-603. doi: 10.1097/qai.0000000000000518. PMID: 25585300. Excluded: wrong population.

Haukoos JS, Lyons MS, Lindsell CJ, et al. Derivation and validation of the Denver Human Immunodeficiency Virus (HIV) risk score for targeted HIV screening. Am J Epidemiol. 2012 Apr 15;175(8):838-46. doi: 10.1093/aje/kwr389. PMID: 22431561. Excluded: wrong population.

Appendix A5. Excluded Studies List

Havens PL, Stephensen CB, Van Loan MD, et al. Decline in bone mass with tenofovir disoproxil fumarate/emtricitabine is associated with hormonal changes in the absence of renal impairment when used by HIV-uninfected adolescent boys and young men for HIV preexposure prophylaxis. Clin Infect Dis. 2017 Feb 01;64(3):317-25. doi: 10.1093/cid/ciw765. PMID: 28013265. Excluded: wrong study design for Key Question.

Hazen R, Hou JG, Kirkham H, et al. Exploring length of therapy and factors associated with HIV pre-exposure prophylaxis medication adherence using pharmacy claims data. Value in Health. 2017;20(5):A10-A1. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Headley J, Lemons A, Corneli A, et al. The sexual risk context among the FEM-PrEP study population in Bondo, Kenya and Pretoria, South Africa. PLoS One. 2014;9(9):e106410. doi: 10.1371/journal.pone.0106410. PMID: 25229403. Excluded: wrong outcome.

Heffron R, Ngure K, Odoyo J, et al. Pre-exposure prophylaxis for HIV-negative persons with partners living with HIV: uptake, use, and effectiveness in an open-label demonstration project in East Africa. Gates Open Res. 2017 Nov 06;1:3. doi: 10.12688/gatesopenres.12752.1. PMID: 29355231. Excluded: wrong study design for Key Question.

Heffron R, Pintye J, Matthews LT, et al. PrEP as peri-conception HIV prevention for women and men. Curr HIV/AIDS Rep. 2016 Jun;13(3):131-9. doi: 10.1007/s11904-016-0312-1. PMID: 26993627. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

Heffron R, Thomson K, Celum C, et al. Fertility intentions, pregnancy, and use of PrEP and ART for safer conception among East African HIV serodiscordant couples. Aids Behav. 2018 Jun;22(6):1758-65. doi: 10.1007/s10461-017-1902-7. PMID: 28894986. Excluded: wrong study design for Key Question.

Hoagland B, Moreira RI, De Boni RB, et al. High pre-exposure prophylaxis uptake and early adherence among men who have sex with men and transgender women at risk for HIV Infection: the PrEP Brasil demonstration project. J Int AIDS Soc. 2017 Apr 06;20(1):1-14. doi: 10.7448/IAS.20.1.21472. PMID: 28418232. Excluded: wrong outcome.

Hoenigl M, Jain S, Moore DJ, et al. Substance-using MSM on HIV preexposure prophylaxis have better adherence. Top Antivir Med. 2017;25(1):413s-4s. Excluded: wrong intervention.

Hoffman RM, Jaycocks A, Vardavas R, et al. Benefits of PrEP as an adjunctive method of HIV prevention during attempted conception between HIV-uninfected women and HIV-infected male partners. J Infect Dis. 2015 Nov 15;212(10):1534-43. doi: 10.1093/infdis/jiv305. PMID: 26092856. Excluded: wrong study design for Key Question.

Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017 Jan;18(1):56-63. doi: 10.1111/hiv.12468. PMID: 27860104. Excluded: inadequate duration.

Hojilla JC, Vlahov D, Crouch PC, et al. HIV pre-exposure prophylaxis (PrEP) uptake and retention among men who have sex with men in a community-based sexual health clinic. Aids Behav. 2018 Apr;22(4):1096-9. doi: 10.1007/s10461-017-2009-x. PMID: 29243109. Excluded: wrong study design for Key Question.

Hojilla JC, Vlahov D, Glidden DV, et al. Skating on thin ice: stimulant use and sub-optimal adherence to HIV pre-exposure prophylaxis. J Int AIDS Soc. 2018 Mar;21(3):e25103. doi: 10.1002/jia2.25103. PMID: 29577616. Excluded: wrong outcome.

Hosek SG. HIV pre-exposure prophylaxis diffusion and implementation issues in nonclinical settings. Am J Prev Med. 2013 Jan;44(1 Suppl 2):S129-32. doi: 10.1016/j.amepre.2012.09.032. PMID: 23253753. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Hsieh YH, Haukoos JS, Rothman RE. Validation of an abbreviated version of the Denver HIV risk score for prediction of HIV infection in an urban ED. Am J Emerg Med. 2014 Jul;32(7):775-9. doi: 10.1016/j.ajem.2014.02.043. PMID: 24768338. Excluded: wrong population.

Huang YA, Tao G, Samandari T, et al. Laboratory testing of a cohort of commercially insured users of HIV preexposure prophylaxis in the United States, 2011-2015. J Infect Dis. 2018 Jan 30;217(4):617-21. doi: 10.1093/infdis/jix595. PMID: 29145597. Excluded: wrong outcome.

Joseph Davey DL, Bekker LG, Gorbach PM, et al. Delivering preexposure prophylaxis to pregnant and breastfeeding women in sub-Saharan Africa: The implementation science frontier. AIDS. 2017;31(16):2193-7. doi: 10.1097/QAD.0000000000001604. PMID: 28723709. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Jotwani V, Scherzer R, Glidden DV, et al. Pre-exposure prophylaxis with tenofovir disoproxil fumarate/emtricitabine and kidney tubular dysfunction in HIV-uninfected individuals. J Acquir Immune Defic Syndr. 2018 Jun 01;78(2):169-74. doi: 10.1097/QAI.0000000000001654. PMID: 29767638. Excluded: wrong outcome.

Appendix A5. Excluded Studies List

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. Excluded: wrong country.

Kelesidis T, Landovitz RJ. Preexposure prophylaxis for HIV prevention. Curr HIV/AIDS Rep. 2011 Jun;8(2):94-103. doi: 10.1007/s11904-011-0078-4. PMID: 21465112. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Kenyon C, Colebunders R. Antiretroviral preexposure prophylaxis for HIV prevention. N Engl J Med. 2013 Jan 3;368(1):82. doi: 10.1056/NEJMc1210464#SA2. PMID: 23281987. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Kmietowicz Z. Pre-exposure prophylaxis protects against HIV infection in real world setting, study finds. BMJ. 2015;350:h1076. doi: 10.1136/bmj.h1076. PMID: 25716462. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Koechlin F, Fonner V, et al. Values and preferences on the use of oral pre-exposure prophylaxis (PrEP) for HIV prevention among populations: a systematic review of the literature. AIDS Behav. 2017;21:1325-35. PMID: 27900502. Excluded: wrong outcome.

Koester KA, Liu A, Eden C, et al. Acceptability of drug detection monitoring among participants in an open-label pre-exposure prophylaxis study. AIDS Care. 2015;27(10):1199-204. doi: 10.1080/09540121.2015.1039958. PMID: 26001026. Excluded: wrong study design for Key Question.

Krakower D, Ware N, Mitty JA, et al. HIV providers' perceived barriers and facilitators to implementing pre-exposure prophylaxis in care settings: a qualitative study. AIDS Behav. 2014 Sep;18(9):1712-21. doi: 10.1007/s10461-014-0839-3. PMID: 24965676. Excluded: wrong outcome.

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. Excluded: wrong outcome.

Lal L, Audsley J, Murphy DA, et al. Medication adherence, condom use and sexually transmitted infections in Australian preexposure prophylaxis users. AIDS. 2017 Jul 31;31(12):1709-14. doi: 10.1097/QAD.0000000000001519. PMID: 28700394. Excluded: wrong outcome.

Lasry A, Sansom SL, Wolitski RJ, et al. HIV sexual transmission risk among serodiscordant couples: assessing the effects of combining prevention strategies. AIDS. 2014 Jun 19;28(10):1521-9. doi: 10.1097/QAD.0000000000000307. PMID: 24804859. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

Lehman DA, Baeten J, McCoy C, et al. PrEP exposure and the risk of low-frequency drug resistance. Top Antivir Med. START: 2014 Mar 3 CONFERENCE END: 2014 Mar 6, 21st Conference on Retroviruses and Opportunistic Infections, CROI 2014 (21)United States;22(e-1):290-1. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Liegler T, Abdel-Mohsen M, Defechereux P, et al. Drug resistance among HIV-1 seroconverters in the FEM-PrEP Study. Antivir Ther. 2012;17(5). Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Lippman SA, Koester KA, Amico KR, et al. Client and provider perspectives on new HIV prevention tools for MSM in the Americas. PLoS One. 2015;10(3):e0121044. doi: 10.1371/journal.pone.0121044. PMID: 25826246. Excluded: wrong study design for Key Question.

Liu A, Cohen S, Follansbee S, et al. Early experiences implementing pre-exposure prophylaxis (PrEP) for HIV prevention in San Francisco. PLoS Med. 2014 Mar;11(3):e1001613. doi: 10.1371/journal.pmed.1001613. PMID: 24595035. Excluded: wrong study design for Key Question.

Liu C, Ding Y, Ning Z, et al. Factors influencing uptake of pre-exposure prophylaxis: some qualitative insights from an intervention study of men who have sex with men in China. Sexual Health. 2018 Feb;15(1):39-45. doi: 10.1071/SH17075. PMID: 28859729. Excluded: wrong outcome.

Luz PM, Osher B, Grinsztejn B, et al. The cost-effectiveness of HIV pre-exposure prophylaxis in men who have sex with men and transgender women at high risk of HIV infection in Brazil. J Int AIDS Soc. 2018 Mar;21(3):e25096. doi: 10.1002/jia2.25096. PMID: 29603888. Excluded: wrong outcome.

Machado DM, de Sant'Anna Carvalho AM, Riera R. Adolescent pre-exposure prophylaxis for HIV prevention: current perspectives. Adolesc Health Med Ther. 2017;8:137-48. doi: 10.2147/AHMT.S112757. PMID: 29238237. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

Appendix A5. Excluded Studies List

Madrasi K, Chaturvedula A, Haberer JE, et al. Markov mixed effects modeling using electronic adherence monitoring records identifies influential covariates to HIV preexposure prophylaxis. J Clin Pharmacol. doi: 10.1002/jcph.843. PMID: 27922719. Excluded: wrong study design for Key Question.

Manavi K, Clutterbuck D, Mackay R, et al. A rapid method for identifying high-risk patients consenting for HIV testing: introducing The Edinburgh Risk Assessment Table for HIV testing. Int J STD AIDS. 2006 Apr;17(4):234-6. PMID: 16595045. Excluded: wrong intervention.

Mannheimer S, Hirsch-Moverman Y, Loquere A, et al. HPTN 067/ADAPT study: A comparison of daily and intermittent pre-exposure prophylaxis dosing for HIV prevention in men who have sex with men and transgender women in New York city. J Int AIDS Soc. 2015;18:24-5. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Marcus JL, Glidden DV, Mayer KH, et al. No evidence of sexual risk compensation in the iPrEx trial of daily oral HIV preexposure prophylaxis. PLoS One. 2013;8(12):e81997. doi: 10.1371/journal.pone.0081997. PMID: 24367497. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Marrazzo J, Rabe L, Kelly C, et al. Herpes simplex virus (HSV) infection in the VOICE (MTN 003) study: Pre-exposure prophylaxis (PrEP) for HIV with daily use of oral tenofovir, oral tenofovir-emtricitabine, or vaginal tenofovir gel. Sex Transm Dis. 2013;89(14). Excluded: wrong study design for Key Question.

Marshall BD, Mimiaga MJ. Uptake and effectiveness of PrEP for transgender women. Lancet HIV. 2015 Dec;2(12):e502-3. doi: 10.1016/S2352-3018(15)00224-6. PMID: 26614960. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Martin M, Vanichseni S, Suntharasamai P, et al. Enrollment characteristics and risk behaviors of injection drug users participating in the Bangkok Tenofovir Study, Thailand. PLoS One. 2011;6(9):e25127. doi: 10.1371/journal.pone.0025127. PMID: 21969870. Excluded: wrong intervention.

