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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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U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

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Prepared by:
Pacific Northwest Evidence-Based Practice Center
Oregon Health & Science University
Mail Code: BICC
3181 SW Sam Jackson Park Road
Portland, OR 97239
www.ohsu.edu/epc

Investigators:
Roger Chou, MD
Christopher Evans, MD, MPH
Adam Hoverman, DO, DTMH
Christina Sun, PhD
Tracy Dana, MLS
Christina Bougatsos, MPH
Sara Grusing, BS
P. Todd Korthuis, MD, MPH

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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 human immunodeficiency virus (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 in order to decrease the risk of acquiring HIV infection.

Purpose: 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.

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.

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 U.S. Preventive Services Task Force.

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% 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). Effects were consistent across HIV risk categories and for PrEP with emtricitabine/tenofovir disoproxil fumarate (TDF-FTC) or tenofovir (TDF). 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 for interaction <0.00001). No trial reported effects of non-daily 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 [ARD] 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%; ARD 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, evidence lacking in adolescents and pregnant women.

Conclusions: In adults at increased risk of HIV infection, oral PrEP with TDF or TDF-FTC is associated with decreased risk of HIV infection compared to placebo or no PrEP, though effectiveness decreases with inadequate adherence. PrEP is associated with increased risk of renal adverse events and gastrointestinal events. Evidence on the accuracy of instruments for identifying people at high risk for 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 ("on-demand" or "event-driven" PrEP) in order 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 the Acquired Immune Deficiency Syndrome (AIDS) in over 90 percent of patients. AIDS is a potentially life-threatening condition that occurs when HIV becomes severe, as defined by CD4 count 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, over 700,000 people diagnosed with AIDS in the United States have died.[3] The Centers for Disease Control and Prevention (CDC) estimates that approximately 1.1 million people in the United States were living with HIV infection in 2015,[3] including 15 percent unaware of their infection.[4] This represents a decrease since 2008, when approximately 20 percent of infected individuals 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 in 2011 to 40,000 each year from 2013 to 2016.[3] Approximately 530,000 people were living with AIDS in 2015.

Groups more affected by HIV infection in the United States include men who have sex with men (MSM), people who are black, and Hispanics/Latinos. Between 2006 and 2009, there was a 21 percent increase in HIV incidence for people ages 13 to 29 years, driven largely by a 34 percent increase in MSM, 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 (13 years of age or older), 7,529 (19%) among adult and adolescent females, and 122 (0.3%) among children younger than 13 years of age.[3] Those between 20 and 34 years of age accounted for half of the new diagnoses and had the highest incidence of HIV

infection (26.2 to 34.8 per 100,000 people). Among adolescents, the incidence of HIV infection rose sharply from 13 to 14 years of age (0.3 per 100,000 people) to 15 to 19 years of age (7.8 per 100,000). By race/ethnicity, 44 percent of new diagnoses occurred in people who are black, 26 percent in people who are white, and 25 percent in Hispanics/Latinos.[3] Among men, MSM is the most common transmission category (83%), followed by heterosexual contact (9.4%), injection drug use (4.0%), and MSM and injection drug use (3.7%). Among females, heterosexual contact is the most common transmission category (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., condomless penile-anal or penile-vaginal intercourse, sex with multiple partners, sex with people with or at high risk of HIV infection), and high viral load in the infected partner.[9,10] In people who inject drugs (PWIDs), 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 individuals remain asymptomatic and show little evidence of progressive immune suppression after 10 or more years of infection, over 90 percent of untreated patients eventually develop AIDS.[1] In the pre-highly active antiretroviral therapy (HAART) era, 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] though 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 for 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 CCR5 delta32 genotype.[35-39]

Risk Factors

People at increased risk for HIV infection include MSM; men and women having condomless vaginal or anal intercourse with more than one partner; men and women who

exchange sex for drugs or money; people with a history of or current injection drug use; people seeking treatment for other STIs; people with a history of blood transfusion between 1978 and 1985; people whose past or present sex partners were HIV-infected, bisexual, or people who inject drugs; transgender individuals; and people 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 >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, in order to identify infected people; ART in HIV-infected people to reduce risk of transmission;[45] and behavioral counseling to reduce high-risk sexual and drug use behaviors.

For people at substantial risk for 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 in order to lower the likelihood of acquiring of HIV infection. It differs from non-occupational 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 for sexual acquisition.,[49] In 2018, the FDA expanded the indication for PrEP to include adolescents weighing at least 35 kg (77 pounds).[50] Because effectiveness of PrEP depends on adherence,[51] there is also interest in non-daily 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, non-daily) dosing of TDF-FTC.[53,54] Research is also ongoing on alternative, non-oral modes of PrEP administration that require infrequent dosing (e.g., long-acting injectables[55] or an intravaginal ring[56]).

Factors that may impact the balance of benefits and harms in people prescribed PrEP include adverse drug-related events, the potential for antiretroviral resistance in people 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., condomless sex 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 due to inadequate treatment in HIV-infected people who inadvertently receive PrEP or in HIV-

uninfected people 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 U.S. Public Health Service issued a guideline recommending TDF-FTC PrEP in adults at high risk of infection, including MSM with a high number of sex partners or inconsistent condom use, MSM and heterosexual individuals in HIV-serodiscordant relationships, other high-risk heterosexual individuals, and PWIDs that share injection equipment; the guideline was updated in 2017.[60] The guideline also includes TDF alone as an option for PrEP in PWIDs 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 for adolescents are insufficient, but were developed prior to 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 people at high risk of sexual acquisition of HIV infection.[61]

Recent data indicate that implementation of PrEP in the United States remains limited. The CDC estimated approximately 1.2 million people eligible for PrEP in 2015 (492,000 MSM, 115,000 PWIDs, and 624,000 heterosexually active adults), but only an estimated 125,000 active PrEP prescriptions.[62,63] Evidence from clinicians in the United States, particularly among primary care providers, indicate gaps in knowledge and uptake of PrEP.[64] A survey of over 500 providers in 10 U.S. cities during 2014-2015 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%).[65] Primary care providers were also less comfortable than HIV providers at 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.[66] 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.[67] Prescribing was associated with greater knowledge about PrEP, positive attitudes towards PrEP, and confidence in prescribing PrEP.

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[68] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) 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 prior to finalization.

Key Questions

1. What are the benefits of PrEP in individuals 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 individuals 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 Question 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 individuals 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.

Study Selection

All titles and abstracts identified through searches were independently reviewed by a trained member of the research team for eligibility against pre-defined inclusion/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 trained 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 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 FDA-approved 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 versus TDF-FTC in effects on risk of HIV acquisition,[69] and is an option for PrEP in PWIDs and heterosexual men and women in the 2017 U.S. 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 maraviroc-containing regimens[70]) or delivery methods (e.g., long-acting injectables,[55] the intravaginal ring,[71-73] or vaginal gel[74-76]), which are not FDA-approved or recommended in other countries. The main comparison was PrEP versus placebo; one trial compared PrEP versus no (delayed) PrEP.[77] To address effects of dosing method on effectiveness, we also included randomized trials of daily versus non-daily (intermittent or event-driven) PrEP.

The population of interest for PrEP was HIV-uninfected people at higher risk for 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 people 13 to <18 years of age). Patient subgroups of interest were based on demographic characteristics (age, sex, race/ethnicity, 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, in order 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 (HCV) infection, renal insufficiency, fractures, gastrointestinal adverse events, and pregnancy-related outcomes. HSV infection is addressed as a potential harm due to possible effects of behavioral risk compensation, thoughtenofovir may have antiviral effects that decrease risk of HSV transmission.[78,79] 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.[80] 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, adherence to alternative regimens), and evidence on effects of resistance due to PrEP on clinical outcomes appears to be very limited.[81]

To assess applicability, we abstracted data regarding the countries in which studies were performed, the demographic characteristics of the patients enrolled, the PrEP interventions utilized, and rates of HIV acquisition, adherence, and use of post-exposure 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.[82,83]

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.[84]

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 A5**).[68] 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.[85]

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.[86] 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 CIs in this situation.[87] We conducted additional

sensitivity and stratified analyses based on study quality, PrEP drug regimen (TDF or TDF-FTC), HIV risk category (MSM, PWIDs, men and women at increased risk due to 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.[88] We analyzed effects of study-level adherence as a categorical variable in a stratified analysis (≥70%, >40% to <70%, or ≤40%)[89] and as a continuous variable through metaregression, 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 non-seroconverters 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).[90]

For all Key Questions, the overall quality of evidence was determined using the approach described in the USPSTF Procedure Manual.[68] 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.[68]

External Review

The draft report was reviewed by content experts (**Appendix A6**), USPSTF members, AHRQ Project Officers, and collaborative partners, and will be posted for public comment; the report will be revised based on reviewer comments prior to finalization.

Chapter 3. Results

Key Question 1. What are the benefits of pre-exposure prophylaxis (PrEP) in individuals 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% confidence interval [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).[52,53,69,75,77,84,91-95]
- There was a strong association between degree of adherence and PrEP effectiveness (p for interaction <0.00001)
    - Adherence ≥70%: 6 trials, RR 0.27, 95% CI 0.19 to 0.39; I^2=0%[52,53,69,77,84,94]
    - Adherence >40% to <70%: 3 trials, RR 0.51, 95% CI 0.38 to 0.70; I^2=0%[91-93]
    - Adherence ≤40%: 2 trials, RR 0.93, 95% CI 0.72 to 1.20; I^2=0%.[75,95]
- 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[69,91,92,95] and sex.[69,91,94]
- 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 MSM[52] evaluated event-driven (as opposed to daily) PrEP (RR 0.14, 95% CI 0.03 to 0.63).
- PrEP was associated with a non-statistically significant trend towards reduced risk of mortality versus no PrEP or placebo (9 trials, RR 0.81, 95% CI 0.59 to 1.11; I^2=0%).[69,75,77,84,91-95]
- No trial reported effects of PrEP versus placebo or no PrEP on quality of life.

Evidence

Twelve RCTs (reported in 29 publications[52-54,69,75,77,84,91-112]) evaluated PrEP versus placebo or no PrEP (**Table 2; Appendix B1**). 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).[77] Six trials[54,69,75,93-95] enrolled men and women at increased risk of HIV infection due to heterosexual contact, four trials[52,77,84,92] MSM or transgender women, one trial[53] both MSM and high-risk women, and one trial[91] PWIDs. The mean age in all trials was <40 years. No trial enrolled pregnant women or people younger than 18 years of age.