Martin M, Vanichseni S, Suntharasamai P, et al. Risk behaviors and risk factors for HIV infection among participants in the Bangkok tenofovir study, an HIV pre-exposure prophylaxis trial among people who inject drugs. PLoS One. 2014;9(3):1-7. doi: 10.1371/journal.pone.0092809. PMID: 24667938. Excluded: wrong comparator.

Martin MT, Vanichseni S, Suntharasamai P, et al. Preliminary follow-up of injecting drug users receiving preexposure prophylaxis. Top Antivir Med. 2015;23:445-6. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Mayer KH, Chan PA, R RP, et al. Evolving models and ongoing challenges for HIV preexposure prophylaxis implementation in the United States. J Acquir Immune Defic Syndr. 2018 Feb 01;77(2):119-27. doi: 10.1097/QAI.0000000000001579. PMID: 29084044. Excluded: wrong outcome.

Mayer KH, Hosek S, Cohen S, et al. Antiretroviral pre-exposure prophylaxis implementation in the United States: a work in progress. J Int AIDS Soc. 2015;18(4 Suppl 3):19980. doi: 10.7448/IAS.18.4.19980. PMID: 26198345. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Mayer KH, Mimiaga MJ, Gelman M, et al. Raltegravir, tenofovir DF, and emtricitabine for postexposure prophylaxis to prevent the sexual transmission of HIV: safety, tolerability, and adherence. J Acquir Immune Defic Syndr. 2012 Apr 1;59(4):354-9. doi: 10.1097/QAI.0b013e31824a03b8. PMID: 22267017. Excluded: wrong intervention.

Mayer KH, Safren SA, Elsesser SA, et al. Optimizing pre-exposure antiretroviral prophylaxis adherence in men who have sex with men: Results of a pilot randomized controlled trial of "Life-Steps for PrEP". AIDS Behav. 2016 Nov 15doi: 10.1007/s10461-016-1606-4. PMID: 27848089. Excluded: wrong intervention.

McCormack S, Dunn D. Pragmatic open-label randomised trial of preexposure prophylaxis: The PROUD Study. Top Antivir Med. 2015;23:9-10. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

McPherson TD, Sobieszczyk ME, Markowitz M. Cabotegravir in the treatment and prevention of human immunodeficiency virus-1. Expert Opin Investig Drugs. 2018 Apr;27(4):413-20. doi: 10.1080/13543784.2018.1460357. PMID: 29633869. Excluded: wrong intervention.

Mehrotra ML, Glidden DV, McMahan V, et al. The effect of depressive symptoms on adherence to daily oral PrEP in men who have sex with men and transgender women: A marginal structural model analysis of The iPrEx OLE Study. AIDS Behav. 2016 Jul;20(7):1527-34. doi: 10.1007/s10461-016-1415-9. PMID: 27125241. Excluded: wrong study design for Key Question.

Minnis AM, Gandham S, Richardson BA, et al. Adherence and acceptability in MTN 001: a randomized cross-over trial of daily oral and topical tenofovir for HIV prevention in women. AIDS Behav. 2013 Feb;17(2):737-47. doi: 10.1007/s10461-012-0333-8. PMID: 23065145. Excluded: wrong intervention.

Minnis AM, van der Straten A, Salee P, et al. Pre-exposure prophylaxis adherence measured by plasma drug level in MTN-001: Comparison between vaginal gel and oral tablets in two geographic regions. AIDS Behav. 2016 Jul;20(7):1541-8. doi: 10.1007/s10461-015-1081-3. PMID: 25969178. Excluded: wrong comparator.

Molina JM, Capitant C, Spire B, et al. On demand PrEP with oral TDF-FTC in MSM: Results of the ANRS ipergay trial. Top Antivir Med. 2015;23(10). Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Molina JM, Charreau I, Spire B, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV. 2017 Sep;4(9):e402-e10. doi: 10.1016/S2352-3018(17)30089-9. PMID: 28747274. Excluded: wrong study design for Key Question.

Montgomery ET, van der Straten A, Stadler J, et al. Male partner influence on women's HIV prevention trial participation and use of pre-exposure prophylaxis: the importance of "understanding". AIDS Behav. 2015 May;19(5):784-93. doi: 10.1007/s10461-014-0950-5. PMID: 25416076. Excluded: wrong outcome.

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. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Muganzi DC, Haberer J, Boum Y, et al. Comparison of adherence measures in a clinical trial of preexposure prophylaxis. Top Antivir Med. 2015;23:448-9. PMID: 26785125. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Mugwanya KK, Baeten JM, Wyatt C, et al. Brief report: Frequency of monitoring kidney function in HIV-uninfected persons using daily oral tenofovir disoproxil fumarate pre-exposure prophylaxis. J Acquir Immune Defic Syndr. 2018 Feb 01;77(2):206-11. doi: 10.1097/QAI.0000000000001575. PMID: 29135656. Excluded: wrong outcome.

Mugwanya KK, Donnell D, Celum C, et al. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for hiv prevention: Post-unblinding analysis of the partners PrEP study. Sex Transm Dis. 2013;89(14). Excluded: wrong study design for Key Question.

Mugwanya KK, Donnell D, Celum C, et al. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention: a longitudinal analysis. Lancet Infect Dis. 2013 Dec;13(12):1021-8. doi: 10.1016/S1473-3099(13)70226-3. PMID: 24139639. Excluded: wrong outcome.

Mugwanya KK, Wyatt C, Celum C, et al. Reversibility of glomerular renal function decline in HIV-uninfected men and women discontinuing emtricitabine-tenofovir disoproxil fumarate pre-exposure prophylaxis. J Acquir Immune Defic Syndr. 2016 Apr 1;71(4):374-80. doi: 10.1097/QAI.0000000000000868. PMID: 26914909. Excluded: wrong outcome.

Mugwanya KK, Wyatt C, Celum C, et al. Reversibility of kidney function decline in HIV-1-uninfected men and women using preexposure prophylaxis. Top Antivir Med. 2015;23(451). Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Mujugira A, Baeten JM, Donnell D, et al. Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention. PLoS One. 2011;6(10):e25828. doi: 10.1371/journal.pone.0025828. PMID: 21998703. Excluded: wrong outcome.

Mujugira A, Celum C, Coombs RW, et al. HIV transmission risk persists during the first 6 months of antiretroviral therapy. J Acquir Immune Defic Syndr. 2016 Aug 15;72(5):579-84. doi: 10.1097/QAI.0000000000001019. PMID: 27070123. Excluded: wrong comparator.

Murnane PM, Heffron R, Ronald A, et al. Pre-exposure prophylaxis for HIV-1 prevention does not diminish the pregnancy prevention effectiveness of hormonal contraception. AIDS. 2014 Jul 31;28(12):1825-30. doi: 10.1097/QAD.0000000000000290. PMID: 24785951. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Nadery S, Geerlings SE. Pre-exposure prophylaxis (PrEP) in HIV-uninfected individuals with high-risk behaviour. Neth J Med. 2013 Jul-Aug;71(6):295-9. PMID: 23956310. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

Nagot N, Kankasa C, Tumwine JK, et al. Extended pre-exposure prophylaxis with lopinavir-ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. Lancet. 2016 Feb 6;387(10018):566-73. doi: 10.1016/S0140-6736(15)00984-8. PMID: 26603917. Excluded: wrong population.

Newcomb ME, Moran K, Feinstein BA, et al. Pre-exposure prophylaxis (PrEP) use and condomless anal sex: Evidence of risk compensation in a cohort of young men who have sex with men. J Acquir Immune Defic Syndr. 2018 Apr 01;77(4):358-64. doi: 10.1097/QAI.0000000000001604. PMID: 29210834. Excluded: wrong study design for Key Question.

Appendix A5. Excluded Studies List

Nguyen VK, Greenwald ZR, Trottier H, et al. Incidence of sexually transmitted infections before and after preexposure prophylaxis for HIV. AIDS. 2018 Feb 20;32(4):523-30. doi: 10.1097/QAD.0000000000001718. PMID: 29239887. Excluded: wrong study design for Key Question.

Orne-Gliemann J, Balestre E, Tchendjou P, et al. Increasing HIV testing among male partners. AIDS. 2013 Apr 24;27(7):1167-77. doi: 10.1097/QAD.0b013e32835f1d8c. PMID: 23343912. Excluded: wrong intervention.

Palanee-Phillips T, Schwartz K, Brown ER, et al. Characteristics of women enrolled into a randomized clinical trial of dapivirine vaginal ring for HIV-1 prevention. PLoS One. 2015;10(6):e0128857. doi: 10.1371/journal.pone.0128857. PMID: 26061040. Excluded: wrong intervention.

Parker S, Chan PA, Oldenburg CE, et al. Patient experiences of men who have sex with men using pre-exposure prophylaxis to prevent HIV infection. AIDS Patient Care STDS. 2015 Dec;29(12):639-42. doi: 10.1089/apc.2015.0186. PMID: 26669791. Excluded: wrong outcome.

Parsons JT, Rendina HJ, Grov C, et al. Accuracy of highly sexually active gay and bisexual men's predictions of their daily likelihood of anal sex and its relevance for intermittent event-driven HIV pre-exposure prophylaxis. J Acquir Immune Defic Syndr. 2015 Apr 1;68(4):449-55. doi: 10.1097/QAI.0000000000000507. PMID: 25559594. Excluded: wrong study design for Key Question.

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. Excluded: wrong outcome.

Pathela P, Braunstein SL, Schillinger JA, et al. Men who have sex with men have a 140-fold higher risk for newly diagnosed HIV and syphilis compared with heterosexual men in New York City. J Acquir Immune Defic Syndr. 2011 Dec 01;58(4):408-16. doi: 10.1097/QAI.0b013e318230e1ca. PMID: 21857351. Excluded: wrong outcome.

Pilcher CD, Bisol CA, Paganella MP, et al. Efficient identification of HIV serodiscordant couples by existing HIV testing programs in South Brazil. PLoS One. 2015;10(11):e0142638. doi: 10.1371/journal.pone.0142638. PMID: 26562436. Excluded: wrong study design for Key Question.

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. Excluded: wrong country.

Plosker GL. Emtricitabine/tenofovir disoproxil fumarate: a review of its use in HIV-1 pre-exposure prophylaxis. Drugs. 2013 Mar;73(3):279-91. doi: 10.1007/s40265-013-0024-4. PMID: 23444256. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Pyra M, Haberer JE, Heffron R, et al. Brief report: PrEP use during periods of HIV risk among East African women in serodiscordant relationships. J Acquir Immune Defic Syndr. 2018 Jan 01;77(1):41-5. doi: 10.1097/QAI.0000000000001561. PMID: 29016523. Excluded: wrong study design for Key Question.

Raymond HF, Chen YH, McFarland W. Estimating incidence of HIV infection among men who have sex with men, San Francisco, 2004-2014. AIDS Behav. 2016 Jan;20(1):17-21. PMID: 26471885. Excluded: wrong outcome.

Riddell Jt, Amico KR, Mayer KH. HIV preexposure prophylaxis: A review. JAMA. 2018 Mar 27;319(12):1261-8. doi: 10.1001/jama.2018.1917. PMID: 29584848. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

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 May;32(5):202-7. doi: 10.1089/apc.2018.0011. PMID: 29672136. Excluded: wrong study design for Key Question.

Rocha GM, Kerr L, Kendall C, et al. Risk behavior score: a practical approach for assessing risk among men who have sex with men in Brazil. Braz J Infect Dis. 2018 Mar - Apr;22(2):113-22. doi: 10.1016/j.bjid.2018.02.008. PMID: 29551334. Excluded: wrong country.

Roche M, Youssef E, Gilleece Y, et al. Do patients adherent on PREP exposed to HIV have seroconversion symptoms and falsely reactive HIV tests? HIV Med. 2014;15(107). Excluded: wrong study design for Key Question.

Sachdev DD, Stojanovski K, Liu AY, et al. Intentions to prescribe preexposure prophylaxis are associated with self-efficacy and normative beliefs. Clin Infect Dis. 2014 Jun;58(12):1786-7. doi: 10.1093/cid/ciu229. PMID: 24729556. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Sagaon-Teyssier L, Suzan-Monti M, Demoulin B, et al. Uptake of PrEP and condom and sexual risk behavior among MSM during the ANRS IPERGAY trial. AIDS Care. 2016 Mar;28 Suppl 1:48-55. doi: 10.1080/09540121.2016.1146653. PMID: 26883400. Excluded: wrong study design for Key Question.