Three trials[84,91,93] evaluated TDF 300 mg, seven trials[52-54,92,94,95] TDF 300 mg-FTC 200 mg, one trial[77] TDF 245 mg-FTC 200 mg, and two trials[69,75] included arms for both TDF 300 mg

alone and TDF 300 mg-FTC 200 mg. PrEP was prescribed daily in eleven trials[53,54,69,75,77,84,91-95] and dosing was intermittent or event-driven in three trials (two of which also included daily dosing arms).[52-54] In one trial (IPERGAY), event-driven PrEP consisted of two tablets of TDF-FTC 2 to 24 hours prior to 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.[77]

Seven trials were conducted in Africa,[53,54,69,75,93-95] one in Thailand,[91] two in Europe or Canada,[52,77] one in the United States,[84] and one trial was international (~10% of patients from U.S. sites).[92] The trial conducted in the United States (n=400) evaluated daily TDF versus placebo in MSM;[84] the two trials conducted in Europe and Canada[52,77] and the international trial[92] also focused on MSM. All trials of people at higher risk of HIV infection due to heterosexual contact were conducted in Africa and the only trial of PWIDs was conducted in Thailand.[91] 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, though 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 not-for-profit organizations. One trial also reported industry funding,[77] three trials reported that study medications were donated by industry,[53,54,95] and one trial noted that two investigators received royalties or funding from industry.[94] One trial[77] was rated fair quality, due to unclear allocation concealment methods and open-label design (**Appendix B2**). 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[52-54,69,75,77,84,91-95] 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 B1**). 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 C1**). Excluding the single fair-quality study[77] 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 iPrEx trial.[88,92]

Two African trials (FEM PrEP and VOICE)[75,95] of women at risk of HIV infection due to 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%;[52,53,69,77,84,94] adherence >40% to <70%: 3 trials, RR 0.51, 95% CI 0.38 to 0.70; I^2=0%;[91-93] and adherence ≤40%: 2 trials, RR 0.93, 95% CI 0.72 to 1.20; I^2=0%[75,95]) and stratification eliminated statistical heterogeneity (**Table 3, Figure 3)**.[52,53,69,75,77,84,91-95]

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 for interaction=0.35) <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%),[52,53,93] ≥1 year to <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%),[77,92,94,95] or ≥2 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%),[69,75,84,91] or whether trials reported receipt of industry support (3 trials, RR 0.58, 95% CI 0.27 to 1.22; I^2=54%)[53,94,95] versus only reporting governmental or non-for-profit funding (8 trials, RR 0.39, 95% CI 0.23 to 0.64; I^2=77%)[52,69,75,77,84,91-93] (**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%)[52,77,84] 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 for interaction=0.004; **Figure 6**).[53,54,69,75,91-95] All three trials conducted in the United States, Europe, or Canada reported high adherence and enrolled MSM.

Mortality

Nine trials[69,75,77,84,91-95] 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; follow up 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 C2**). 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 1.1.4).

Quality of Life

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

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 due to heterosexual contact (5 trials, RR 0.54, 95% CI 0.31 to 0.97, I^2=82%),[54,69,75,93-95] MSM or transgender women (4 trials, RR 0.23, 95% CI 0.08 to 0.62, I^2=64%),[52,77,84,92] or PWIDs (1 trial, RR 0.52, 95% CI 0.29 to 0.92; p for interaction=0.43; **Figure 8**),[91] though evidence of effectiveness in PWIDs was limited to one Asian trial. 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.[75,95]

Five trials performed within-study subgroup analyses of PrEP effectiveness (**Table 4**).[69,91,92,94,95] Four trials[69,91,92,95] found no clear differences in PrEP effectiveness in subgroups defined according to age and three trials[69,91,94] found no clear differences between males and females. A post-hoc analysis of the iPrEx trial[92] found that PrEP was effective in MSM (hazard ratio [HR] 0.50, 95% CI 0.34 to 0.75) but not in transgender women (HR 1.1, 95% CI 0.5 to 2.7), though 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 people.[92] Among three trials conducted in the United States, Europe, or Canada, the proportion of participants who were white ranged from 73 to 91 percent.[52,77,84]

Data were limited regarding effects of risk behaviors on effectiveness of PrEP. One trial found PrEP was effective in transgender women and MSM who reported receptive anal intercourse (HR 0.42, 95% CI 0.26 to 0.68) but not in those who did not report receptive anal intercourse (HR 1.59, 95% CI 0.66 to 3.84, p for interaction=0.01).[92] 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.[69] This trial also found both TDF and TDF-FTC associated with similar effectiveness when analyzed according to sexual risk behaviors and viral load (**Appendix B1**).[110] A trial of PWIDs (the Bangkok Tenofovir Study) found no association between drug injection or needle sharing in the 12 weeks prior to enrollment and effectiveness of PrEP.[91]

Mortality

When stratified according to patient population, pooled estimates for effects of PrEP versus placebo or no PrEP on mortality were similar (p for interaction=0.90) in trials of women and men at increased risk of HIV infection due to heterosexual contact (4 trials, RR 0.71, 95% CI 0.36 to 1.42; I^2=0%),[69,75,94,95] MSM or transgender women (4 trials, RR 0.87, 95% CI 0.22 to 3.41; I^2=0%),[77,84,92,93] and PWIDs (1 trial, RR 0.85, 95% CI 0.58 to 1.23; **Figure 9**).[91]

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%)[69,75,84,91,93] or TDF-FTC (8 trials, RR 0.44, 95% CI 0.27 to 0.72, I^2=74%, p for interaction=0.79, **Table 3**; **Figure 2**).[52,53,69,75,77,92,94,95] Among the trials that utilized 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 MSM (RR 0.14, 95% CI 0.03 to 0.63). Although the estimate was stronger than 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**),[69,75,77,84,91-95] 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).[53,69,77,84,94] 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 post-sex) or event-driven (dosing pre- and post-sex) TDF-FTC PrEP in MSM or transgender women[113] (n=357) and heterosexual African women[114] (n=178) (**Appendix B1**), but was not powered to evaluate effects of dosing on HIV infection risk (five total post-randomization cases across all risk groups and dosing regimens).

Data on the effects of use of post-exposure prophylaxis on efficacy of PrEP was limited. In the open-label PROUD trial, PrEP was more effective than no PrEP at reducing risk of HIV infection in MSM (RR 0.14, 95% CI 0.03 to 0.63), despite much less frequent use of post-exposure prophylaxis (4.4% vs. 32%) and an increased rate of receptive anal sex without a condom with ≥10 partners (21% vs. 12%) in people randomized to PrEP.[77] No other trial reported the proportion of patients who utilized post-exposure prophylaxis, though three trials described post-exposure prophylaxis as an HIV prevention intervention offered to all patients;[52,69,92] 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 utilized TDF or TDF-FTC (p for interaction=0.65; **Figure 7**).

Key Question 2. What is the diagnostic accuracy of provider or patient risk assessment tools in identifying individuals at increased risk of HIV acquisition who are candidates for PrEP?

Summary

- Three studies of different instruments for predicting incident HIV infection in MSM 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).[115-118] Two

studies found poorer discrimination of risk prediction instruments in black MSM (AUROC 0.49 to 0.63).[119,120] 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 PWIDs reported an AUROC of 0.72, but had methodological limitations and required validation.[121]
- No study evaluated a U.S.-applicable instrument for predicting incident HIV infection in women or men at risk for HIV infection due to heterosexual contact.
- No study evaluated an instrument for predicting incident HIV infection in people not pre-identified as belonging to an HIV risk category.

Evidence

Seven studies evaluated instruments developed and validated in U.S. cohorts for predicting incident HIV infection[115-121] (**Appendix B3**). Six studies evaluated risk prediction instruments in MSM[115-120] and one study in PWIDs.[121] Samples sizes (including development and validation cohorts) ranged from 300 to 9,481 patients (total N=32,279). For MSM, 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 MSM, black participants were 6 and 7.8 percent of the population in two studies;[115,116] one study reported that 23 percent of the population was non-white, Asian, or Pacific Islander,[117] and one study reported that the proportion non-White was 14 percent.[118] Two studies evaluated the performance of previously developed risk assessment in MSM cohorts in which 46 percent[120] or all participants[119] were black. The instrument for predicting risk in PWIDs 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 MSM; HIV incidence was 11 percent in the study on PWIDs.

All studies had methodological shortcomings (**Appendix B4)**. 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 MSM, new HIV infections were identified based on a single test for markers for acute or early HIV infection.[116] Three studies used cohorts that included people who underwent HIV testing prior to the year 2000.[117,118,121] In five studies, the predictive utility of risk assessment instruments was tested (validated) in cohorts independent from the one used to develop the instrument.[116-120] In two studies, accuracy was only reported for the cohort used to develop the instrument.[115,121] Cutoffs to define a positive test were pre-defined in two studies.[119,120]

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 United States or U.S.-applicable settings.[122-124] No study evaluated instruments for predicting risk of HIV infection in people not pre-identified as having an HIV risk factor (e.g., MSM, injection drug use, high-risk heterosexual behaviors). One study evaluated patients attending a clinic for lesbian, gay, bisexual, and

transgender people[115] and one study evaluated patients attending an STI clinic;[117] the other studies evaluated people enrolled in research studies.

Men Who Have Sex With Men

Six studies evaluated risk prediction instruments in MSM.[115-120] Items assessed in all of the risk instruments were presence of STIs, condomless sex (particularly receptive anal sex), and number of sex partners (**Appendix B3**). 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.[116-118] A fourth study[115] found that a 10-item instrument developed using data from the Los Angeles LGBT Center was associated with better goodness of fit based on the Akaike Information Criterion score than instruments developed in two other studies[117,118] or criteria from the 2014 CDC guidelines for offering PrEP in MSM.[60] However, the instrument was not validated using a separate (non-development) 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 MSM, with AUROCs ranging from 0.49 to 0.63.[119,120]

The 6-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.[118] 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 (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 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 4-item instrument by Menza et al. (score range 0 to 19) was validated using the same validation cohort as ARCH-MSM.[117] A cutoff score of ≥3 with this instrument provided comparable sensitivity (76%) and specificity (43%) to ARCH-MSM at a cutoff of ≥10, 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 ARCH-MSM (0.72, CI not reported). Methamphetamine and inhaled nitrite use were included as a single item in the Menza instrument.

The 4-item San Diego Early Test (SDET) score (range 0 to 10 points) was developed using a more contemporary (2008-2014) cohort.[116] 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 resulted in a sensitivity (73%) and specificity (48%) most comparable to ARCH-MSM at a cutoff of ≥10. 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 score 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).[115] 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, 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's Information and Schwarz Bayesian Criteria was slightly better with this instrument than the ARCH-MSM and similar to the Menza instrument, but this finding is difficult to interpret because goodness of fit was evaluated using data from the same cohort used to develop this instrument, and the other instruments included items that were not an exact match with data available in this database.

The 2014 CDC guideline includes recommended indications for PrEP in MSM (any anal sex without condoms in past 6 months, any STI diagnosed or reported in past 6 months, or ongoing sexual relationship with 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.[115]

Two studies found that risk prediction instruments performed more poorly in black MSM. In one study of MSM, the AUROC for the ARCH-MSM, SDET, and Menza instruments ranged from 0.51 to 0.62 overall, from 0.49 to 0.63 in the subgroup of black MSM, and from 0.60 to 0.67 in white MSM.[120] In the other study, the AUROC for the ARCH-MSM was 0.57 in black MSM, and similar using criteria derived from the CDC recommendations (AUROC 0.51) or the PrEP package insert (AUROC 0.54).[119]

People Who Inject Drugs

The 7-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 PWIDs in Baltimore.[121] 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, 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 PWIDs (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 Due to Heterosexual Contact

Three studies evaluated instruments for predicting risk of HIV infection in men and women at increased risk of HIV infection due to heterosexual contact but did not meet inclusion criteria because they were developed using data from African cohorts. One instrument focused on serodiscordant couples,[123] one in women,[124] and one in pregnant women.[122] The 2014 CDC guideline includes recommended indications for PrEP in men and women at increased risk for HIV infection due to heterosexual contact (man who has sex with women and men, infrequently uses condoms during sex with one or more partners of unknown HIV status who are known to be

at substantial risk of HIV infection, or 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. MSM (mean age 34-36 years) found adherence to PrEP of 66 to 90 percent, based on a tenofovir—diphosphate (TFV-DP) level of ≥700 fmol/punch on dried blood spot sampling (consistent with ≥4 doses/week).[80,125,126]
- Two observational studies of younger U.S. MSM (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 on dried blood spot sampling (consistent with ≥4 doses/week).[127,128] The proportion with a TFV-DP level of ≥350 fmol/punch (consistent with ≥2 doses/week) was 49 and 26 percent at 48 weeks.
- An RCT of U.S. MSM found adherence was higher with daily (48%) than intermittent (31%) or event-driven (17%) PrEP on weeks in which sex was reported, based on a TFV-DP level of ≥326 fmol/punch (consistent with ≥2 doses/week).[113]
- In two studies of U.S. MSM, adherence based on self-report was highly correlated with adherence based on drug levels on dried blood spot sampling.[84,129]
- No study evaluated rates of adherence to PrEP in U.S. PWIDs or women and men at increased risk of HIV infection due to heterosexual contact.