Appendix A5. Excluded Studies List

Seidman DL, Weber S, Cohan D. Offering pre-exposure prophylaxis for HIV prevention to pregnant and postpartum women: a clinical approach. J Int AIDS Soc. 2017 Mar 08;20(Suppl 1):24-30. doi: 10.7448/IAS.20.2.21295. PMID: 28361503. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Seifert SM, Glidden DV, Meditz AL, et al. Dose response for starting and stopping HIV preexposure prophylaxis for men who have sex with men.[Erratum appears in Clin Infect Dis. 2015 Jul 1;61(1):143; PMID: 25957827]. Clin Infect Dis. 2015 Mar 1;60(5):804-10. doi: 10.1093/cid/ciu916. PMID: 25957827. Excluded: wrong study design for Key Question.

Shen M, Xiao Y, Rong L, et al. The cost-effectiveness of oral HIV pre-exposure prophylaxis and early antiretroviral therapy in the presence of drug resistance among men who have sex with men in San Francisco. BMC Med. 2018 Apr 24;16(1):58. doi: 10.1186/s12916-018-1047-1. PMID: 29688862. Excluded: wrong outcome.

Singh S, Song R, Johnson AS, et al. HIV incidence, prevalence, and undiagnosed infections in U.S. men who have sex with men. Ann Intern Med. 2018 May 15;168(10):685-94. doi: 10.7326/M17-2082. PMID: 29554663. Excluded: wrong study design for Key Question.

Sivay MV, Zhang Y, Hudelson SE, et al. Characterization of HIV seroconverters in a TDF/FTC PrEP study: HPTN 067. Top Antivir Med. 2017;25(1):404s. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Solomon MM, Schechter M, Liu AY, et al. The safety of HIV pre-exposure prophylaxis in the presence of hepatitis B infection. J Int AIDS Soc. 2015;18(46). Excluded: not a study (letter, editorial, non-systematic review article, no original data).

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. Excluded: wrong study design for Key Question.

Stack C, Oldenburg C, Mimiaga M, et al. Sexual behavior patterns and PrEP dosing preferences in a large sample of North American men who have sex with men. J Acquir Immune Defic Syndr. 2016 Jan 1;71(1):94-101. doi: 10.1097/QAI.0000000000000816. PMID: 26371786. Excluded: wrong study design for Key Question.

Tang EC, Vittinghoff E, Anderson PL, et al. Changes in kidney function associated with daily tenofovir disoproxil fumarate/emtricitabine for HIV preexposure prophylaxis use in the United States Demonstration Project. J Acquir Immune Defic Syndr. 2018 Feb 01;77(2):193-8. doi: 10.1097/QAI.0000000000001566. PMID: 28991887. Excluded: wrong study design for Key Question.

Tetteh RA, Yankey BA, Nartey ET, et al. Pre-exposure prophylaxis for HIV prevention: Safety concerns. Drug Saf. 2017 Apr;40(4):273-83. doi: 10.1007/s40264-017-0505-6. PMID: 28130774. Excluded: wrong study design for Key Question.

Thaden JT, Gandhi M, Okochi H, et al. Seroconversion on preexposure prophylaxis: a case report with segmental hair analysis for timed adherence determination. AIDS. 2018 Jun 01;32(9):F1-F4. doi: 10.1097/QAD.0000000000001825. PMID: 29683856. Excluded: wrong study design for Key Question.

Thavorn K, Kugathasan H, Tan DHS, et al. Economic evaluation of HIV pre-exposure prophylaxis strategies: protocol for a methodological systematic review and quantitative synthesis. Syst Rev. 2018 Mar 15;7(1):47. doi: 10.1186/s13643-018-0710-0. PMID: 29544530. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Vaccher SJ, Grulich AE, Haire BG, et al. Validation of participant eligibility for pre-exposure prophylaxis: Baseline data from the PRELUDE demonstration project. PLoS One. 2017;12(9):e0185398. doi: 10.1371/journal.pone.0185398. PMID: 28950022. Excluded: wrong study design for Key Question.

van der Straten A, Stadler J, Montgomery E, et al. Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa. PLoS One. 2014;9(2):e89118. doi: 10.1371/journal.pone.0089118. PMID: 24586534. Excluded: wrong outcome.

2Veloso VG, Mesquita F, Grinsztejn B. Pre-exposure prophylaxis for men and transgender women who have sex with men in Brazil: opportunities and challenges. J Int AIDS Soc. 2015;18(4 Suppl 3):20010. doi: 10.7448/IAS.18.4.20010. PMID: 26198347. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Venter WD, Cowan F, Black V, et al. Pre-exposure prophylaxis in Southern Africa: feasible or not? J Int AIDS Soc. 2015;18(4 Suppl 3):19979. doi: 10.7448/IAS.18.4.19979. PMID: 26198344. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Vermeersch S, Callens S, De Wit S, et al. Health and budget impact of combined HIV prevention - first results of the BELHIVPREV model. Acta Clin Belg. 2018 Feb;73(1):54-67. doi: 10.1080/17843286.2017.1339978. PMID: 28673201. Excluded: wrong study design for Key Question.

Appendix A5. Excluded Studies List

Volk JE, Marcus JL, Phengrasamy T, et al. No new HIV infections with increasing use of HIV preexposure prophylaxis in a clinical practice setting. Clin Infect Dis. 2015 Nov 15;61(10):1601-3. doi: 10.1093/cid/civ778. PMID: 26334052. Excluded: wrong outcome.

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. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Volk JE, Nguyen DP, Hare CB, et al. HIV infection and drug resistance with unsupervised use of HIV pre-exposure prophylaxis. AIDS Res Hum Retroviruses. 2018 Apr;34(4):329-30. doi: 10.1089/AID.2017.0285. PMID: 29262689. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Whetham J, Taylor S, Charlwood L, et al. Pre-exposure prophylaxis for conception (PrEP-C) as a risk reduction strategy in HIV-positive men and HIV-negative women in the UK. AIDS Care. 2014;26(3):332-6. doi: 10.1080/09540121.2013.819406. PMID: 23876052. Excluded: wrong study design for Key Question.

Wilton J, Noor SW, Schnubb A, et al. High HIV risk and syndemic burden regardless of referral source among MSM screening for a PrEP demonstration project in Toronto, Canada. BMC Public Health. 2018 02 27;18(1):292. doi: 10.1186/s12889-018-5180-8. PMID: 29486737. Excluded: wrong intervention.

Wright E, Grulich A, Roy K, et al. Australasian society for HIV, viral hepatitis and sexual health medicine HIV pre-exposure prophylaxis: clinical guidelines. Update April 2018. J Virus Erad. 2018 Apr 01;4(2):143-59. PMID: 29682309. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

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. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

Yah CS. Nurturing the continuum of HIV testing, treatment and prevention matrix cascade in reducing HIV transmission. Ethiop J Health Sci. 2017 Nov;27(6):621-30. PMID: 29487471. Excluded: wrong study design for Key Question.

Ying R, Sharma M, Heffron R, et al. Cost-effectiveness of pre-exposure prophylaxis targeted to high-risk serodiscordant couples as a bridge to sustained ART use in Kampala, Uganda. J Int AIDS Soc. 2015;18(4 Suppl 3):20013. doi: 10.7448/IAS.18.4.20013. PMID: 26198348. Excluded: wrong outcome.

Yun K, Xu JJ, Zhang J, et al. Female and younger subjects have lower adherence in PrEP trials: a meta-analysis with implications for the uptake of PrEP service to prevent HIV. Sex Transm Dis. 2018 May;94(3):163-8. doi: 10.1136/sextrans-2017-053217. PMID: 28756409. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

Zablotska IB, Selvey C, Guy R, et al. Expanded HIV pre-exposure prophylaxis (PrEP) implementation in communities in New South Wales, Australia (EPIC-NSW): design of an open label, single arm implementation trial.[Erratum appears in BMC Public Health. 2018 Feb 28;18(1):297; PMID: 29490635]. BMC Public Health. 2018 02 02;18(1):210. doi: 10.1186/s12889-017-5018-9. PMID: 29394918. Excluded: wrong study design for Key Question.

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

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/Page/Name/methods-and-processes.

Appendix A7. Expert Reviewers of the Draft Report

- Christopher J. Graber, MD, MPH, Associate Clinical Professor of Medicine, David Geffen School of Medicine at University of California, Los Angeles, Greater Los Angeles Healthcare System, Department of Veterans Affairs
- Sybil Hosek, PhD, Cook County Health and Hospitals System's Stroger Hospital, Chicago
- Douglas Krakower, MD, Assistant Professor of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School
- Albert Liu, MD, MPH, Clinical Research Director, HIV Prevention Interventions, San Francisco Department of Public Health, Assistant Clinical Professor, University of California, San Francisco School of Medicine
- Jamie P. Morano, MD, MPH, Director, Infectious Disease Telehealth Program, James A Haley Veterans Affiars Hospital, Assistant Professor, University of South Florida, Morsani College of Medicine
- Jeffrey Murray, MD, MPH, Deputy Director, Division of Antiviral Products, Center for Drug Evaluation Research, U.S. Food and Drug Aministration
- Brandy Peaker, MD, MPH, Liaison, Centers for Disease Control and Prevention
- Dawn Smith, MD, MPH, MS, Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention

Note: Reviewers provided comments on a prior version of the draft report and may or may not agree with the report findings.

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

Study name Author, year	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 067/ADAPT Bekker 2018[122]	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
ADAPT/ HPTN 067 Grant, 2018[123]	Same as Bekker 2018	Two centers Thailand (Bangkok), U.S. (NY, Harlem)	Two centers Thailand (Bangkok), U.S. (NY, Harlem)	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-	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%	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	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
					infected partner or partner of unknown HIV infection status	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.			

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

Study name Author, year	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
						20% ≥10 Condomless anal intercourse in past 6 months: 80% vs. 67% vs. 83%			
Bangkok Tenofovir Study Choopanya, 2013[97]* and Martin, 2015[109]	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	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

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

Study name Author, year	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
						partner in past 12 weeks: 36% vs. 40%			
Bangkok Tenofovir Study Martin, 2014[108]	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
FEM-PrEP Van Damme, 2012[120]* and Agot, 2015[95]	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

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

Study name Author, year	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 Mandala, 2014[106]	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[85]* (CDC Safety Study)	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
Liu, 2011[104] (companion to Grohskopf, 2013)	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 Latino/Hispanic: 5% vs. 10% Other race: 1% vs.	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

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

Study name Author, year	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
						8% Heavy alcohol use in past 3 months: 4% vs. 6% Any recreational drug use in past 3 months: 44% vs. 52%			
IAVI Kenya Study Mutua, 2012[53]	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:	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	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
						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			
IAVI Uganda Study Kibengo, 2013[54]	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%	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	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
						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%			
IPERGAY Molina, 2015[52]	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	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	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**	**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**
				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		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%			
iPrEx Grant, 2010[100]*	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	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:	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%	Good	National Institutes of Health and Bill and Melinda Gates Foundation

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

Study name Author, year	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
					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)	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%	(182/1,225)		
iPrEx Deutsch, 2015[98]	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
iPrEx Liu, 2014[105]	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

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

Study name Author, year	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 Marcus, 2014[107]	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[114]	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%	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	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
						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			
iPrEx Solomon, 2014[118]	See above	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/Latino: 80% vs. 81% Non-Hispanic/Latino: 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

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

Study name **Author, year**	**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[70]*	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)

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

Study name Author, year	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 Celum 2014[80]	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
Partners PrEP Donnell, 2014[99]	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[101]	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[102]	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

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

Study name Author, year	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 Lehman, 2015[103]	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[110]	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 duration of the study.	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 partner; 53% no effective contraception; 8% STI	Same as Baeten 2012 Enrolled: 4,747 serodiscordant couples Analyzed: 1,785	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Mugo, 2014[112]	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

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

Study name Author, year	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 Mugwanya, 2015[113]	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[115]	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 Murnane, 2015[116]	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[121]	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**	**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[94]	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	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[78]	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

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

Study name Author, year	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
Study of TDF Peterson, 2007[117]	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 pregnant during the 12 months of study participation	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**	**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**
TDF2 Thigpen, 2012[119]*	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[96]	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
VOICE Marrazzo, 2015[76]*	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-	Women ages 18 to 45 years who were neither pregnant nor breastfeeding and who reported recent vaginal	A vs. B vs. C vs. D vs. E Age (mean): 26 vs. 25 vs. 25 vs. 25 vs. 25 years	Screened: 12,320 Eligible: NR Enrolled: 5,029 Analyzed: 4,969 Withdrawals: NR	Good	National Institutes of Health

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

Study name Author, year	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
				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)	intercourse, were using effective contraception, and had normal renal, hematologic, and hepatic function	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%	Loss to followup: 0.1% (38/5,029)		

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

Study name Author, year	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
						Bacterial vaginosis present: 42% vs. 41% vs. 40% vs. 40% vs. 39%			
VOICE Mirembe, 2016[111]	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

*Main study publication.