Evidence

Ten studies evaluated rates of adherence to PrEP in U.S. primary care and primary care-applicable settings (**Table 5**).[80,84,113,125-131] Three studies were RCTs (**Appendix B1**)[84,113,130] and seven were observational (**Appendix B5**).[80,125-129,131] Six studies assessed adherence based on drug levels from dried blood spot samples,[80,113,125-128] one study used plasma drug levels,[130] three studies used self-report,[80,125,129] two used a medication event monitoring system,[84,113] one used pill counts,[84] and one used prescription refill data.[131] In the RCTs, the number of participants randomized to PrEP ranged from 20 to 373 (total N=572)[84,113,130] and in the observational studies, the number of participants on PrEP ranged from 35 to 1,086 (total N=2,605).[80,125-130] Two RCTs evaluated daily TDF-FTC in MSM[84,130] and one RCT evaluated daily, intermittent, or event-driven TDF-FTC in MSM (97%) and transgender women (1.1%).[113] The observational studies all evaluated TDF-FTC. The largest observational study (n=1,086) did not report HIV risk behaviors or indications for PrEP.[131] In the other observational studies, all or nearly all (≥89%) of the population was MSM. One large (n=557) observational study, the Demo Project, enrolled MSM (98%) and transgender women (1.4%);[80] two smaller studies enrolled a small proportion of heterosexual men and women.[125,129] Two observational studies reported injection drug use in 1.6 to 3 percent of participants,[80,126] one reported no patients with a history of injection drug use,[125] 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.[84,130] Methodological shortcomings in the fair-quality RCT included unclear randomization and allocation concealment methods; in addition, it was unclear if outcomes

assessors were blinded.[128,130] 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 (**Appendices B2 and B6**).[80,125-129]

Six studies assessed PrEP drug levels based on intracellular drug concentrations of tenofovir-diphosphate (TFV-DP, the active moiety of tenofovir) in dried blood spot samples, which reflect longer-term cumulative drug exposure than tenofovir plasma levels.[80,113,125-128] In five observational studies of primarily MSM, based on presence of TFV-DP levels of ≥700 fmol/punch (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%[132-134] [see Key Question 4]), adherence rates ranged from 22 percent to over 90 percent.[80,125-128] 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),[80] 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) patients met the drug level adherence threshold at a mean PrEP duration of 4.4 months.[125] In two studies, adherence rates based on self-report were similar to rates based on dried blood spot testing.[80,125] The adherence rates in these studies were higher than in the iPrEx open-label extension study (52% meeting 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.[135]

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.[127,128] Both focused on younger MSM (mean ages 20 and 16 years) than the studies described above (mean ages >30 years). The proportion of patients meeting the adherence threshold for ≥4 doses/week was around 50 percent at week 12, decreasing to 34 and 22 percent at week 48. The proportion of patients with levels ≥350 fmol/punch (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, medication electronic monitoring systems) were not reported.

An RCT of MSM and transgender women enrolled at a U.S. site compared adherence with daily, intermittent, and event-driven PrEP, based on TFV-DP levels ≥326 fmol/punch (consistent with 2 or more PrEP pills taken per week; 2 doses per week associated with an estimated reduction in risk of HIV acquisition of 76 percent[134] [see Key Question 4][113]). 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 MSM (n=20 randomized to PrEP) evaluated adherence based on plasma TFV levels.[130] 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 sampling. Results were consistent with the observational studies of young MSM, 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 (people at risk due to heterosexual contact in Africa)[136] and 86 percent in the IPERGAY trial (MSM in Europe and Canada).[52] Both trials found PrEP to be effective. In Partners PrEP, the proportion of patients with plasma TDF

levels >40 ng/mL (consistent with dosing within the last 2 days) was about 70 percent[136] 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.[134]

Three U.S.-based studies reported adherence using methods other than drug levels.[84,129,131] A U.S.-based RCT of MSM (n=373)[84] reported adherence based on medication event monitoring system data of 79 percent of doses taken and based on 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 (IQR 0.40 to 0.92).[131] An observational study of primarily MSM (n=267)[129] 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,[75,96,130,137,138] though other RCTs have shown greater concordance.[77] 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 due to low adherence) or social desirability bias (patients might over-report adherence to avoid disappointing study personnel with whom they have developed relationships).[139]

No study evaluated adherence to PrEP in U.S. PWIDs or women and men at increased risk for HIV infection due to 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 to placebo for reducing risk of HIV infection than lower adherence.
- 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 (ORs ranged from 0.10 to 0.54).[69,75,91,94,95,105,136]
- 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[52,69,75,91-93,95,96,105,136] (**Appendix B1**) and five observational studies[80,126-128,140] (**Appendix B5**) 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 in the observational studies from 78 to 1,345 (total N=2,006). Three of the observational studies were conducted in the U.S.;[80,127,128,141] the other studies were conducted in Asia or Africa or were international studies. One RCT focused on people who inject drugs,[104] four RCTs on women and men at increased risk due to heterosexual contact,[69,75,94,95] and three in MSM and transgender women.[52,77,92]

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 to placebo for reducing risk of HIV infection than lower adherence (**Table 6**).[69,91,92,105,136] All of the trials evaluated daily dosing. A trial of PWIDs (the Bangkok Tenofovir Study), in which patients could choose between daily directly observed therapy or monthly visits without directly observed therapy, found a HR of 0.51 in those with ≥60 percent adherence and HR of 0.16 in those with ≥97.5 percent adherence.[91,105] Similarly, a trial of MSM and transgender women (iPrEx) found greater effectiveness at ≥90 percent adherence based on pill counts (HR 0.27, 95% CI 0.12 to 0.59) than with ≥50 percent adherence (HR 0.50, 95% CI 0.30 to .82).[92] 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 >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).[69]

Five RCTs evaluated the association between plasma tenofovir levels among participants randomized to PrEP and likelihood of HIV seroconversion (**Table 6**).[69,75,91,94,95,105,136] All of the trials evaluated daily dosing. In four trials, TDF levels in plasma were associated with decreased likelihood of HIV infection (ORs ranged from 0.10 to 0.54).[69,91,94,95,105,136] 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).[95] In this study, having a plasma TDF concentration of >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).[75] Unlike FEM-PrEP and the other three studies, it found no clear association between ever having a detectable TDF 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), though 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 ng/mL to >40 ng/mL).[69,136]

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.[134] 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.[134]

The 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.[140] 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 <350 fmol/punch (equivalent to ≤2 tablets/week) and 0.16 (95% CI 0.01 to

0.79) at 350-699 fmol/punch (equivalent to 2-3 tablets/week). There were no cases of seroconversion at ≥700 fmol/punch (equivalent to ≥4 tablets/week).

One other RCT[52] and four observational studies[80,126-128] 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%).[52-54,69,75,77,84,91-95]
- PrEP was associated with a trend towards 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%).[52,69,92,93,95]
- 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%; ARD 0.56%, 95% CI 0.09 to 1.04%) versus no PrEP or placebo.[52-54,69,75,77,84,91-95] 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;[52-54,69,75,77,84,91-95] gastrointestinal events were generally not serious and diminished over time.
- PrEP was associated with a trend towards increased risk of fracture that was not statistically significant (7 trials, RR 1.23, 95% CI 0.97 to 1.56; I^2=0%).[52,69,75,84,91,92,94]
- 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%).[69,77,92,94,95]
- 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 HCV infection (2 trials, RR 0.73, 95% CI 0.25 to 2.10, I^2=0%).[52,77,79,94,103]
- 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%).[54,95,107] One trial found no differences between PrEP versus placebo in pregnancy rate, risk of preterm birth, birth anomalies, or postpartum infant mortality.[107]

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**)[52-54,69,75,77,84,91-95] 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 (p value for Egger test=0.53; **Appendix C3).** 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%)[69,75,84,91,93] or TDF-FTC (9 trials, RR 1.02, 95% CI 0.81 to 1.30; I^2=46%; p for interaction=0.23) (**Figure 11**).[52-54,69,75,77,92,94,95] One trial (PROUD) found TDF-FTC associated with a greater risk of serious adverse events than placebo (7.6% [21/375] versus 2.2% [6/269], RR 3.42, 95% CI 1.40 to 8.35).[77]) 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**).[52,69,92,93,95] One trial[93] reported no withdrawals with either PrEP or placebo. In the other trials, PrEP was associated with a trend towards increased risk of withdrawal due to adverse events versus 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 for interaction=0.67) (**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).[95] The majority (~90%) of withdrawals in this trial were due to laboratory abnormalities (grade 2 or higher). In FEM-PrEP, there was no difference in risk of withdrawal due to clinical adverse events, though the estimate was imprecise (RR 3.53, 95% CI 0.73 to 17).

Fracture

Tenofovir exposure is associated with bone loss,[94,101,109,142] which could result in increased fracture risk. PrEP was associated with a trend towards 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%;; absolute risk difference [ARD] 0.21%, 95% CI -0.21 to 0.62%; **Table 7; Figure 13**).[52,69,75,84,91,92,94] The meta-analysis was heavily weighted (64%) by the Bangkok Tenofovir Study of PWIDs, which reported a relatively high fracture rate (7.8% vs. 6.0%, RR 1.29, 95% CI 0.96 to 1.74).[91] 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.[88]

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,[84] iPrEx,[92] and Partners PrEP[69]) and the

FDA review[88] of these trials (**Appendix B1**). 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**).[52-54,69,75,77,84,91-95] 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 (p for Egger's test=0.29; **Appendix C4**). 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 trial 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 for interaction=0.31). 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 B1**).

Six trials[53,54,69,102,104,111] evaluated whether renal adverse events on PrEP were persistent (**Appendix B1**). Three studies[69,102,111] 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.[108] In one other trial, the Bangkok Tenofovir Study of PWIDs, among seven cases of ≥grade 2 creatinine elevation, all but one case resolved following PrEP cessation.[104]

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).**[52-54,69,75,77,84,91-95] 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 (p for Egger's test=0.81; **Appendix C5**). 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 B1**).[114] 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%)[69,75,84,91,93] and TDF-FTC (9 trials, RR 1.84, 95% CI 1.26 to 2.70; I^2=49%),[52-54,69,75,77,92,94,95] with no statistically significant interaction (p=0.30) (**Figure 16**). Among studies that reported rates of diarrhea[52,69,75,77,84,94,95] or vomiting[75,95] separately, none reported a significant difference between PrEP and placebo (**Appendix B1**). Three trials reported that the risk of gastrointestinal events diminished over time.[91,92,94] Serious gastrointestinal events were rare in the trials that reported this outcome, with no differences between PrEP and placebo (**Appendix B1**).[75,77,92-95]

Sexually Transmitted Infections

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).**[69,77,92,94,95] Combined STIs were defined as gonorrhea, chlamydia, or trichomonas in one trial[69] and gonorrhea, chlamydia, or syphilis in the other.[77] 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 impact risk of STIs if participants who don't know if they are on PrEP or placebo behave differently than those who know whether or not they are taking PrEP. The open-label PROUD trial, which enrolled MSM, 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), chlamydia (RR 1.32, 95% CI 0.98 to 1.79), though estimates generally indicated trends towards 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 screens (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 partners in men randomized to PrEP (20%) versus deferred PrEP (12%).[77] In the non-randomizzed Demo Project (PrEP demonstration project in MSM), 26 percent of participants had an STI at baseline and approximately 50 percent had an STI while on PrEP.[80]

PrEP was not associated with increased risk of bacterial STIs when trials (open-label or blinded) were stratified according to whether they evaluated MSM or people at risk of HIV infection due to heterosexual contact (**Table 8; Figures 21-24**). The only trial conducted in PWIDs did not report risk of sexually transmitted infection.[91] 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**).[79,94,103] Two trials evaluated the risk of HSV infection based on serology in participants who were seronegative for HSV at baseline;[79,103] the other trial did not report the method for diagnosing HSV infection.[94] When stratified according to HIV risk category, PrEP was associated with decreased risk of HSV infection versus placebo in two trials of people at risk due to heterosexual contact (RR 0.73, 95% CI 0.56 to 0.96, I^2=0%)[69] but not in one trial of MSM (RR 1.12, 95% CI 0.80 to 1.56)[103] (**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 MSM, PrEP was not associated with decreased risk of a serological diagnosis of HSV infection, but was associated with lower risk of incident HSV infection with an ulcer (5.9% vs. 2.9%, p<0.05).[103]

Hepatitis C Virus Infection

There was no difference between PrEP versus placebo or no PrEP in risk of HCV 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%)[52,77] (**Figure 26**). Both trials (PROUD and IPERGAY) evaluated PrEP with TDF-FTC in MSM. There were six cases of HCV infection in one trial[77] and eight 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 due to pregnancy.[54,95,107] In one trial, only one pregnancy occurred among women randomized to PrEP;[54] in the other two trials 74 and 192 pregnancies occurred.[69,95] All of the trials were conducted in Africa and evaluated women at increased risk of HIV infection due to 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 B1**; **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).[107] TDF-FTC was associated with a trend towards increased risk of spontaneous abortion that was not statistically significant (RR 1.32, 95% CI 0.86 to 2.01, I^2=0%).[54,95,107] 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 B1**).[107]

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.[84] Implementation studies conducted in U.S. populations indicate differences in adherence related to race, 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.[80] It enrolled MSM (98%) and transgender women (1.4%) in three cities (mean age 34-35 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 to 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 (versus 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 (versus the San Francisco site, adjusted OR 0.32, 95% CI 0.17 to 0.60), with no difference between the San Francisco and Washington, DC 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.[129] The population was primarily (~90%) MSM, with smaller proportions of

heterosexual men and women (~10%) and transgender women (~1%). At 6 months, it found no clear association between age, race, educational level, being an MSM, income, or insurance status and likelihood of retention in care.

A study of younger (18 to 22 years of age) MSM (n=200), in whom overall adherence was lower than in studies of older MSM (see Key Question 3), found that those who reported engaging in recent condomless sex had higher TFV-DP levels than those who did not report this behavior (p=0.01).[128] There was a similar, but non-statistically significant trend towards 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 non-adherent (p=0.02). The study did not report the association between factors such as race, 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 (age 50 to 64 years versus age <35 years; adjusted OR 2.00, 95% CI 1.37 to 2.92), male sex (versus female sex; adjusted OR 3.39, 95% CI 1.37 to 8.42) and white race (versus Black race; adjusted OR 2.02, 95% CI 1.43 to 2.87) associated with increased adherence.[131] 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 PWIDs are lacking. In an open-label extension to the Bangkok Tenofovir Study RCT, which focused on PWIDs who could elect to receive directly observed therapy, people 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). People who injected heroin or had been in prison were more likely to choose PrEP than those 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).[143]

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 due to 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 versus having sex with condoms with a primary partner), and heavy alcohol use (adjusted OR 2.8, 95% CI 1.4 to 5.5).[144] 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 Partners PrEP 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)[145] or plasma tenofovir levels.[136,145] The VOICE trial, which enrolled heterosexual African women, reported low overall adherence based on plasma tenofovir levels.[75] Factors associated with presence of detectable plasma tenofovir in VOICE were 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 individuals 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 people randomized to PrEP (n=8,661) (**Table 9**).[52,69,75,77,84,91-95] One trial evaluated event-driven PrEP[52] and the other nine trials evaluated daily PrEP. Five trials evaluated PrEP with TDF alone[69,75,84,91,93] and seven trials evaluated TDF-FTC;[52,69,92,95] two trials[69,75] 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%, or 2/3,149).[69,75,84,91] In seven trials of TDF-FTC, 14 patients had resistance mutations (0.3%, or 14/5,085).[52,69,75,77,92,94,95] 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 two cases of HIV infection among those 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.[52,69,75,77,91-95] In seven of the trials, there were no cases of tenofovir resistance mutations (n=198),[52,75,77,91,92,93,95] and two trials reported one or two cases (n=10[94] and n=35[69]). Two of the three cases of tenofovir resistance were HIV-infected upon trial enrollment, presumably due to undiagnosed acute infection. Both involved the K65R mutation (including one case of multiple resistance mutations to K65R, M184V and A62V).[69,94] No other case of multidrug resistance was identified in patients randomized to PrEP. The third case of tenofovir resistance, which was not HIV-infected on trial enrollment, had the K65N mutation.[69]

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).[52,69,75,77,92,94,95] 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 people who were HIV-infected upon trial enrollment, including one case of multiple resistance mutations described above.

Data on drug resistance mutations were also available from the iPrEX-OLE observational study,[140] 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**).[80,125,127,128] All of the observational studies evaluated PrEP with daily TDF-FTC. Among a total of 1936 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.[140] Among the 4 U.S.-based studies, one of ten patients diagnosed with HIV infection while on PrEP was found to have multiple antiretroviral drug mutations.[125]

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 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 five cases of drug resistance.[100] 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.[146] 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%).[52-54,69,75,77,84,91-95] The absolute difference in risk of HIV infection was ~2 percent after 4 months to 4 years, for a number needed to treat with PrEP in order to prevent one case of HIV infection of ~50. In three trials conducted in the United States and Europe, each of which evaluated MSM (HIV incidence 4% to 8% with placebo or no PrEP), the pooled absolute difference was ~5% after 9 months to 2 years (range 4% to 6%), for a number needed to treat of ~20.[52,77,84] 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.[75,95] 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, the pooled RR was 0.27 (95% CI, 0.19 to 0.39; I^2=0%), with no statistical heterogeneity.[52,53,69,77,84,94]

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 people using PrEP.[69,75,91,92,94,95,105,136] Modeling based on trial data indicates that PrEP is highly effective in MSM taking four doses per week (estimated reduction in risk 96%) and reduction in risk is high even at two doses per week (reduction in risk 76%),[134] suggesting important benefits of PrEP even with incomplete adherence. These findings also suggest the potential utility of event-driven (targeted at periods of higher HIV risk) or intermittent (regular non-daily) dosing strategies in this population. In fact, one trial (IPERGAY) found event-driven PrEP in MSM associated with substantially reduced risk of HIV infection versus no PrEP (RR 0.14, 95% CI 0.03 to 0.63).[52] IPERGAY evaluated a population of MSM with relatively frequent sexual intercourse (median 10 episodes per month) and dosing of PrEP (median 15 doses per month), potentially 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 doses per month (HIV incidence 0 versus 9.3/100 person-years, relative reduction in risk of HIV infection 100%, 95% CI 20 to 100).[147]

The applicability of evidence on effects of adherence and event-driven or intermittent dosing from studies of MSM to other populations is uncertain. Tenofovir accumulates rapidly and at high concentrations in rectal compared with vaginal tissue, which could reduce the effectiveness of non-daily dosing in women in whom the primary mode of transmission is through receptive vaginal intercourse. A modeling study estimated that ≥98 percent of the

population achieved protective mucosal tissue levels by the third day of exposure with TDF-FTC, though six doses/week were required to protect the lower female genital tract, compared to two doses/week to protect colorectal tissue.[148] 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.[149] No study evaluated effectiveness of intermittent or event-driven dosing in women or PWIDs.

Findings regarding effectiveness of PrEP were robust in subgroup and stratified analyses based on HIV risk category (MSM, PWID, or people at risk of HIV infection due to heterosexual contact), study duration, study quality, age, and sex. However, evidence in PWIDs was limited to one Thai 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),[91] and all trials of individuals at risk due to heterosexual contact were conducted in Africa, which might limit applicability to United States 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% 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 antiretroviral therapy). No study evaluated effectiveness of PrEP according to an HIV-infected sexual partner's use of antiretroviral therapy or viral load,[52,77,84] 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 MSM 15 to 17 years of age that found a similar safety profile for TDF-FTC compared with the safety profile observed in adults.[127]

Evidence on beneficial effects of PrEP on clinical outcomes other than HIV infection was sparse. PrEP was associated with a non-statistically significant trend towards 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.[52,53,69,75,77,84,91-95] No trial reported effects of PrEP on quality of life, though limited qualitative research suggests that PrEP may reduce anxiety or worry about getting HIV.[150]

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[52-54,69,75,77,84,91-95] and there was a non-statistically significant trend toward increased risk of withdrawal due to adverse events (RR 1.25, 95% CI 0.99 to 1.59).[52,69,92,93,95] PrEP was associated with increased risk of gastrointestinal events (RR 1.63, 95% CI 1.26 to 2.11; ARD 1.95%),[52-54,69,75,77,84,91-95] 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%),[52-54,69,75,77,84,91-95] which generally appeared mild and resolved with cessation of PrEP. Consistent with effects of tenofovir on bone loss, PrEP was associated with a non-statistically significant trend towards increased risk of fracture (RR 1.23, 95% CI 0.97 to 1.56);[52,69,75,84,91,92,94] results of the fracture meta-analysis heavily weighted by the Bangkok Tenofovir Study.[91] 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 people who were HIV-infected at baseline, underscoring the importance of clinical history and HIV testing to rule out acute or chronic HCV infection prior to 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.[151] 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.[100]

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.[69,77,92,94,95] However, in most trials, patients were blinded to whether they were randomized to PrEP or placebo, which might impact sexual behaviors differently than when they 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 MSM, but there was a trend towards increased risk, consistent with the higher prevalence of risky sexual behaviors among men randomized to PrEP that was observed in this trial.[77] 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 MSM 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.[80] A recent systematic review that included PROUD, the U.S. demonstration study, and other open-label, non-randomized 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).[152] Methodological shortcomings of the non-randomized 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 prior to initation of PrEP. Some data suggest that individuals who engage in riskier behaviors tend to be more adherent to PrEP (see Contextual Question 1),[80,91,128] which might offset negative effects related to any increase in risky behaviors. There was no association between PrEP and risk of HSV infection,[79,94,103] though some trials[79,94] found decreased risk or a trend towards decreased risk, consistent with antiviral effects of tenofovir on HSV.[78,79] Cases of acute HCV infection have been reported in U.S. MSM using PrEP,[153] but data from randomized trials are too limited to determine effects on risk of HCV infection.[52,77]

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.[89,154,155] For example, a review by Fonner and colleagues also found a roughly linear relationship between adherence and PrEP effectiveness (based on the log RR).[89] Our findings were strengthened with the addition of recent large new trials that were published subsequent to the prior reviews, including the only trial of event-driven PrEP (IPERGAY)[52] and an open-label pragmatic trial (PROUD).[77] 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 non-oral PrEP, was based on relatively few studies

reporting plasma levels, and did not include some recently published trials.[156] Prior reviews also reported similar findings of no increased risk of serious adverse events or any adverse event, though most reviews did not focus on individual harms.[89,154,155] 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 1.39, 95% CI 1.09 to 1.71).[157]