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**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
ADAPT/ HPTN 067 Bekker 2018[122]	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[123]	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
Bangkok Tenofovir Study Choopanya, 2013[97]* and Martin, 2015[109]	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

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

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Bangkok Tenofovir Study Martin, 2014[108]	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**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
FEM-PrEP Van Damme, 2012[120]* and Agot, 2015[95]	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 HIV-uninfected at time of enrollment 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%

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

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
FEM-PrEP Mandala, 2014[106]	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[85]* (CDC Safety Study)	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)	A vs. B HIV infection: 0% (0/201) vs. 3.5% (7/199); RR 0.07 (95% CI, 0.004 to 1.15); NNT 29	A vs. B Death: 0.5% (1/201) vs. 0% (0/199); RR, 2.97 (95% CI, 0.12 to 72.5) 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	No K65R mutations were noted among any seroconverting participants (n=7; 3 TDF, 4 placebo)
Liu, 2011[104] (companion to Grohskopf, 2013)	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)	Same as Grohskoph 2013

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

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
			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	
IAVI Kenya Study Mutua, 2012[53]	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 reported; narrative report of increase from median 3 to 4 partners at month 4	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
IAVI Uganda Study Kibengo, 2013[54]	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	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	Interventions	Clinical health outcomes	Adverse events	Resistance
		reported) Risk behavior, number of sexual partners: Reported to be 1 (IQR, 1 to 1) for all groups		
IPERGAY Molina, 2015[52]	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)	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) 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**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
iPrEx Grant, 2010[100]*	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[98]	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[105]	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010
iPrEx Marcus, 2014[107]	*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	Same as Grant 2010

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

Study name Author, year	Interventions	Clinical health outcomes	Adverse events	Resistance
			Groin ulcer on STI exam: 3% vs. 2%; p=NS	
iPrEx Mulligan, 2015[114]	*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[118]	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
Partners PrEP Baeten, 2012[70]*	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)

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

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
				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) HIV infected at time of enrollment 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) HIV uninfected at time of enrollment A vs. B vs. C

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

Study name Author, year	Interventions	Clinical health outcomes	Adverse events	Resistance
				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[80]	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[99]	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Haberer, 2013[101]	Same as Baeten 2012	NA	NA	NA
Partners PrEP Heffron, 2014[102]	A. TDF or FTC B. Placebo	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Lehman, 2015[103]	*Seroconverters only* A. Once-daily TDF 300 mg + placebo TDF-FTC (n=39) B. Once-daily TDF-FTC 300/200 mg + placebo	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)

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

Study name Author, year	Interventions	Clinical health outcomes	Adverse events	Resistance
	TDF (n=25) C. Placebo TDF + placebo TDF-FTC (n=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[110]	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
Partners PrEP Mugo, 2014[112]	*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%	Same as Baeten 2012	Same as Baeten 2012

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

Study name Author, year	Interventions	Clinical health outcomes	Adverse events	Resistance
		(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		
Partners PrEP Mugwanya, 2015[113]	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[115]	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Murnane, 2015[116]	Same as Baeten 2012	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**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Partners PrEP Were, 2014[121]	*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[94]	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)	NR	A vs. B vs. C Serious adverse events: None Nausea at 8 weeks: 24% vs 0% vs 6% ART resistance: NR	NR
PROUD McCormack, 2016[78]	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)	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.

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

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
			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)	not assessed
Study of TDF Peterson, 2007[117]	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[119]*	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**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
TDF2 Chirwa, 2014[96]	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
VOICE Marrazzo, 2015[76]*	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)	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	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)	A vs. B vs. C <u>Total population</u> K65R mutation (TDF resistance): 0% (0/70) vs. 0% (0/71) vs. 0% (0/69)

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

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
	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)	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)	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)	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	Interventions	Clinical health outcomes	Adverse events	Resistance
VOICE Mirembe, 2016[111]	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

*Main study publication.

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**	**Factors associated with adherence (U.S. applicable)**	**Adherence and effectiveness**	**Subgroups**
ADAPT/ HPTN 067 Bekker 2018[122]	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%; mean difference, A vs. B: 10.0% (95% CI, 3.8% to 16.0%); A vs. C: 22.0% (95% CI, 15.3% to 30.0%) Proportion 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) Proportion with plasma TDF consistent with ≥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) Proportion with plasma TDF consistent with 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) Proportion with PBMC TDF-DP consistent with ≥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) Proportion with PBMC TDF-DP consistent with 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> Proportion with plasma TDF consistent with ≥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) Proportion with plasma TDF consistent with 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) Proportion with PBMC TDF-DP consistent with ≥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) Proportion with PBMC TDF-DP consistent with 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> Proportion with plasma TDF consistent with ≥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) Proportion with plasma TDF consistent with 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) Proportion with PBMC TDF-DP consistent with ≥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) Proportion with PBMC TDF-DP consistent with 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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
ADAPT/ HPTN 067 Grant, 2018[123]	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	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

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Study name Author, year	Interventions	Adherence method of assessment and rate	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
Bangkok Tenofovir Study Choopanya, 2013[97]* and Martin, 2015[109]	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 (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 <u>Sex - efficacy (based on HR)</u> Female: 78.6% (95% CI, 16.8 to 96.7) Male: 37.6% (95% CI, -17.8 to 67.9) <u>Sex - adherence</u> Female: 95.6% (95% CI, 81.1 to 98.9) Male: 93.8% (95% CI, 78.8 to 98.7) <u>Age - efficacy (based on HR)</u> 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) <u>Age - adherence</u> <40 years: 92.3% (95% CI, 75.5 to 98.2) ≥40 years: 98.2% (95% CI, 93.5 to 99.5) <u>Injected during 12 weeks before enrollment - efficacy (based on HR)</u> Yes: 44.3% (95% CI, -12.5 to 72.4) No: 57.4% (95% CI, -17.0 to 86.6) <u>Shared needles 12 weeks before enrollment - efficacy (based on HR)</u> 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**	**Factors associated with adherence (U.S. applicable)**	**Adherence and effectiveness**	**Subgroups**
Bangkok Tenofovir Study Martin, 2014[108]	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
FEM-PrEP Van Damme, 2012[120]* and Agot, 2015[95]	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 (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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
FEM-PrEP Van Damme, 2012[120]* and Agot, 2015[95] (Cont'd)	See above	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)	See above	See above	See above

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**	**Factors associated with adherence (U.S. applicable)**	**Adherence and effectiveness**	**Subgroups**
FEM-PrEP Mandala, 2014[106]	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[85]* (CDC Safety Study)	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	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
Liu, 2011[104] (companion to Grohskopf, 2013)	Same as Grohskopf 2013	Same as Grohskoph 2013	Same as Grohskopf 2013	Same as Grohskopf 2013	Same as Grohskopf 2013

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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
IAVI Kenya Study Mutua, 2012[53]	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) 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) Intermittent regimen: Median unadjusted adherence rate (MEMS data): B vs. D: 80% (IQR, 74–86) vs. 78% (IQR, 67–86); p=0.60 Median adjusted adherence rate (MEMS, adjusted for daily openings and extra pills removed): B vs. D (Monday, Friday doses only): 91% (IQR, 78–102) vs. 88% (IQR, 69–94); p=0.25 B vs. D (MEMS + text reporting, postcoital doses only): 40% (IQR, 23–58) vs. 53% (IQR, 15–79); p=0.45 B vs. D (timeline followback + text, postcoital doses within 2 hours only): 39% (IQR, 29–58) vs. 31% (IQR, 21–59); p=0.58 Adherence rates did not differ by gender	NA	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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
IAVI Uganda Study Kibengo, 2013[54]	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 Adherence rates did not differ by gender	NA	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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
IPERGAY Molina, 2015[52]	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 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 TDF plasma levels over 10 months (among 113 participants): 82% to 100% (86% overall) vs. 0% to 6% FTC plasma levels 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)	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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
iPrEx Grant, 2010[100]*	A. TDF-FTC 300/200 mg (n=1,251) B. Placebo (n=1,248)	Plasma sample (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[98]	*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
iPrEx Liu, 2014[105]	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%	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) No significant association for other factors	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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
iPrEx Liu, 2014[105] (cont'd)		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 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) No association for other factors 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) 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[107]	*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

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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
iPrEx Mulligan, 2015[114]	*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[118]	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
Partners PrEP Baeten, 2012[70]*	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 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

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**	**Factors associated with adherence (U.S. applicable)**	**Adherence and effectiveness**	**Subgroups**
Partners PrEP Celum 2014[80]	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
Partners PrEP Donnell, 2014[99]	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)	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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
Partners PrEP Donnell, 2014[99] (cont'd)				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 (95% CI, 0.04 to 0.19)	
Partners PrEP Haberer, 2013[101]	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[102]	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)

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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
Partners PrEP Lehman, 2015[103]	*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
Partners PrEP Matthews, 2014[110]	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[112]	*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

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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
Partners PrEP Mugwanya, 2015[113]	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 Mean eGFR (mL/min/1.73 m^2) 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) Serum GFR decline ≥25% from baseline 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

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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
Partners PrEP Murnane, 2013[115]	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

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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
Partners PrEP Murnane, 2015[116]	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[121]	*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

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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
Project PrEPare ATN 082 Hosek, 2013[94]	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[78]	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
Study of TDF Peterson, 2007[117]	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

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	Factors associated with adherence (U.S. applicable)	Adherence and effectiveness	Subgroups
TDF2 Thigpen, 2012[119]*	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 Estimated pill counts: 84% vs. 83% 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
TDF2 Chirwa, 2014[96]	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.

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**	**Factors associated with adherence (U.S. applicable)**	**Adherence and effectiveness**	**Subgroups**
VOICE Marrazzo, 2015[76]*	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 TDF at quarterly plasma sample: 30% vs. 39% 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) <u>Living situation</u> 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) <u>Living situation</u> 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)
VOICE Mirembe, 2016[111]	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

*Main study publication.