Data on effects on PrEP in pregnancy was 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)[54,95,107] or other adverse pregnancy outcomes. A systematic review of HIV- or hepatitis B (HBV)-infected women 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.[158] 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,[159] though methodological issues in the trial have been noted,[160] and applicability to U.S. practice is uncertain. TDF-FTC is FDA pregnancy category B 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. MSM (mean age 34 to 35 years) found high levels of adherence (80% to 90%) based on documentation of highly protective drug levels.[80,125] Studies of younger (mean age 16 to 20 years of age) U.S. MSM found lower levels of adherence that declined over time, highlighting the need for additional PrEP adherence support strategies in this population.[127,128] One RCT of U.S. MSM found higher adherence with daily than intermittent or event-driven PrEP.[113] Data on adherence to PrEP in U.S. PWIDs and people at risk due to 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 MSM found moderate discrimination (AUROC estimates ranged from 0.66 to 0.72), but require further validation.[115-118] 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 PWIDs also reported moderate discrimination, but has not been validated.[121] 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 MSM, PWIDs, and people at risk due to heterosexual activity, but more validation is needed.[47] No study evaluated an instrument for predicting incident HIV infection in people not already identified as belonging to a risk category. This is relevant because patients who are at risk for 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.[87] 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, though 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.[161,162] 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.[90] Funnel plot asymmetry was present (**Appendix C1**) 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.[88] 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.[92] A sensitivity analysis which used the FDA data resulted in similar results for iPrEx (RR 0.58, 95% CI 0.41 to 0.82) compared to 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 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,[163] and is undergoing evaluation in combination with FTC for PrEP.[164] Tenofovir could also be delivered as a biodegradable, long-acting implant.[165]

Maraviroc is a CCR5 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.[166] A similarly designed trial of 406 MSM and transgender women was also not powered to assess efficacy, but reported five cases of HIV infection with maraviroc alone, one with maraviroc with TDF, and none with maraviroc with FTC or TDF-FTC ($p=0.32$ for differences by regimen).[167]

Long-acting injectable formulations of antiretroviral drugs that provide sustained drug delivery can be dosed as infrequently as once every 2 or 3 months.[168] Two long-acting injectable agents are cabotegravir and rilpivirine, though 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 a gel or ring. Although one trial found pericoital 1 percent tenofovir gel associated with a reduction in risk of HIV transmission of nearly 40 percent;[74] other trials found no effect,[75,76] with some evidence in the trials 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,[72,73] 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 (less than 21 years of age) women, a subgroup with lower adherence.

Relevance for Priority Populations, Particularly Racial/Ethnic Minorities

In the United States, HIV disproportionately impacts racial/ethnic minorities, in particular

black and Hispanic individuals. One trial found no difference in effectiveness of PrEP between Hispanic and non-Hispanic individuals[92] and trials found PrEP to be effective in diverse racial and 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),[169] 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 due to 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,[169] despite accounting for ~40 percent of PrEP-eligible individuals.[63] Another study found that only 2.5 percent of people with commercial insurance prescribed PrEP were women.[170] 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 MSM. In U.S. MSM who met CDC criteria for PrEP, over half were unwilling to take it or believed they were inappropriate candidates.[171] Less than 10 percent of those who were appropriate candidates were using and adherent to PrEP. A study of young (age 16 to 29 years) MSM found that ~12 percent reported ever taking PrEP; among black participants the proportion was even lower, at 4.7 percent.[172] A study of young (16 to 29 years of age) black MSM found that over 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.[173]

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.[174] Although it is unlikely that there are significant drug interactions between hormone treatments and PrEP, pharmacological interaction studies in transgender women are lacking,[175] though several studies are underway.[176-178] Randomized trials that included transgender women have not been powered to evaluate effectiveness in this subgroup. A post-hoc analysis of iPrEx[92] found that PrEP was effective in MSM (HR 0.50, 95% CI 0.34 to 0.75) but not in transgender women (HR 1.1, 95% CI 0.5 to 2.7), though the interaction was not statistically significant (p=0.09),[98] precluding reliable conclusions about a subgroup difference. In iPrEx, adherence was lower in transgender women than MSM, particularly among those who reported condomless receptive anal intercourse. 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.[179]

One Asian trial found PrEP to be effective in PWIDs.[91] Uptake of PrEP in PWIDs appears relatively low. A 2012 study of PWIDs in Washington DC found that only 13 percent had ever heard of PrEP and none had ever used PrEP or knew someone who had.[180] 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 2012-2013 study of PWIDs in Vancouver, Canada, found that approximately one third expressed willingness to use PrEP.[181] Factors associated with willingness to use PrEP included younger age, engaging in sex work, and reporting multiple recent sexual partners. Further PrEP studies in PWID 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. Individuals younger than 25 years of age represent about 7.5 percent of PrEP initiators.[169] A recent implementation study of MSM 15 to 17 years of age in which patients were permitted to autonomously consent found low adherence that decreased over time, with a high incidence of STIs and HIV infection.[127] Two recent NIH-funded studies found that daily oral TDF-FTC and the dapivirine vaginal ring were safe and acceptable in adolescents.[182,183]

Future Research

A number of trials of PrEP are ongoing. These include trials on the safety and efficacy of injectable cabotegravir compared to daily oral TDF-FTC for PrEP in HIV-uninfected women, MSM, and transgender women,[184,185] 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,[164] a trial of injectable rilpivirine in HIV-uninfected women,[186] and a trial on of an enhanced versus standard PrEP adherence intervention in young black MSM.[187] Trials that compare daily versus event-driven or intermittent dosing and are sufficiently powered to evaluated effects on risk of HIV acquisition would be helpful for clarifying effective and efficient dosing strategies in different populations. A recent African trial (n=622) of daily, intermittent (twice weekly with an additional dose after sexual intercourse) or event-driven (24-48 hours before and within 2 hours after sexual intercourse) TDF-FTC for PrEP in MSM and women at risk of HIV infection due to heterosexual contact was not designed to assess comparative efficacy for preventing HIV infection, and reported only five cases of seroconversion following randomization, though adherence was highest with the daily regimen.[113,114] Research is needed to better understand the adherence implications of different dosing regimens in U.S. populations and impact on PrEP effectiveness.

Randomized trials or demonstration projects of PrEP in U.S. populations of women at high risk due to heterosexual contact and PWIDs are needed to verifying the applicability of trials conducted in low-income settings to the U.S., 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 and 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 accountl 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 impact HIV acquisition risk. Research is also needed on effects of PrEP on HCV infection, particularly in populations at high risk for HCV (e.g., PWIDs, MSM).

Research is also needed to develop and validate instruments for identifying those at high risk for acquiring HIV infection. Existing instruments in MSM and PWIDs 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 and ethnic minorities. Initial instruments of MSM were developed using cohorts in which racial and ethnic minorities were underrepresented, with some studies showing poor predictive utility of existing instruments in black MSM.[119,120] A study of a new risk instrument (Sex Pro) specifically designed for black MSM has been conducted, but only published as a conference abstract.[188] 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 to placebo or no PrEP, though effectiveness decreases with inadequate adherence. PrEP is associated with increased risk of renal adverse events, gastrointestinal events, and fracture, but the incidence of non-gastrointestinal adverse events is low and most adverse events appear mild and reversible with discontinuation of PrEP. Evidence on the accuracy of instruments for identifying people at high risk for HIV infection is limited, with further validation required.

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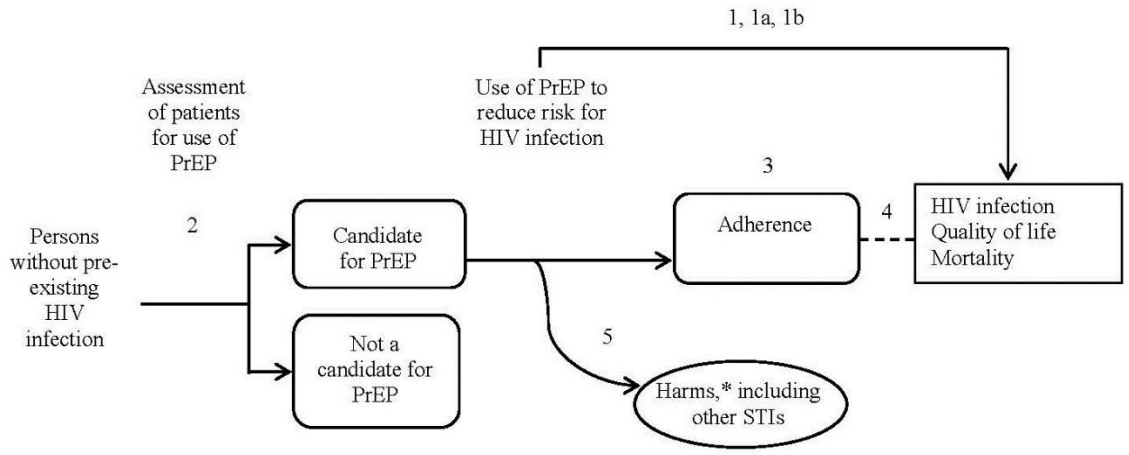
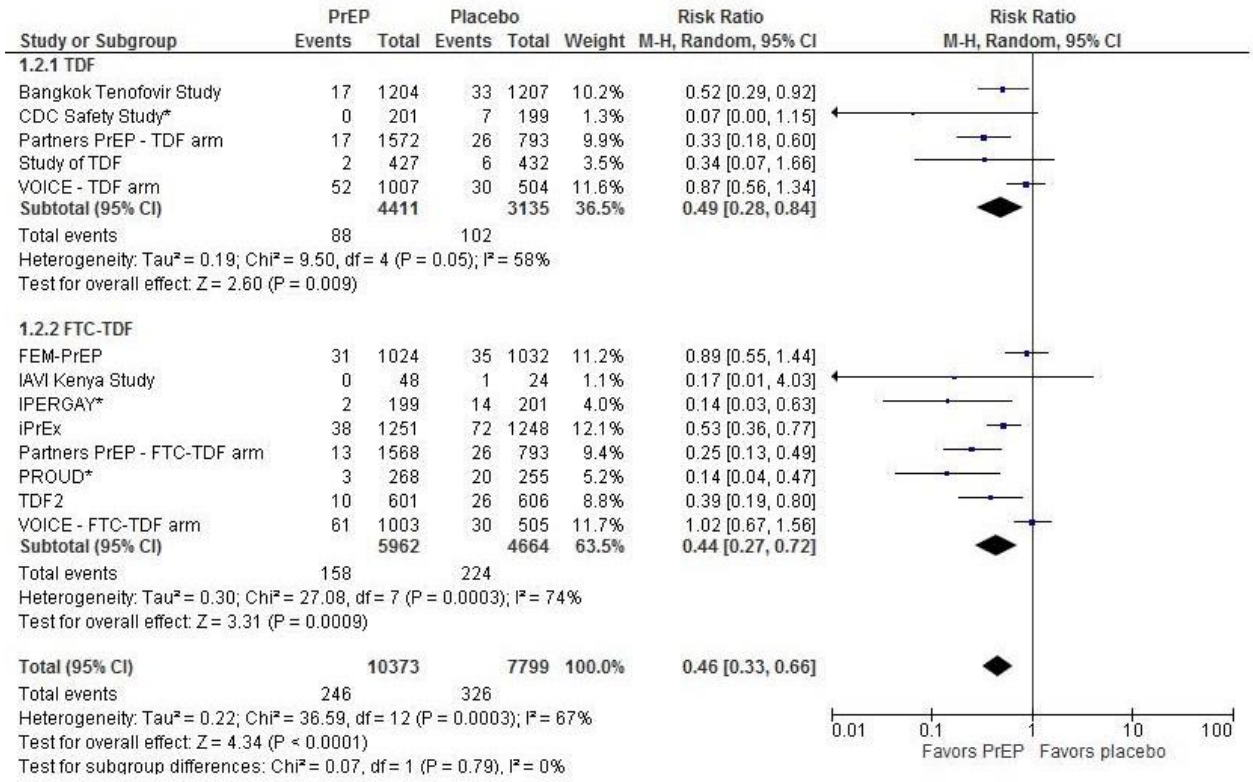
Figure 1. Analytic Framework



*Harms also include renal insufficiency, fractures, pregnancy-related outcomes, infection with antiretroviral drug–resistant HIV, gastrointestinal harms, headaches, and discontinuation due to adverse events.
Note: The numbers on the analytic framework correspond to the numbers of the key questions.

Abbreviations: HIV=human immunodeficiency virus; PrEP=pre-exposure prophylaxis; STI=sexually transmitted infection.

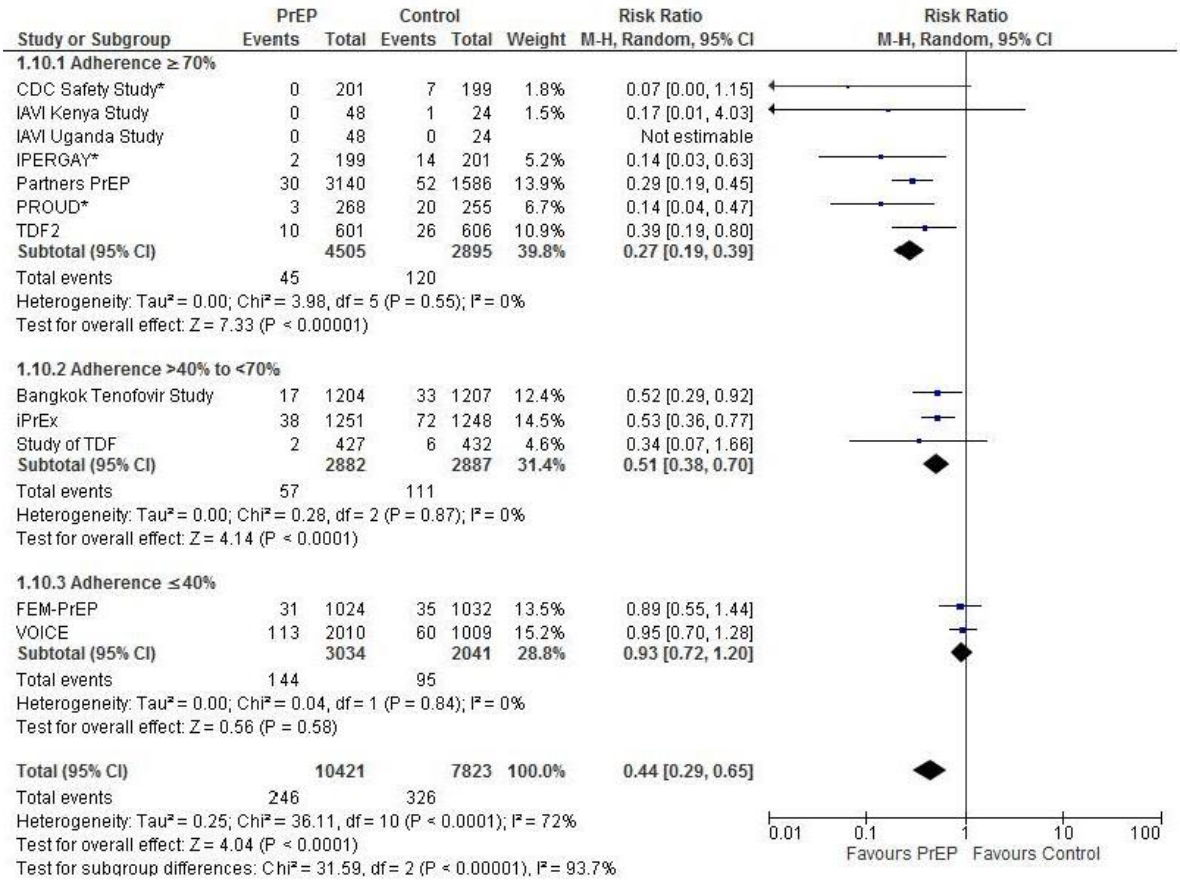
Figure 2. Meta-analysis - HIV Infection Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; PWID=people who inject drugs; TDF=tenofovir disoproxil fumarate.

Figure 3. Meta-analysis - HIV Infection Stratified by Adherence



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

*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; PrEP=pre-exposure prophylaxis; TDF=tenofovir.

Figure 4. Meta-regression – PrEP Efficacy Versus Adherence

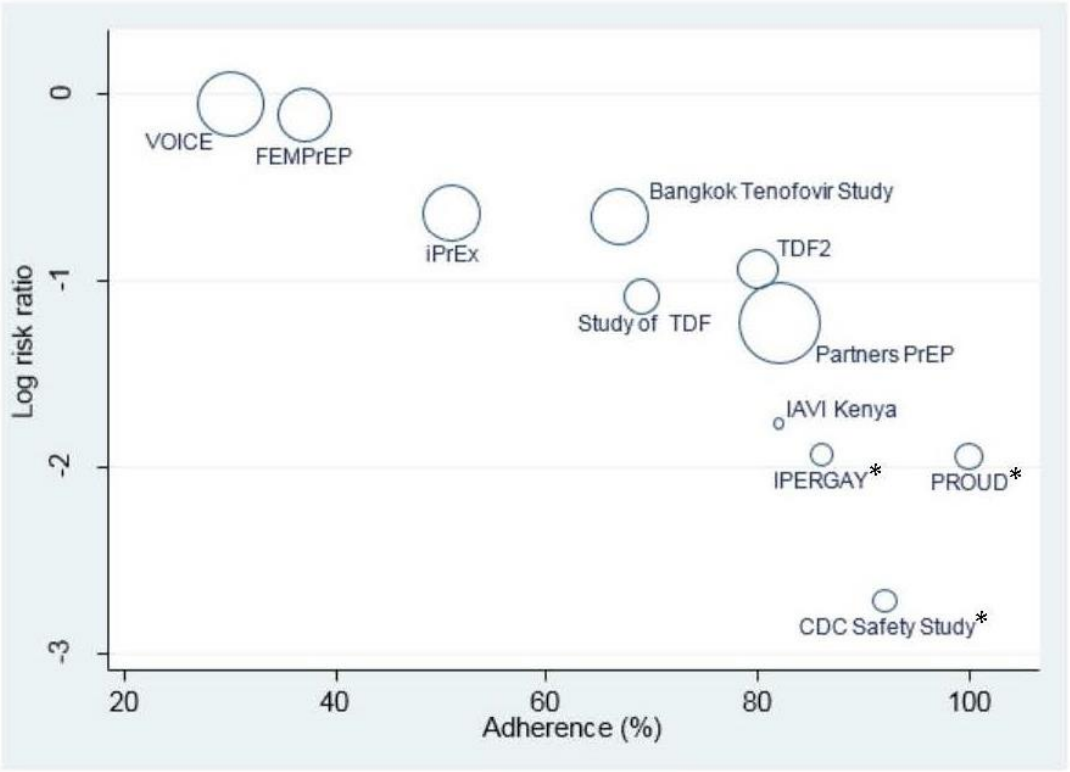
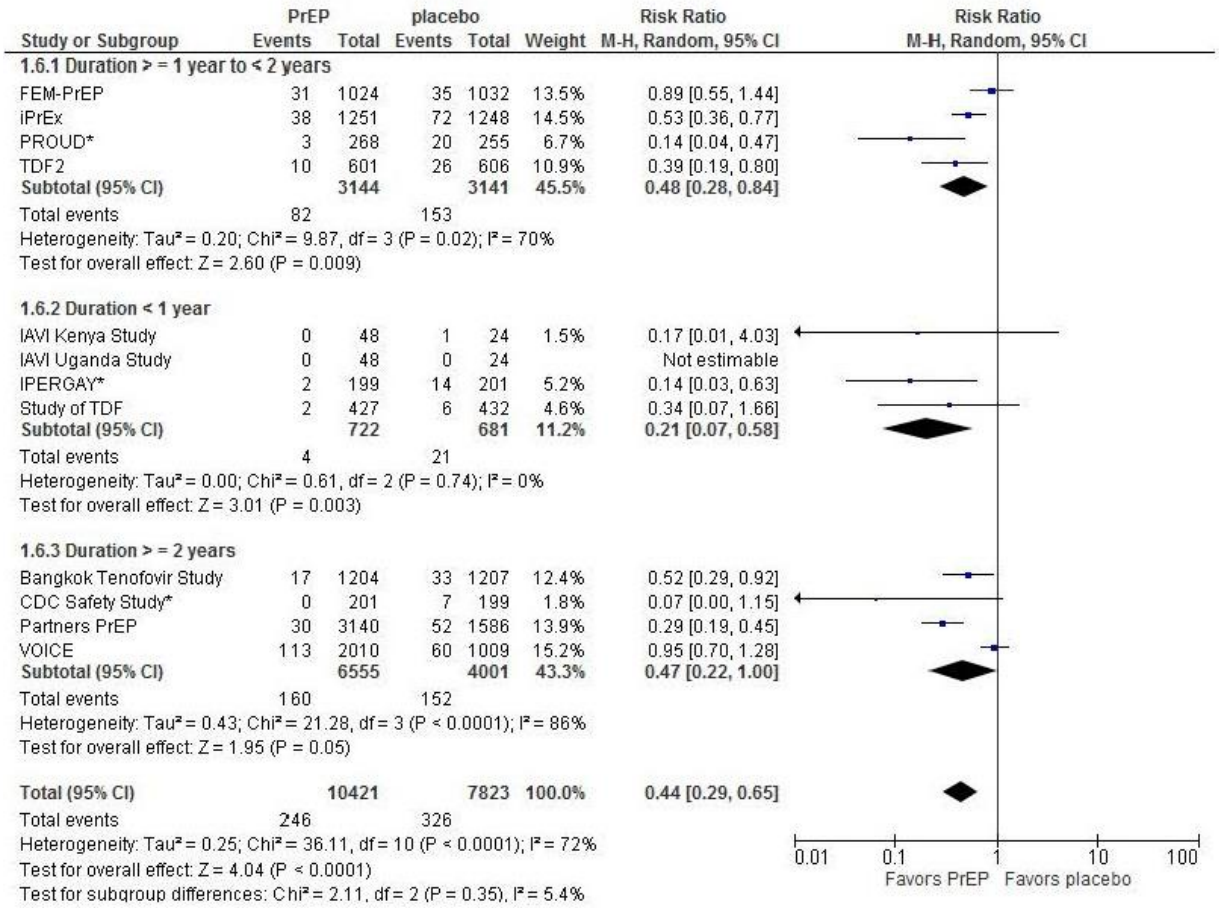


Figure Legend: The X-axis indicates adherence in each trial as measured by (in order of preference) presence of detectable tenofovir on drug level testing, MEMS data, pill counts, or self-report and the Y-axis represents the logRR from each trial for PrEP vs. placebo or no PrEP. The size of the bubble for each study indicates the weighted sample size.

*U.S, Canada, or Europe.