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; 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; 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	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 randomized?	Quality
ADAPT/HPTN Bekker 2018[122], Grant, 2018[123]	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Fair
Bangkok Tenofovir Study Choopanya, 2013[97]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
FEM-PREP Van Damme, 2012[120]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Grohskopf, 2013[85]	Yes, see Liu 2011	Yes, see 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[53]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
IAVI Uganda Study Kibengo, 2013[54]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
IPERGAY Molina, 2015[52]	Yes	Yes	Yes (except race)	Yes	Yes	Unclear	Yes	Yes	No	Yes	Good
iPrEX Grant, 2010[100]	Yes	Yes	Yes	Yes	Yes	Yes, see protocol	Yes	Yes	No	Yes	Good

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

Study name Author, year	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 randomized?	Quality
Partners PrEP Baeten, 2012[70]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Project PrEPare ATN 082 Hosek 2013[94]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Yes	Fair
PROUD McCormack, 2016[78]	Yes	Unclear	Yes	Yes	No	No	No	Yes	No	Yes	Fair
Study of TDF Peterson, 2007[117]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
TDF2 Thigpen, 2012[119]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
VOICE Marrazzo, 2015[76]	Yes	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; 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	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
Beymer, 2017[129]	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[130] SDET score	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[135] A: ARCH-MSM B: Menza C: SDET	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)	A: ARCH-MSM: See Smith 2012 (drug use questions modified from last 6 to last 12 months) B: SDET: See Hoenigl 2015 C: 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	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
Lancki, 2018[134] A: ARCH-MSM B: CDC criteria C: Gilead indications	Cohort Self-identiified 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)	A: ARCH-MSM: See Smith 2012 (drug use questions modified from last 6 to last 12 months) B: 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 C: 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
Menza, 2009[131]	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% Chalmydia on STI testing: 8.8% Methamphetamine use in past 6 months: 6.7% Inhaled nitrites in past 6 months: 8.9% Crack/cocaine in past 6 months: 2.8%	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	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
			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%			
Smith, 2012[132] HIRI-MSM (now ARCH-MSM)	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)

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

Study, Year	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items
Smith, 2015[133] ARCH-IDUs	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

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; 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; LGBT=lesbian, gay, bisexual, and transgender; MSM=men who have sex with men; NR=not reported; PWID=persons who inject drugs; RCT=randomized, controlled trial; SDET=San Diego Early Test; 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[129]	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[130] 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[135] 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
Lancki, 2018[134] 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

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

Study, Year	Cutoff	Proportion meeting cutoff	Sensitivity	Specificity	AUROC	Comments
Menza, 2009[131]	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
Smith, 2012[132] 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[133] 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

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; AUROC=area under the receiver operating characteristic curve; CDC=Centers for Disease Control and Prevention; CI=confidence interval; HIRI-MSM=HIV Incidence Risk Index for Men Who Have Sex With Men; NR=not reported; SDET=San Diego Early Test.

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 evalauted in a sample independent from the one used to develop the test?	Quality rating
Beymer, 2017[129]	Yes	No	Unclear	Yes	No	Fair
Hoenigl, 2015[130] SDET	Yes	No	Unclear	Unclear	Yes	Fair
Jones, 2017[135] A: ARCH-MSM B: Menza C: SDET	Yes	Yes	Unclear	Yes	Yes	Fair
Lancki, 2018[134] A: ARCH-MSM B: CDC criteria C: Gilead indications	Yes	Yes	No	Yes	No (for CDC and Gilead criteria)	Fair
Menza, 2009[131]	Yes	No	Unclear	Yes	Yes	Fair
Smith, 2012[132] HIRI-MSM (now ARCH-MSM)	Yes	No	Unclear	Yes	Yes	Fair
Smith, 2015[133] ARCH-IDUs	Yes	No	Unclear	Yes	No	Fair

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; HIRI-MSM=HIV Incidence Risk Index for Men Who Have Sex With Men; SDET=San Diego Early Test.

Appendix B Table 8. HIV Pre-Exposure Prophylaxis Cohort Studies: Study Characteristics

Study Author, year	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
Chan, 2016[124]	Cohort	3 U.S. (Providence Rhode Island, Jackson Mississippi, St. Louis Missouri)	20 months	Oral FTC and TDF	Patients at 1 of 3 clinics with behaviors associated with HIV acquisition	Total population Mean age 32 years (SD, 10) 91% male; 8% female; >1% transgender Race: 44% white; 41% black; 3% Asian; 13% other; 12% Hispanic/Latino Risk behaviors: 89% MSM; 11% MSF; 7% FSM; 31% serodiscordant couple; 61% condomless anal sex with another man; 25% anal sex with HIV+ man Substance use: Alcohol: 78%; PWID: 0%; methamphetamine: 2%; amyl nitrate ("popper"): 15%	Screened: NR Eligible: 267 Enrolled: 267 Analyzed: 171 Withdrawals: 8 Loss to followup: 19	Fair	Gilead Sciences, Inc.
Hosek, 2017[93] Project PrEPare, ATN 110	Open-label PrEP demon-stration project and safety study	12 U.S.	48 weeks	TDF-FTC	HIV-uninfected YMSM, ages 18 to 22 years at time of signed informed consent	Mean age 20 years (SD, 1.3; median, 20 years) 100% male (at birth) 47% Black; 1% Asian; 21% white non-Hispanic; 11% white Hispanic; 21% other/mixed race Risk factors: 81% condomless sex in the previous month; 58% condomless receptive anal intercourse with last partner; 22% any positive STI test	Screened: 2,186 Eligible: 400 Enrolled: 200 Analyzed: 142 Withdrawals: 58 Loss to followup: 34	Fair	ATN: National Institutes of Health (Eunice Kennedy Shriver National Institute of Child Health and Human Development); National Institute on Drug Abuse; and National Institute of Mental Health. Study drug was donated by Gilead Sciences, Inc., along with supplemental funds for a portion of the dried blood spot testing. Various authors receive funding from

Appendix B Table 8. HIV Pre-Exposure Prophylaxis Cohort Studies: Study Characteristics

Study Author, year	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
									Gilead.
Hosek 2017[92] Project PrEPare, ATN 113	Cohort	14 U.S.	48 weeks	TDF-FTC	Ages 15 to 17 years, male at birth, HIV-uninfected, self-reported risk for HIV acquisition	Mean age 16.5 years (SD, 0.73) 3% Asian/Pacific Islander; 29% Black/African American; 14% white; 21% Hispanic; 33% other/mixed race/ethnicity Risk behaviors: 17% ever been paid for sex; 3% exchanged sex for a place to stay; 87% engaged in high-risk sex acts with men; 60% unprotected receptive anal sex	Screened: 2,864 Eligible: 260 Enrolled: 78 Analyzed: 78 Withdrawals: 13 Loss to followup: 19	Fair	ATN: National Institute of Child Health and Human Development; National Institute on Drug Abuse; National Institute of Mental Health. Study drugs were donated by Gilead Sciences along with funding for a portion of the dried blood spot testing and overall study costs.
iPrEx-OLE Grant, 2014[125]	Cohort	Multisite U.S., Brazil, Peru, Ecuador, South Africa and Thailand	72 weeks	TDF-FTC	HIV-uninfected former participants of 3 randomized PrEP trials	Participants who received PrEP (n=1,225; data missing for some participants) Mean age NR; 18 to 24 years: 20%; 25 to 29 years: 26%; 30 to 39 years: 32%; ≥40 years: 22% 100% male (at birth); 11% transgender Race NR Risk behaviors: 100% reported anal intercourse with men; 34% condomless receptive anal intercourse; 20% ≥5 alcoholic drinks on days when drinking; 2% methamphetamine use; 9% cocaine use STIs: 16% syphilis; 50% HSV2; 2% gonorrhea	Screened: NR Eligible: 1,603 Enrolled: 1,345 Analyzed: 1,225 Withdrawals: 84 Loss to followup: 31	Good	Gilead Sciences, Inc. U.S. National Institutes of Health HIV Prevention Trial Network

Appendix B Table 8. HIV Pre-Exposure Prophylaxis Cohort Studies: Study Characteristics

Study Author, year	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-OLE Glidden, 2016[142]	Cohort	Same as Grant 2014	Same as Grant 2014	Same as Grant 2014	Same as Grant 2014	Same as Grant 2014	Same as Grant 2014	Same as Grant 2014	Same as Grant 2014
Landovitz 2017[126] *PATH-PrEP*	Cohort	2 centers U.S.	48 weeks	TDF-FTC PrEP (n=278) Study also included a postexposure prophylaxis group (PEP; n=23)	Self-identified MSM, MSMW, and transgender women age ≥18 years, HIV uninfected at study entry by rapid ELISPOT and viral load, with adequate screening laboratory parameters, and without symptoms suggestive of primary HIV infection	n=301 (PrEP: 278; PEP: 23; 19 of whom subsequently crossed over to PrEP group) Median age 34 years (range, 20–69) 100% male/transgender woman 50% white; 28% Hispanic; 11% black; 6% Asian/Pacific Islander; 5% other Risk behaviors: 77% any substance use in the past 30 days; 56% polysubstance use in the past 30 days; 12% methamphetamine use in the past 30 days; 3% injection drug use in the past 3 months; 61% binge drinking in past 12 months; 27% PEP use in the past 12 months; 84% unprotected anal intercourse in the past 30 days; 13% STI diagnosis	Screened: 328 Eligible: 307 Enrolled: 301 Analyzed: 283 Withdrawals: 23 Loss to followup: 52	Fair	California HIV Research Program; Gliead Sciences; Center for HIV Identification, Prevention, and Treatment, University of California, Los Angeles Center for AIDS Research; National Center for Advancing Translational Sciences
Montgomery, 2016[127]	Retrosp-ective cohort	1 site U.S.	6 months	Oral TDF-FTC	Patients receiving PrEP at an outpatient infectious disease clinic in Providence, RI, between February 2013 and June 2014	Mean age 34 years (range, 18–58) 94% male 63% white non-Hispanic; 6% black non-Hispanic; 23% Hispanic/Latino; 9% other Risk factors: 91% MSM; 2% MSMW; 6% WSM; 46% serodiscordant couple; 3% no insurance; 38% referred from STI clinic	Screened: NR Eligible: NR Enrolled: 50 Analyzed: 35 Withdrawals: NR Loss to followup: NR	Fair	Gilead Grant. National Institute of Allergy and Infectious Diseases

Appendix B Table 8. HIV Pre-Exposure Prophylaxis Cohort Studies: Study Characteristics

Study Author, year	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
U.S. PrEP Demon-stration Project Liu, 2016[81] and Cohen, 2015[146]	Cohort	3 sites U.S.	16 months	TDF-FTC	Male at birth, age ≥18 years, MSM or transgender, fluent in English or Spanish, negative HIV antibody result at screening and enrollment, negative 4th-generation antibody-antigen test at screening	Mean age NR; 18 to 25 years: 20%; 26 to 35 years: 38%; 36 to 45 years: 24%; ≥45 years: 18% 99% male; 1% transgender women 48% white; 34% Latino; 7% black; 5% Asian; 6% other Risk behaviors: 12% ≥5 drinks/day when drinking; 46% "popper" or other inhalant use; 20% cocaine or crack use; 15% methamphetamine use; 23% club drug use; 32% erectile dysfunction drug use; 44% marijuana use; 2% PWID in the last 3 months; 23% condomless insertive anal sex; 64% condomless receptive anal sex; 5% exchange sex in the last 3 months STIs: 4% syphilis; 15% gonorrhea, any site; 14% chlamydia, any site; 17% rectal gonorrhea or chlamydia	Screened: 557 Eligible (at 48 weeks): 437 Enrolled (completed 5 visits): 383 Analyzed: 294 (attending followup visits) Withdrawals: NA Loss to followup: NA	Fair	National Institute of Allergy and Infectious Diseases; National Institute of Mental Health; National Institutes of Health; Gilead (study drug)
van Epps, 2018[128]	Retrosp-ective cohort	Database (Veterans Health Administration Corporate Data Warehouse) U.S.	1 year	TDF-FTC PrEP (n=1,086)	Veterans with at least 1 TDF-FTC fill of more than 30 days in the observation period; no other fills for ART within 180 days of the date of first TDF-FTC fill; no ICD 9 or 10 diagnosis codes for HIV or HBV infection; no ICD 9 or 10 codes for needle-stick exposure within 60 days of the date of first TDF-FTC fill.	Mean age NR; 39% <35 years; 35% 35 to 49 years; 21% 50 to 64 years; 6% 65 to 79 years 4% female 22% black; 67% white; 6% other 21% substance use problem	Screened: NA Eligible: 1,086 Enrolled: 1,086 Analyzed: 1,086 Withdrawals: NA Loss to followup: NA	Fair	Veterans Affairs; Veterans Health Administration Office of Rural Health; Veterans Affairs Health Services Research & Development

Abbreviations: ART=antiretroviral therapy; FSM=females who have sex with males; ELISPOT=Enzyme-Linked ImmunoSpot assay; FTC=emtricitabine; HSV2=herpes simplex virus 2; iPrEx-OLE=Pre-Exposure Prophylaxis Initiative–Open Label Extension study; MSF=males who have sex with females; MSM=men who have sex with men; MSMW=men who have sex with men and women; NA=not applicable; NR=not reported; PEP=post-exposure prophylaxis; PrEP=pre-exposure prophylaxis; PWID=persons who inject drugs; SD=standard deviation; STI=sexually transmitted infection; TDF=tenofovir disporoxil fumarate; U.S.=United States; WSM=women who have sex with men; YMSM=young men who have sex with men.