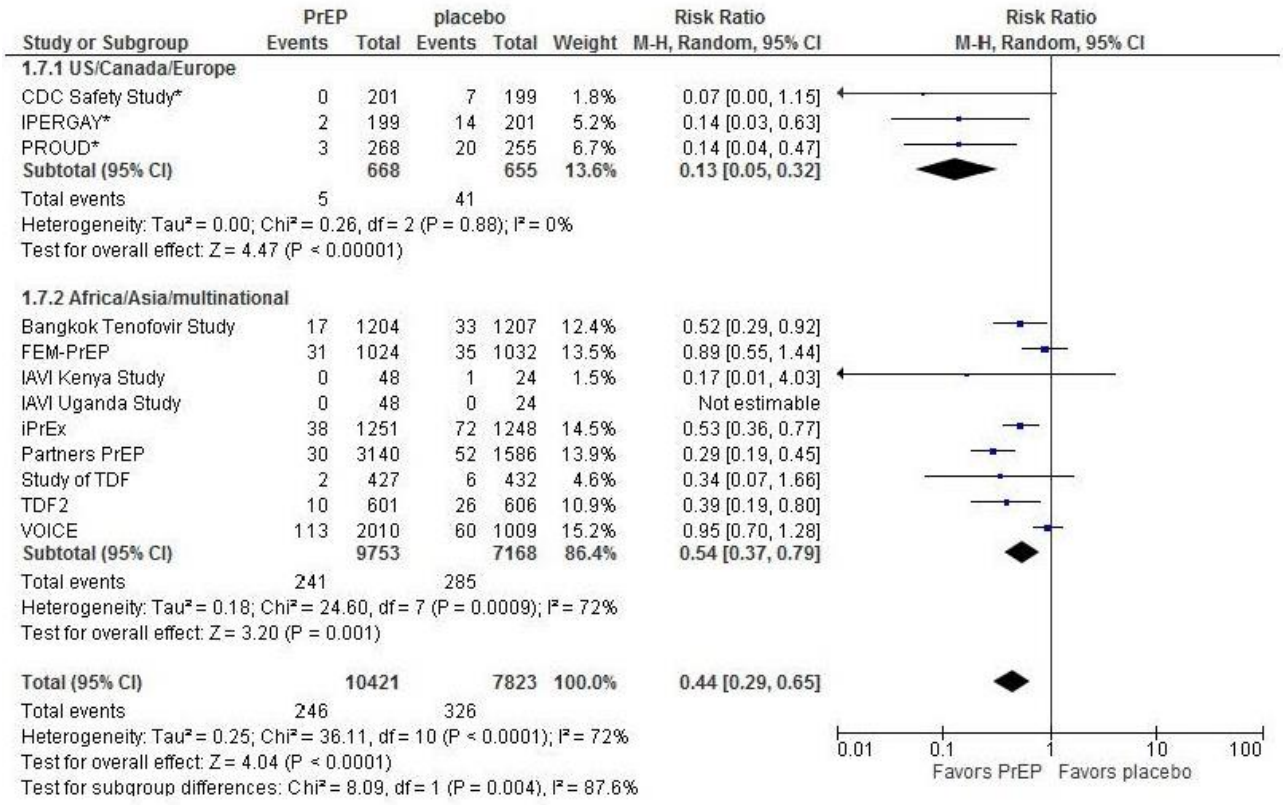
Figure 5. Meta-analysis - HIV Infection Stratified by Study Duration



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; PrEP=pre-exposure prophylaxis; TDF= tenofovir disoproxil fumarate; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

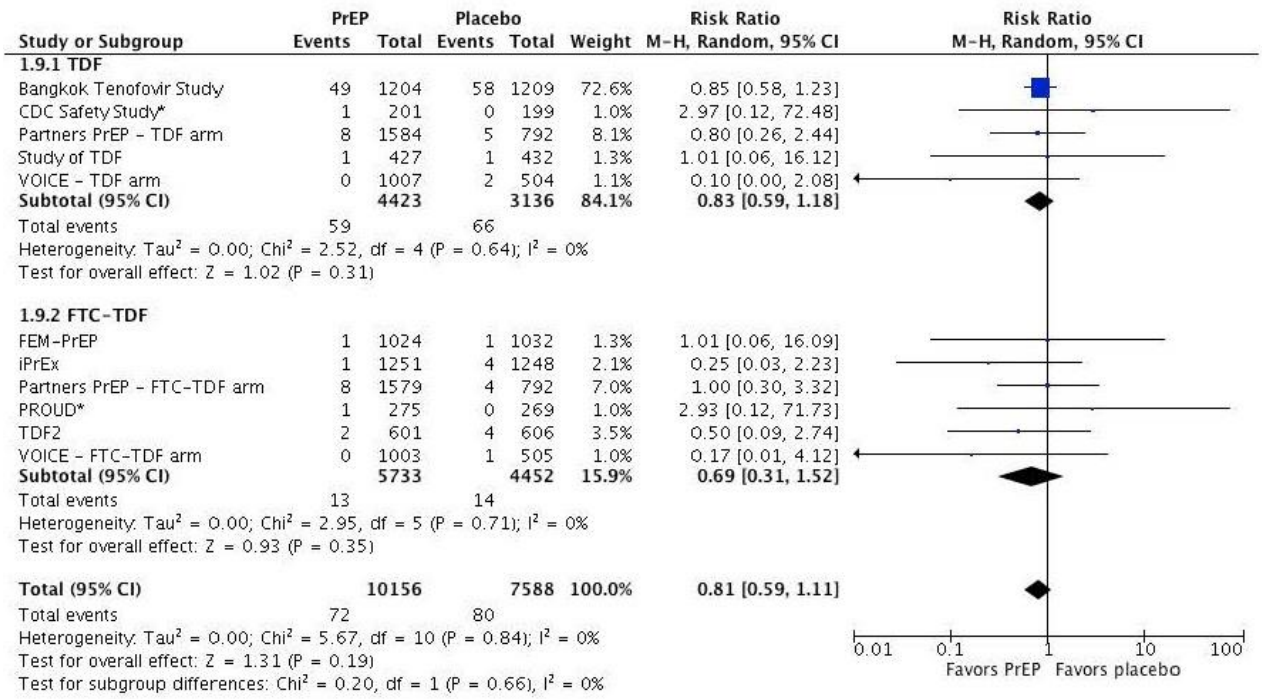
Figure 6. Meta-analysis - HIV Infection Stratified by Geographic Setting



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate; VOICE=Vaginal and Oral Interventions to Control the Epidemic; US=United States.

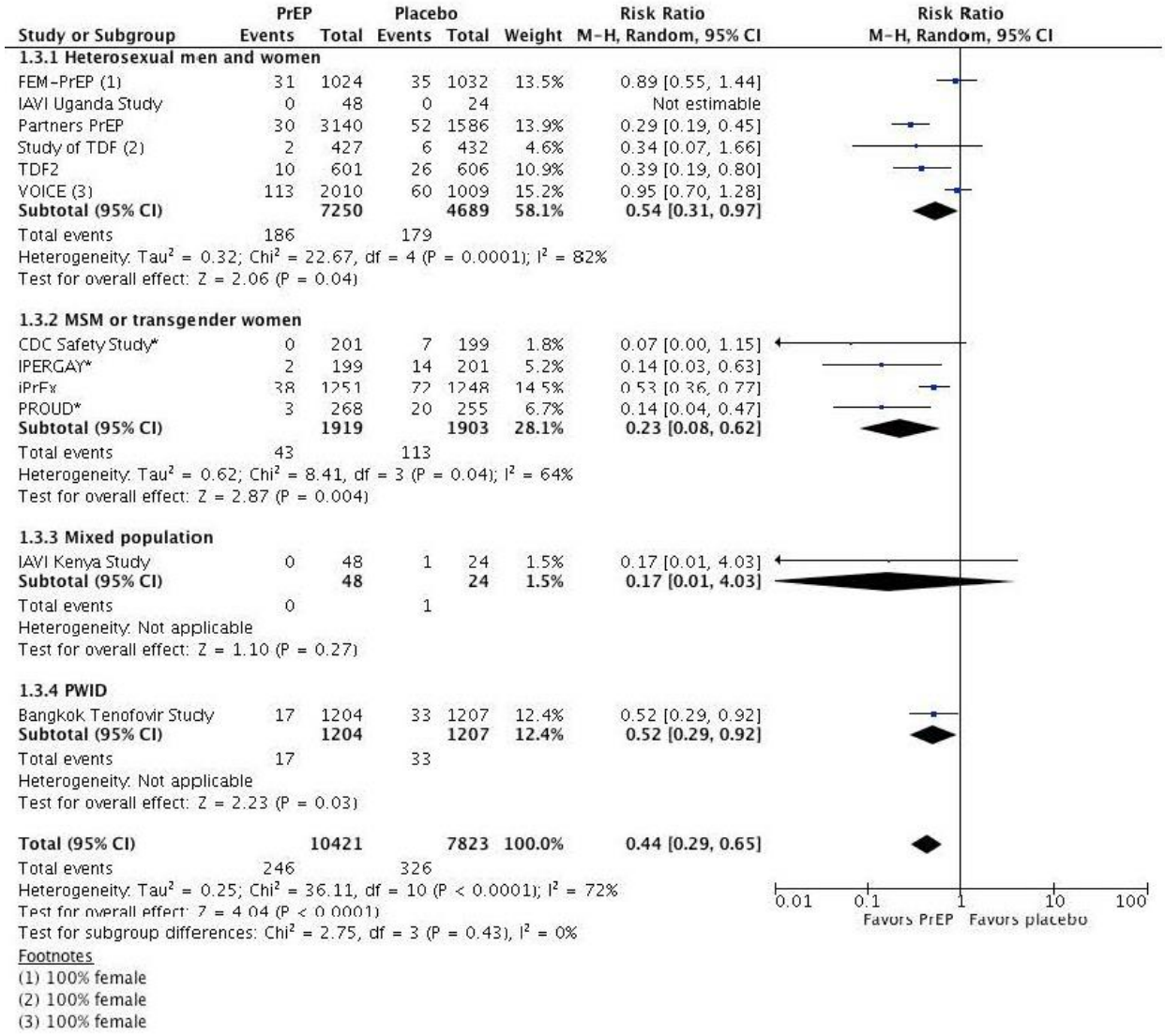
Figure 7. Meta-analysis – Mortality Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC= emtricitabine; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate; VOICE=Vaginal and Oral Interventions to Control the Epidemic; US=United States.