Appendix B Table 9. HIV Pre-Exposure Prophylaxis Cohort Studies: Results

Study Author, year	Interventions	Clinical health outcomes	Adverse events
Chan, 2016[124]	Oral TDF-FTC	HIV infection: 1% (3/267) Prior to PrEP approval: 0.4% (1/267) 3 month visit: 0.4% (1/267) 6 month visit: 0.4% (1/267) (patient was known to be nonadherent to PrEP)	Adverse events, 3 months: 1% (3/267) Adverse events, 6 months: 0.4% (1/267)
Hosek, 2017[93] Project PrEPare, ATN 110	TDF-FTC	Overall STI incidence rate was 66.44% (95% CI, 50.53 to 82.35), with greater STI incidence in the first 24 weeks (76.48/100 person-years) than the latter half (60.99/100 person-years) 4 HIV seroconversions occurred during the study (1 per week at 4, 32, 40, and 38 weeks), for an incidence rate of 3.29/100 person-years (95% CI, 0.07 to 6.52)	Grade 3 adverse events (nausea, weight loss, headache): 9% (18/200) Grade 1 serum creatinine elevation: 0.5% (1/200) Social harm: 1% (2/200; 1 coerced condomless sex; 1 threat of eviction from home) Hip BMD, median change from baseline, week 24: -0.44%; p<0.001 Whole body BMD, median change from baseline, week 24: -0.23%; p<0.001 Spine Z-score, median change from baseline, week 24: -0.10; p<0.001 Hip Z-score, median change from baseline, week 24: -0.02; p=0.017 Whole body Z-score, median change from baseline, week 24: -0.10; p<0.001
Hosek 2017[92] Project PrEPare, ATN 113	TDF-FTC	HIV infection: 3/78; annualized incidence, 6.4 (95% CI, 1.3 to 18.7) infections/100 person-years STI rate, 0 to 24 weeks: 18.1/100 person-years (95% CI, 9.7 to 34) STI rate, 24 to 48 weeks: 9.4/100 person-years (95% CI, 3.4 to 26)	Grade 3 or higher adverse events: 13% (10/78)
iPrEx-OLE Grant, 2014[125]	TDF-FTC	28 HIV infections	PrEP interruption due to side effects: 8% (93/1,225) Grade 1 serum creatinine concentration: 0.2% (3/1,225)
iPrEx-OLE Glidden, 2016[142]	Same as Grant 2014	NR	PrEP interruption due to adverse events: 5% (56/1,225) Withdrawal due to adverse event: 3% (34/1,225) Any non-GI symptom, 1 month: 23% (281/1,225) Any non-GI symptom, 3 months: 17% (208/1,225) Any GI symptom, 1 month: 17% (208/1,225) Any GI symptom, 3 months: 11% (135/1,225) Multiple GI symptoms, 1 month: 11% (135/1,225) Multiple GI symptoms, 3 months: 5% (61/1,225) Headache, 1 month: 18% (220/1,225) Headache, 3 months: 13% (159/1,225) Nausea, 1 month: 13% (159/1,225) Nausea, 3 months: 5% (61/1,225) Flatulence, 1 month: 10% (123/1,225) Flatulence, 3 months: 5% (61/1,225) Diarrhea, 1 month: 10% (123/1,225) Diarrhea, 3 months: 7% (86/1,225) Abdominal pain, 1 month: 3% (37/1,225) Abdominal pain, 3 months: 1% (12/1,225)

Appendix B Table 9. HIV Pre-Exposure Prophylaxis Cohort Studies: Results

Study Author, year	Interventions	Clinical health outcomes	Adverse events
Landovitz 2017[126] *PATH-PrEP*	TDF-FTC PrEP (n=278) Study also included a postexposure prophylaxis group (n=23)	HIV incidence rate: 0.4/100 person-years Mortality: 0 events Urethral gonorrhea incidence rate: 2.5/100 person-years Urethral chlamydia: 7.1/100 person-years Rectal gonorrhea: 19.7/100 person-years Rectal chlamydia: 37.8/100 person-years Pharyngeal gonorrhea: 21/100 person-years Syphilis: 11.8/100 person-years	Number of participants with Grade 3 or 4 GI event: 21 Injury: 1 ALT elevation: 13 AST elevation: 8 Blood bilirubin elevation: 9 Blood creatinine elevation: 1 Blood phosphorus decrease: 8 Muscle spasms: 1 Myalgia: 1 Headache: 1 Psychiatric disorder: 3 Glycosuria:1
Montgomery, 2016[127]	Oral TDF-FTC	1 HIV seroconversion found at 3 month followup; HIV mutations D67N, M184V, T21S, K219, and L10I	NR
U.S. PrEP Demonstration Project Liu, 2016[81] and Cohen, 2015[146]	TDF-FTC	HIV infection: 2/557; incidence 0.43/100 person-years (95% CI, 0.05 to 1.54) STI incidence, per 100 person-years: -Chlamydia: 48 (95% CI, 42 to 55) -Gonorrhea: 43 (95% CI, 37 to 49) -Syphillis: 12 (95% CI, 9 to 16) -Any STI: 90 (95% CI, 81 to 99)	Serious adverse events: 3% (19/557) Psychiatric adverse events: 1% (8/557) Elevation in serum creatinine: 4% (23/557) Bone fracture: 2% (12/557)
van Epps, 2018[128]	TDF-FTC PrEP (n=1,086)	NR	NR

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ATN=Adolescent Trials Network for HIV/AIDS Interventions; BMD=bone mineral density; CI=confidence interval; FTC=emtricitabine; GI=gastrointestinal; iPrEx-OLE=Pre-Exposure Prophylaxis Initiative–Open Label Extension Study; NR=not reported; PrEP=pre-exposure prophylaxis; STI=sexually transmitted infection; TDF=tenofovir disoproxil; U.S.=United States.

Appendix B Table 10. HIV Pre-Exposure Prophylaxis Cohort Studies: Adherence

Study Author, year	Interventions	Methods for reporting/measuring adherence	Association between adherence and effectiveness	Adherence rates	Factors associated with adherence
Chan, 2016[124]	Oral TDF-FTC	Self-report: Patients were asked whether they had missed any doses in the previous 7 and 30 days Past week adherence: taking ≥4 pills or 100% adherence in the past 7 days Past-month adherence: having missed ≤5 pills or 100% adherence in the past month	NR	Total population In program for ≥6 months and received prescription for PrEP: 100% (171/171) Initiated PrEP: 81% (139/171) Retained in PrEP Care at 3 months: 73% (124/171) Retained in PrEP Care at 6 months: 60% (102/171) Providence site only In program for ≥6 months and received prescription for PrEP: 100% (80/80) Initiated PrEP: 76% (61/80) Retained in PrEP Care at 3 months: 69% (55/80) Retained in PrEP Care at 6 months: 54% (43/80) Jackson site only In program for ≥6 months and received prescription for PrEP: 100% (61/61) Initiated PrEP: 85% (52/61) Retained in PrEP Care at 3 months: 70% (43/61) Retained in PrEP Care at 6 months: 62% (38/61) St. Louis site only In program for ≥6 months and received prescription for PrEP: 100% (30/30) Initiated PrEP: 87% (26/30) Retained in PrEP Care at 3 months: 87% (26/30) Retained in PrEP Care at 6 months: 70% (21/30)	MSM only, PrEP initiation Age (per year): OR, 0.99 (95% CI, 0.96 to 1.03); aOR, 0.97 (95% CI, 0.93 to 1.02) Black vs. all others: OR, 1.24 (95% CI, 0.54 to 2.82); aOR, 1.32 (95% CI, 0.42 to 4.15) MSM vs. all others: OR, 1.18 (95% CI, 0.36 to 3.83); aOR: NA No insurance vs. any insurance: OR, 1.36 (95% CI, 0.57 to 3.25); aOR, 1.42 (95% CI, 0.44 to 4.51) MSM, 3-month retention to care Age (per year): OR, 1.05 (95% CI, 0.99 to 1.12); aOR, 1.03 (95% CI, 0.93 to 1.14) Black vs. all others: OR, 0.24 (95% CI, 0.08 to 0.74); aOR, 0.13 (95% CI, 0.02 to 0.77) MSM vs. all others: OR, 2.33 (95% CI, 0.58 to 9.45); aOR: NA No insurance vs. any insurance: OR, 2.64 (95% CI, 0.86 to 8.11); aOR, 1.48 (95% CI, 0.33 to 6.55) MSM, 6-month retention to care Age (per year): OR, 1.02 (95% CI, 0.98 to 1.05); aOR, 1.00 (95% CI, 0.95 to 1.05) Black vs. all others: OR, 0.66 (95% CI, 0.30 to 1.42); aOR, 0.74 (95% CI, 0.25 to 2.16) MSM vs. all others: OR, 2.00 (95% CI, 0.66 to 6.07); aOR: NA No insurance vs. any insurance: OR, 1.17 (95% CI, 0.48 to 2.84); aOR, 0.87 (95% CI, 0.27 to 2.75)

Appendix B Table 10. HIV Pre-Exposure Prophylaxis Cohort Studies: Adherence

Study Author, year	Interventions	Methods for reporting/measuring adherence	Association between adherence and effectiveness	Adherence rates	Factors associated with adherence
Hosek, 2017[93] Project PrEPare, ATN 110	TDF-FTC	Direct blood spot for TFV-DP levels, every 4 weeks up to week 12 and every 12 weeks up to week 48	None of the 4 participations who seroconverted had detectable levels of TFV-DP in the sample that was drawn closest to the seroconversion date No ART resistance was detected	TFV-DP, ≥350 fmol/punch: Week 4: 92% (159/173) Week 8: 96% (157/164) Week 12: 92% (146/159) Week 24: 81% (120/148) Week 36: 78% (105/134) Week 48: 69% (83/120)	Adherent participants vs. nonadherent participants: Worried less about getting HIV (p=0.01) Felt more comfortable having sex with an HIV-infected partner (p=0.01) Feared developing medication resistance if they contracted HIV (p=0.004) Significantly more nonadherent participants reported not liking taking pills than adherent participants (p=0.02) Participants who reported engaging in recent condomless sex, TFV- DP levels were consistently higher (p=0.01) and remained higher over the course of the study Reasons for missing study pills: "Often" or "sometimes" forgot: 29% Were away from home: 27% Too busy with other things: 27% Wanting to avoid side effects: 4% Did not want others to seem them taking the medication: 2% Believed the pill was harmful: 2%
Hosek 2017[92] Project PrEPare, ATN 113	TDF-FTC	Dried blood spot TFV-DP	3 HIV seroconversions, TFV-DP levels all consistent with <2 doses PrEP/week	TFV-DP indicating ≥4 doses/week (>700 fmol/punch; n=72): 4 weeks: 54% 8 weeks: 47% 12 weeks: 49% 24 weeks: 28% 36 weeks: 17% 48 weeks: 22%	Nonadherent participants: 29% likely to endorse the statement “I worry others will see me taking pills and think I am HIV-positive” Reasons for missing dose included being away from home (32%), being too busy (28%), forgetting (26%), and changes in routine (18%)

Appendix B Table 10. HIV Pre-Exposure Prophylaxis Cohort Studies: Adherence

Study Author, year	Interventions	Methods for reporting/measuring adherence	Association between adherence and effectiveness	Adherence rates	Factors associated with adherence
iPrEx-OLE Grant, 2014[125]	TDF-FTC	Dried blood spot: any quantifiable TDF Self-report, week 12: PrEP use in past 3 days	HIV infection: No quantifiable TDF: 18 infections; incidence, 4.70 (95% CI, 2.99 to 7.76); HR, 1.25 (95% CI, 0.60 to 2.64) vs. concurrent off-PrEP <350 fmol/punch (estimated dose <2 tablets/week): 9 infections; incidence, 2.25 (95% CI, 1.19 to 4.79); HR, 0.56 (95% CI, 0.23 to 1.31) vs. concurrent off-PrEP 350–699 fmol/punch (estimated dose 2–3 tablets/week): 1 infection; incidence, 0.56 (95% CI, 0.00 to 2.50); HR, 0.16 (95% CI, 0.01 to 0.79) vs. concurrent off-PrEP 700–1,249 fmol/punch (estimated dose 4–6 tablets/week): no HIV infections; HR, 0.00 (95% CI, 0.00 to 0.21)	Dried blood spot, 12 weeks: 92% (264/288) Dried blood spot, 24 weeks: 92% (258/280) Dried blood spot, 36 weeks: 91% (253/277) Dried blood spot, 48 weeks: 92% (235/255) Dried blood spot, 60 weeks: 93% (219/236) Dried blood spot, 72 weeks: 93% (199/213) Self- report, 12 weeks: 85% (583/688)	Predictors of drug concentration in dried blood spot, aOR (95% CI): Condom use vs. condomless insertive anal intercourse: 1.06 (0.71 to 1.58); vs. condomless receptive anal intercourse: 1.66 (1.37 to 2.02) 1 to 3 male sexual partners in 3 months before study entry vs. 2 to 4 partners: 1.22 (1.09 to 1.62); vs. ≥5 partners: 1.82 (0.85 to 1.30) HIV-infected partner: 1.44 (1.05 to 1.99) STI at time of open-label enrollment: 1.05 (0.85 to 1.30) Transgender: 0.72 (0.55 to 0.94) Ages 18 to 24 years vs. 25 to 29 years: 1.19 (0.92 to 1.55); vs. 30 to 39 years: 1.64 (1.26 to 2.15); vs. ≥40 years: 3.29 (2.39 vs. 4.53) <5 vs. ≥5 alcohol drinks/day: 0.81 (0.65 to 1.02) Methamphetamine use in 30 days before enrollment: 0.78 (0.43 to 1.42) Cocaine use in 30 days before enrollment: 1.07 (0.83 to 1.38)
iPrEx-OLE Glidden, 2016[142]	Same as Grant 2014	Same as Grant 2014	NR	Same as Grant 2014	Adherence and symptoms: GI symptoms and dried blood ≥700 fmol/punch: range, 0% to 94% No GI symptoms and dried blood ≥700 fmol/punch: range, 37% to 91% Non-GI symptoms, by dried blood spots stratum, week 4: aOR, 1.2 (95% CI, 0.40 to 3.7) GI symptoms, by DBS stratum, week 4: aOR, 0.47 (95% CI, 0.23 to 0.96) Estimated 7% (95% CI, 4 to 11) of use at <4 pills/week (<700 fmol/punch) associated with GI symptoms

Appendix B Table 10. HIV Pre-Exposure Prophylaxis Cohort Studies: Adherence

Study Author, year	Interventions	Methods for reporting/measuring adherence	Association between adherence and effectiveness	Adherence rates	Factors associated with adherence
					Relationship between adherence, symptoms, and age: GI symptoms and age <30 years: 23% DB ≥700 fmol/punch No GI symptoms and age <30 years: 47% DB ≥700 fmol/punch GI symptoms and age ≥30 years: 57% DB ≥700 fmol/punch No GI symptoms and age ≥30 years: 64% DB ≥700 fmol/punch; p=0.09 for interaction Relationship between adherence and symptoms at 1 month vs. 2 and 3 months: 1 vs. 2 months: OR, 0.85 (95% CI, 0.38 to 1.86) 1 vs. 3 months: OR, 0.47 (95% CI, 0.25 to 0.92)
Landovitz 2017[126] *PATH-PrEP*	TDF-FTC PrEP (n=278) Study also included a postexposure prophylaxis group (n=23)	Dried blood spot	One HIV seroconversion: occurred in a participant who attended study visits per protocol through week 24 and then was lost to followup. Despite initially good adherence (weeks 4 and 12), his week 24 dried blood spot specimen suggested adherence, on average, of <2 doses per week over the previous 4 to 8 weeks.	Adherence, ≥700 fmol/punch (4–7 tablets/week): Week 4: 83.1%; Week 12: 83.4%; Week 24: 75.7%; Week 36: 71.6%; Week 48: 65.5% <u>By race/ethnicity</u> Non-Hispanic white, adherence, ≥700 fmol/punch (4–7 tablets/week); Week 4: 86.0%; Week 12: 89.3%; Week 24: 82.0%; Week 36: 80.0%; Week 48: 68.7% Non-Hispanic black, adherence, ≥700 fmol/punch (4–7 tablets/week); Week 4: 59.4%; Week 12: 56.3%; Week 24: 43.8%; Week 36: 37.5%; Week 48: 40.6% Hispanic/Latino, adherence, ≥700 fmol/punch (4–7 tablets/week); Week 4: 84.1%; Week 12: 81.7%; Week 24: 73.2%; Week 36: 64.6%; Week 48: 64.6% Mixed race/other, adherence, ≥700 fmol/punch (4–7 tablets/week); Week 4: 90.6%; Week 12: 87.5%; Week 24: 84.4%; Week 36: 84.4%; Week 48: 78.1%	<u>Adherence, ≥4 doses/week</u> Age, vs. 18–25 years: 26–35 years: aOR, 1.38 (95% CI, 0.63 to 3.03); 36–45 years: aOR, 4.75 (95% CI, 1.68 to 13.47); ≥46 years: aOR, 2.82 (95% CI, 1.14 to 6.96) Race/ethnicity, vs. white: Hispanic: aOR, 1.17 (95% CI, 0.59 to 2.34); Hispanic: aOR, 0.35 (95% CI, 0.16 to 0.74); Black/African American: aOR, 2.03 (95% CI, 0.62 to 6.64); Asian/Pacific Islander: aOR, 2.03 (95% CI, 0.62 to 6.64); other race/ethnicity: aOR, 1.49 (95% CI, 0.42 to 5.26) Exchange sex in the past 30 days, vs. yes: aOR, 1.30 (95% CI, 0.62 to 2.73) No significant difference in unadjusted ORs for condomless receptive anal intercourse within 3 months, binge drinking within 12 months, or substance or methamphetamine use within 30 days (comparisons, yes vs. no)

Appendix B Table 10. HIV Pre-Exposure Prophylaxis Cohort Studies: Adherence

Study Author, year	Interventions	Methods for reporting/measuring adherence	Association between adherence and effectiveness	Adherence rates	Factors associated with adherence
Montgomery, 2016[127]	Oral TDF-FTC	Dried blood spot samples Self-report: provider verbally asking patients the number of doses missed in the past 7 and 30 days	No correlation between TFV-DP concentration and past 30-day adherence (r=0.13; p=0.58)	Dried blood spot, proportion with TFV-DP concentrations: <2 doses/week (BLQ <349 fmol/punch): 5% (1/21) 2 to 3 doses/week (350–699 fmol/punch): 5% (1/21) ≥4 doses/week (≥700 fmol/punch): 90% (19/21) Dried blood spot, mean TFV-DP (n=21): 1493.5 fmol/punch (range, 31.9 to 4141.1) Dried blood spot, mean FTC-TP (n=19): 0.296 (range, 0.190 to 0.466) pmol/punch Self-report doses in the previous 7 days (n=35): 6.2 Self-report doses in the previous 30 days (n=35): 26.8	NR
U.S. PrEP Demonstration Project Liu, 2016[81] and Cohen, 2015[146]	TDF-FTC	Dried blood spotsamples: collected at all scheduled followup visits and at any visit when PrEP was stopped, measured in approximately 100 randomly selected participants per site and all black and transgender participants (underrepresented populations) Pill counts Medication ration: number of dispensed pills/number of days between visits Self-report: interviewer administered questionnaire rating scale	2 HIV seroconversions Case 1: last self-report PrEP 37 days before seroconversion; TFV-DP consistently indicated <2 doses/week Case 2: seroconversion detected at week 48, 4 weeks after study drugs were dispensed; TFV-DP consistent with daily dosing only at week 4	TFV-DP indicating ≥4 doses/week (n=294): 4 weeks: 86% 12 weeks: 85% 24 weeks: 82% 36 weeks: 85% 48 weeks: 80% All time points (n=272): 62.5% Pill counts: 81.6% Medication ratio (n=533): 85.9% Self-rated adherence described as very good or excellent (2,242 visits): 87.4%	Study site, Miami vs. San Francisco (ref): aOR, 0.32 (95% CI, 0.17 to 0.60) African American vs. white (ref): aOR, 0.28 (95% CI, 0.12 to 0.64) Living situation, rent or own vs. other (with friends, family, public housing, or homeless [ref]): aOR, 2.02 (95% CI, 1.14 to 3.55) Condomless receptive anal sex, ≥2 partners vs. 0 to 1 partner (ref): aOR, 1.82 (95% CI, 1.14 to 2.89) Health insurance, yes or no (ref): unadjusted OR, 1.71 (95% CI, 1.03 to 2.85) No association for other factors including age, education level, referral status, prior PrEP knowledge, depression, condomless receptive anal sex in the last 3 months, alcohol consumption, or drug use

Appendix B Table 10. HIV Pre-Exposure Prophylaxis Cohort Studies: Adherence

Study Author, year	Interventions	Methods for reporting/measuring adherence	Association between adherence and effectiveness	Adherence rates	Factors associated with adherence
van Epps, 2018[128]	TDF-FTC PrEP (n=1,086)	Prescription refill data	NR	Proportion of days covered by PrEP prescription: median, 0.74 (IQR, 0.40 to 0.92) Proportion of days covered >0.8: 40%	Adherence, proportion of days covered >0.8 Age <35 vs. 35–49 years: aOR, 1.36 (95% CI, 1.00 to 1.85); vs. 50–64 years: aOR, 2.00 (95% CI, 1.37 to 2.92); vs. 65–79 years: aOR, 1.78 (95% CI, 0.98 to 3.22) Male vs. female sex: aOR, 3.39 (95% CI, 1.37 to 8.42) Black race vs. white: aOR, 2.02 (95% CI, 1.43 to 2.87); other race: aOR, 2.05 (95% CI, 1.14 to 3.71) Comorbid substance use vs. nonuse: aOR, 0.91 (95% CI, 0.65 to 1.27); depression vs. no depression: aOR, 0.98 (95% CI, 0.75 to 1.28); hypertension vs. no hypertension: aOR, 0.77 (95% CI, 0.55 to 1.08); diabetes vs. no diabetes: aOR, 2.02 (95% CI, 1.25 to 3.28) Rural vs. urban: aOR, 0.88 (95% CI, 0.46 to 1.70)

Abbreviations: aOR=adjusted odds ratio; ATN=Adolescent Trials Network for HIV/AIDS Interventions; BLQ=below the level of quantification; CI=confidence interval; FTC=emtricitabine; FTC-TP emtricitabine triphosphate; GI=gastrointestinal; HR=hazard ratio; IQR=interquartile range; MSM=men who have sex with men; NA=not applicable; NR=not reported; OR=odds ratio; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil; TFV-DP= tenofovir-diphosphate; U.S.=United States.

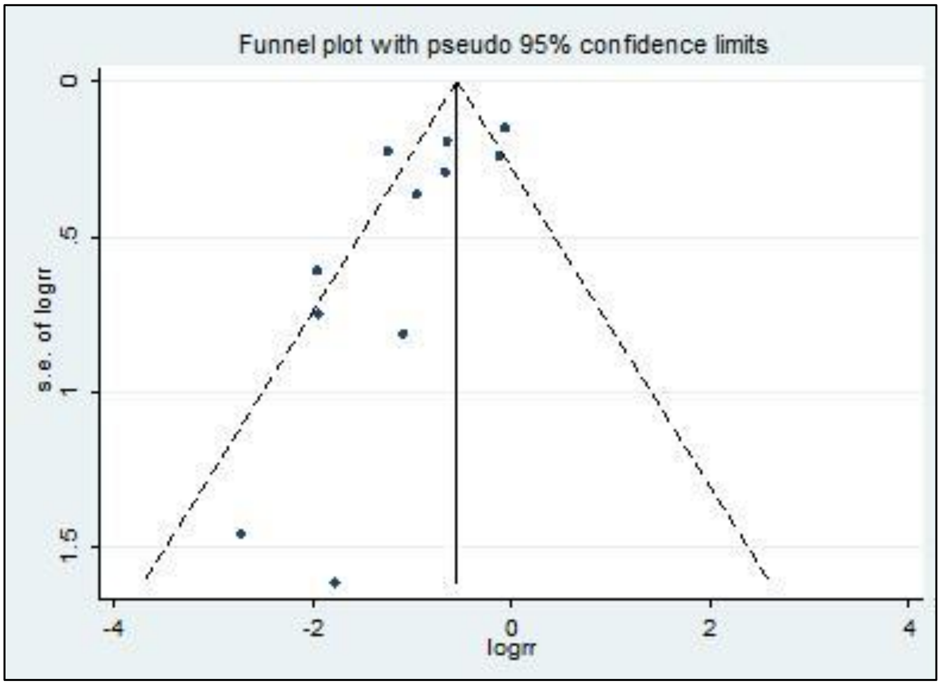
Appendix B Table 11. HIV Pre-Exposure Prophylaxis Cohort Studies: Quality Assessment

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Is there high attrition?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating
Chan, 2016[124]	Yes	Yes	Unclear	Yes	Yes; 27% at 3 months and 40% at 6 months	Yes	Fair
Hosek, 2017[93]	Unclear	Yes	No	Yes	No	Yes	Fair
Hosek, 2017[92]	Unclear	Yes	No	Yes	Yes; 44% discontinued	Yes	Fair
iPrEx-OLE Grant, 2014[125], Glidden, 2016[142]	Yes	Yes	No	Yes	No	Yes	Good
Landovitz, 2017[126]	Unclear	Yes	No	Yes	Yes	Yes	Fair
Montgomery, 2016[127]	Yes; consecutive	Yes	No	Yes	Yes; 30%	Yes	Fair
U.S. PrEP Demonstration Project Liu, 2016[81]	Unclear; likely yes	Yes	No	Yes	No	Yes	Fair
van Epps, 2018[128]	Yes	Yes	Unclear	Yes	Yes, 44%	Yes	Fair

Note: Standard cohort quality criteria modified for single-arm studies.

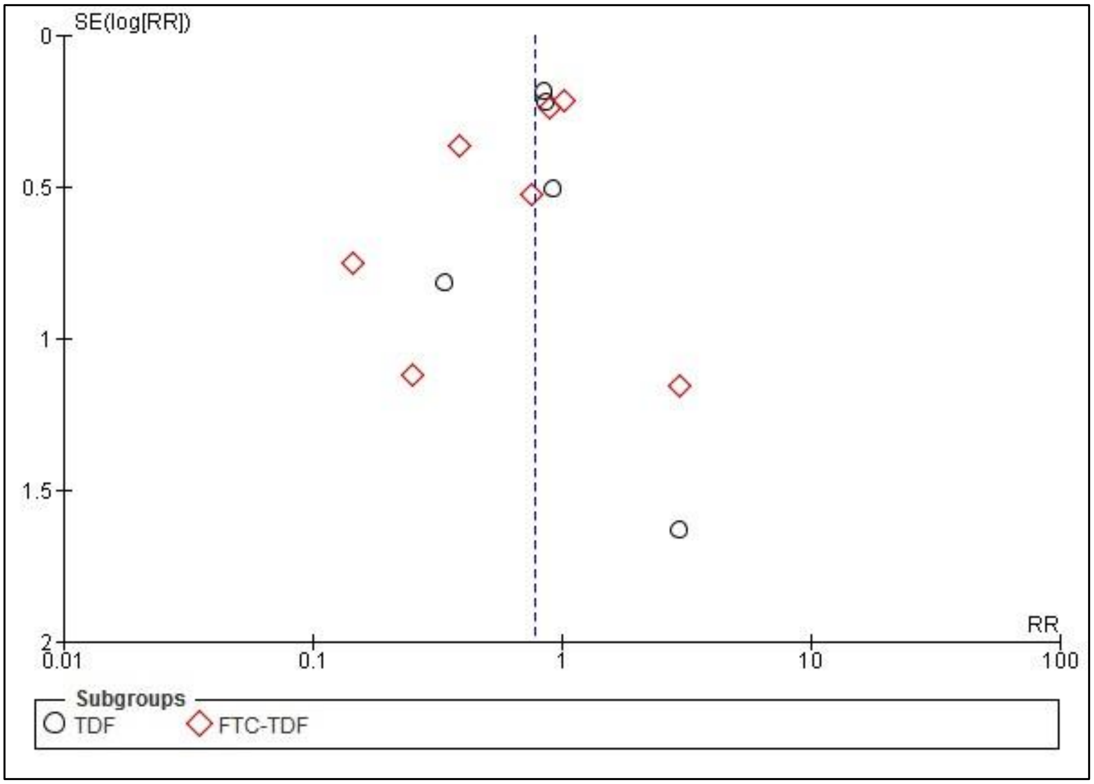
Abbreviations: iPrEx-OLE=Pre-Exposure Prophylaxis Initiative–Open Label Extension Study; PrEP=pre-exposure prophylaxis; U.S.=United States.

Appendix C Figure 1. Funnel Plot: HIV Infection



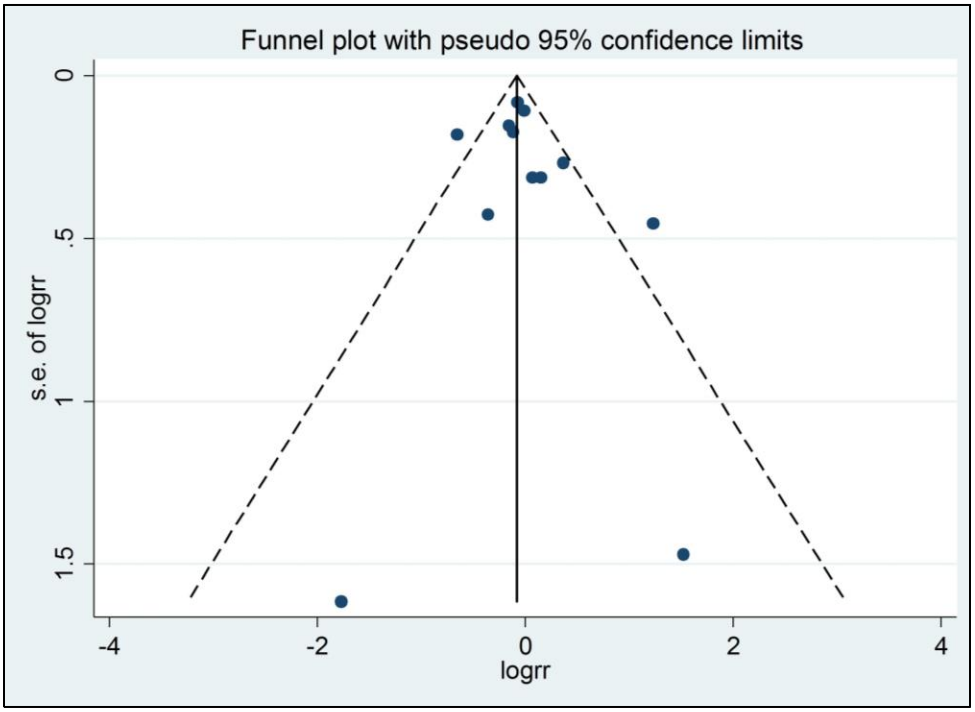
Abbreviation: s.e.=standard error.

Appendix C Figure 2. Funnel Plot: Mortality



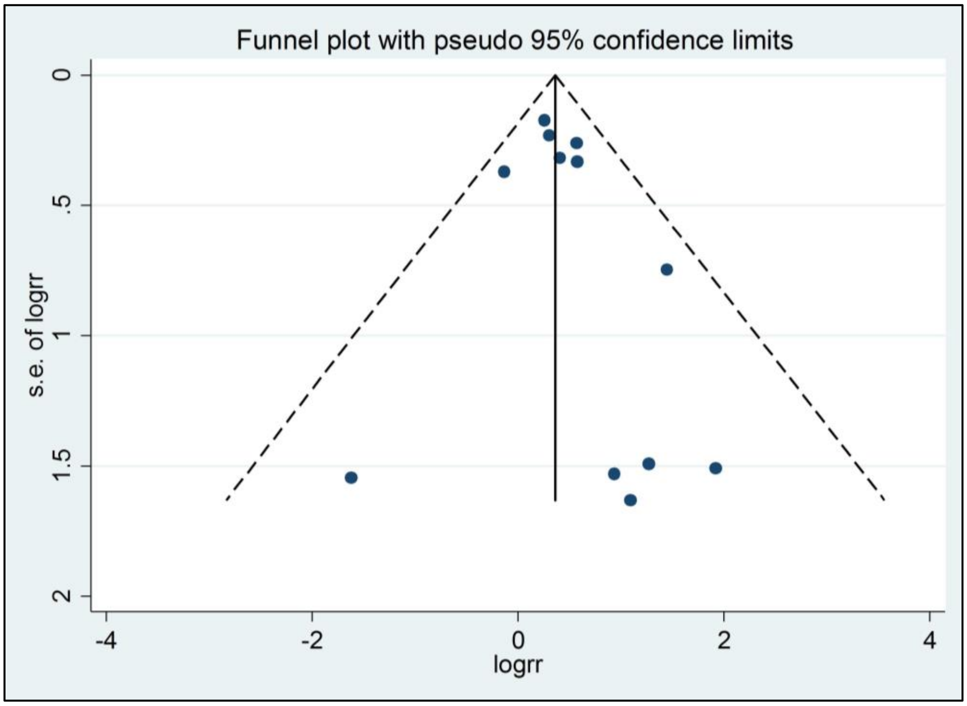
Abbreviations: FTC=emtricitabine; RR=relative risk; SE=standard error; TDF=tenofovir disoproxil.

Appendix C Figure 3. Funnel Plot: Serious Adverse Events



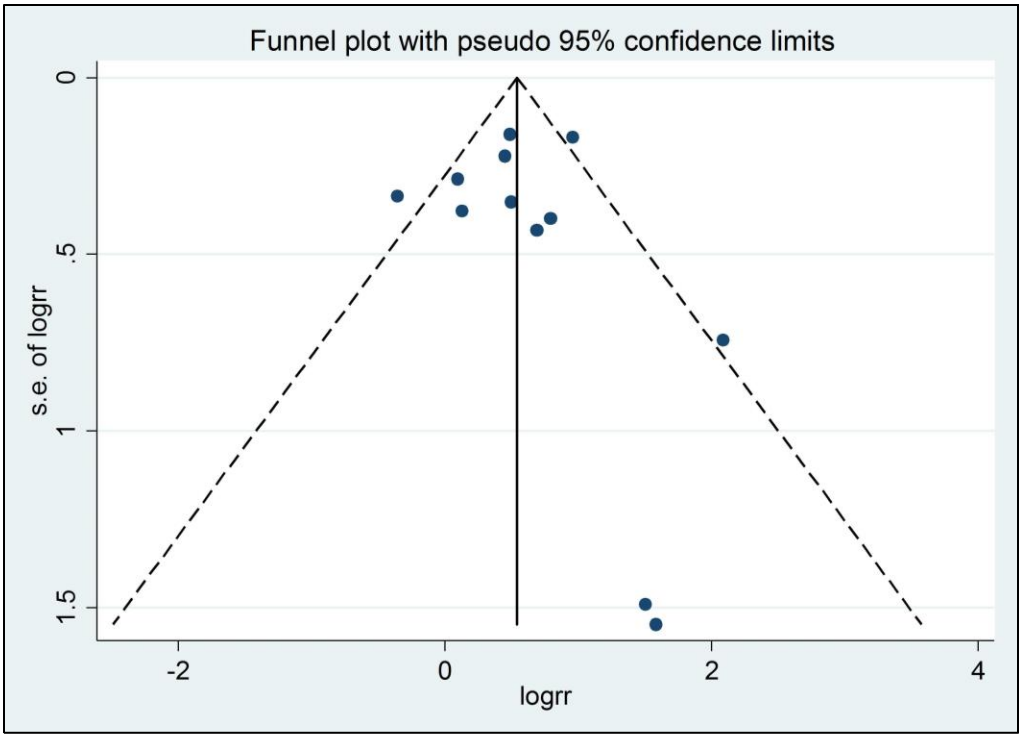
Abbreviation: s.e.=standard error.

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.