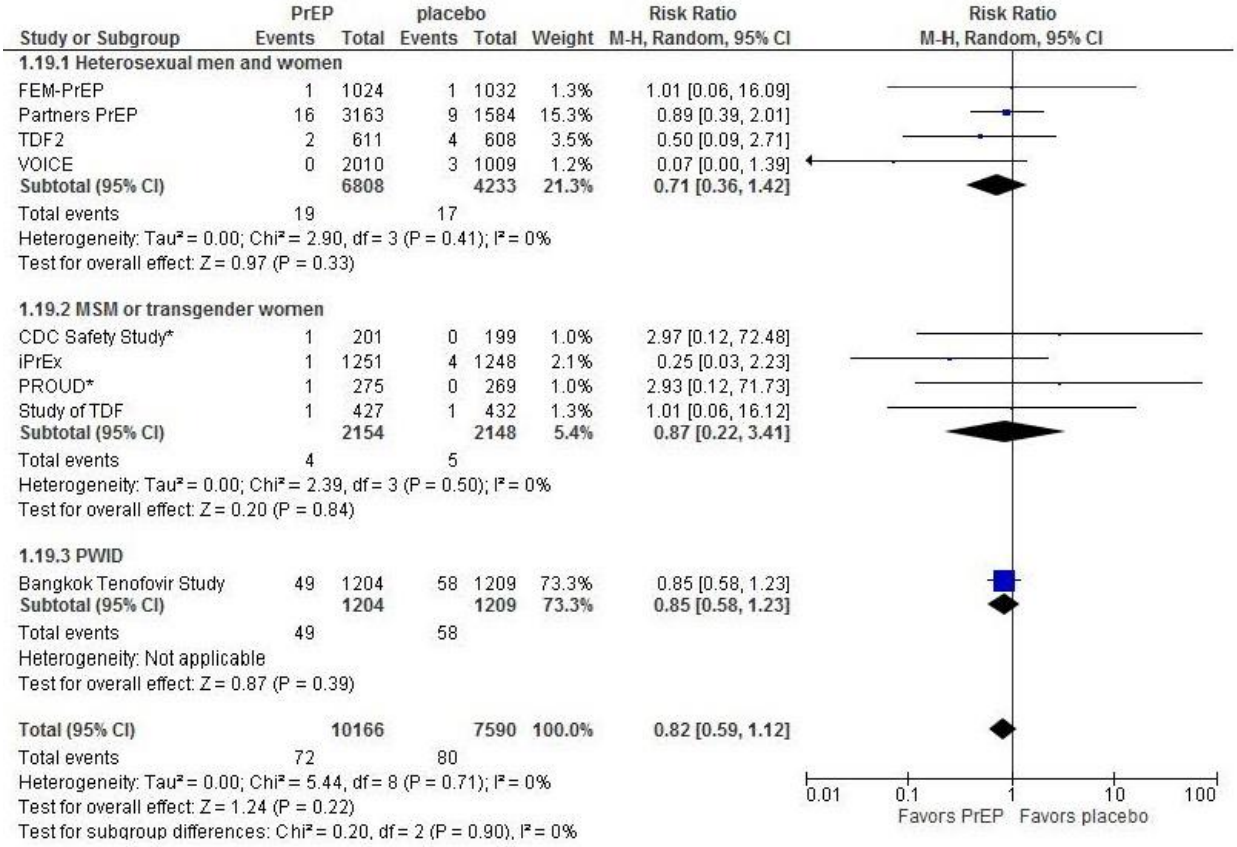
Figure 8. Meta-analysis - HIV Infection Stratified by HIV Risk Category



*U.S, Canada, or Europe.

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

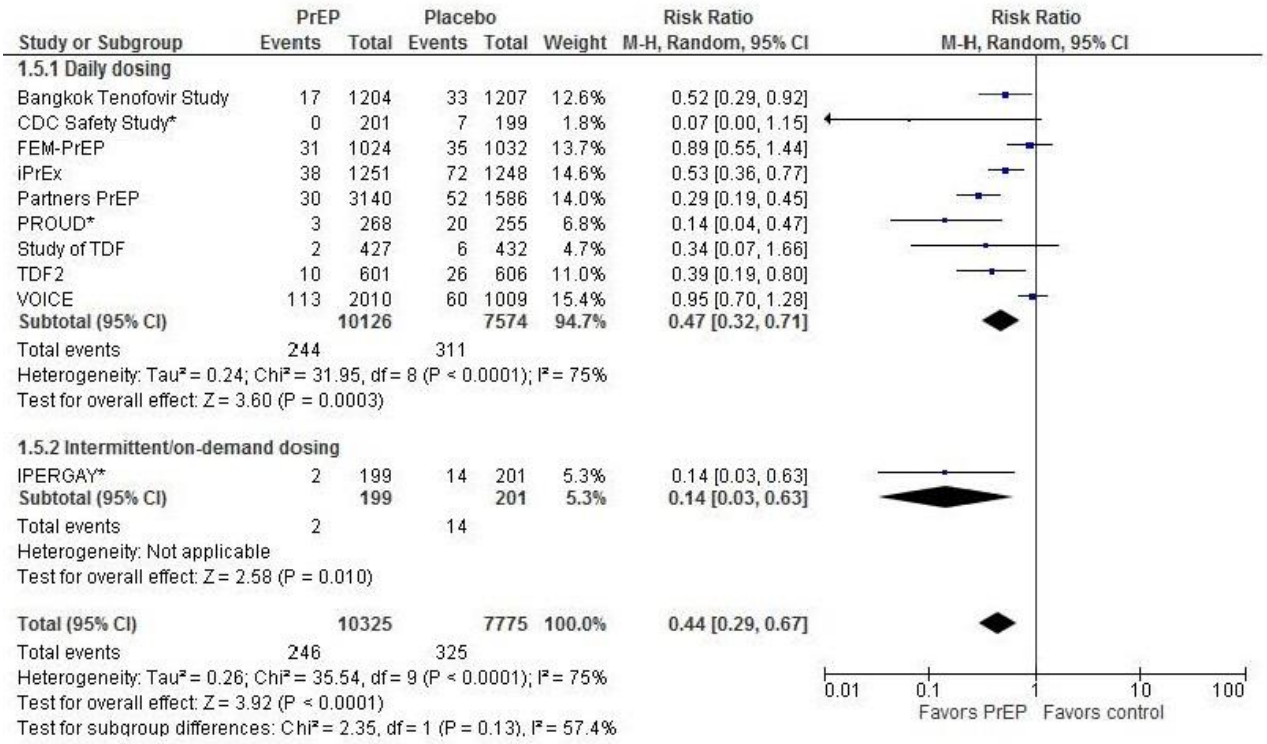
Figure 9. Meta-analysis - Mortality Stratified by HIV Risk Category



*U.S, Canada, or Europe.

Abbreviatons: CI=confidence interval; MSM=men who have sex with men; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate.

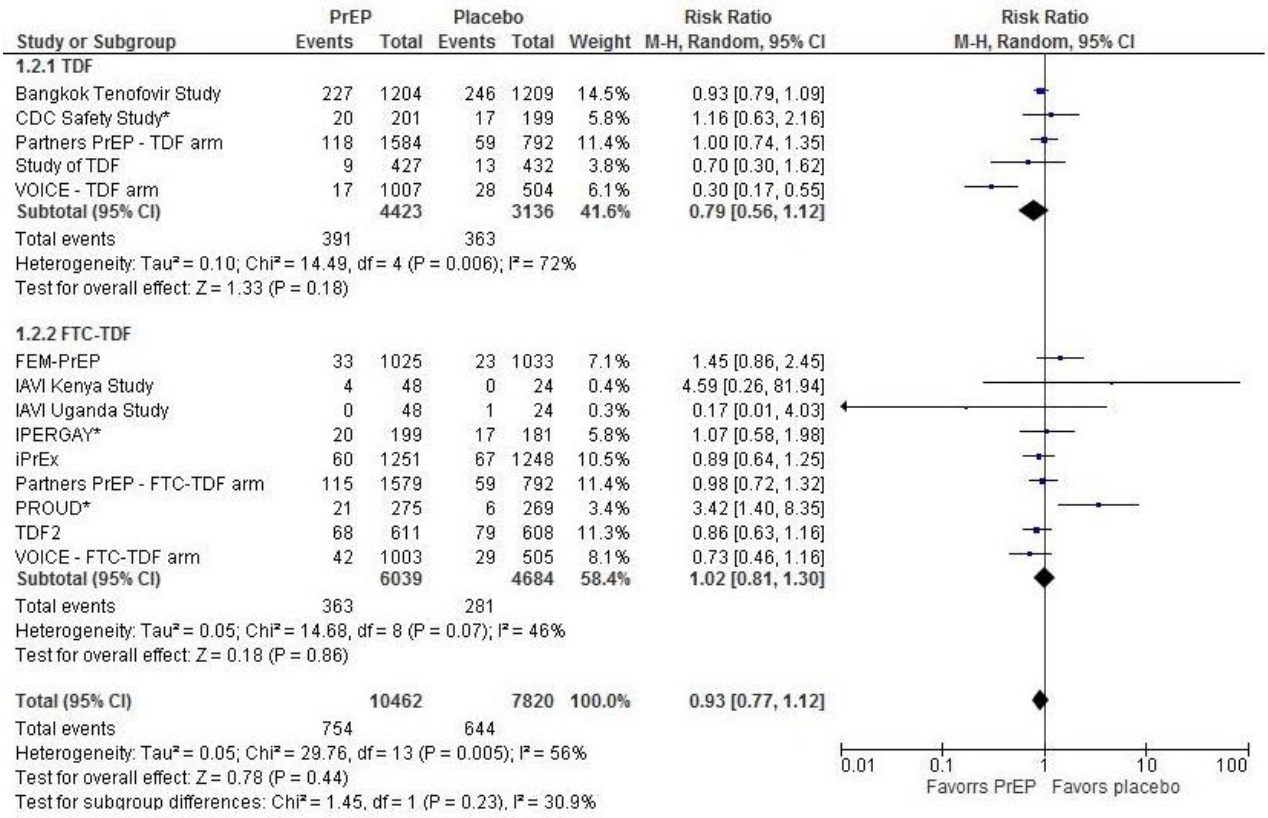
Figure 10. Meta-analysis - HIV Infection Stratified by Dosing Strategy



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

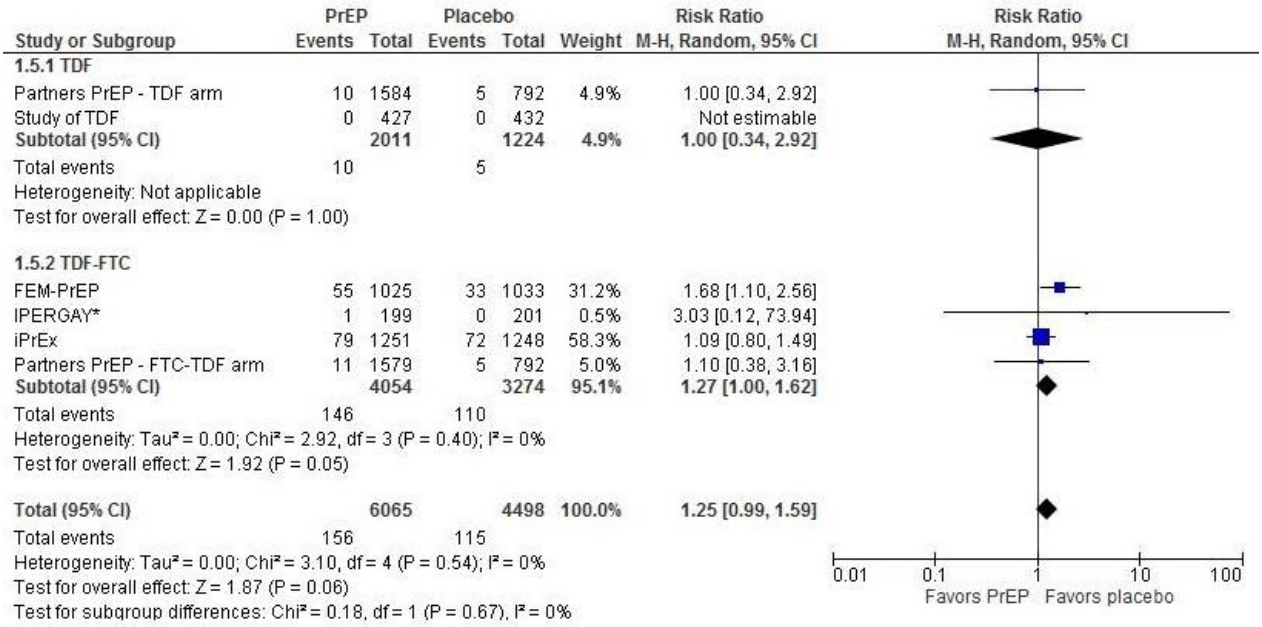
Figure 11. Meta-analysis - Serious Adverse Events Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate; VOICE=Vaginal and Oral Interventions to Control the Epidemic.

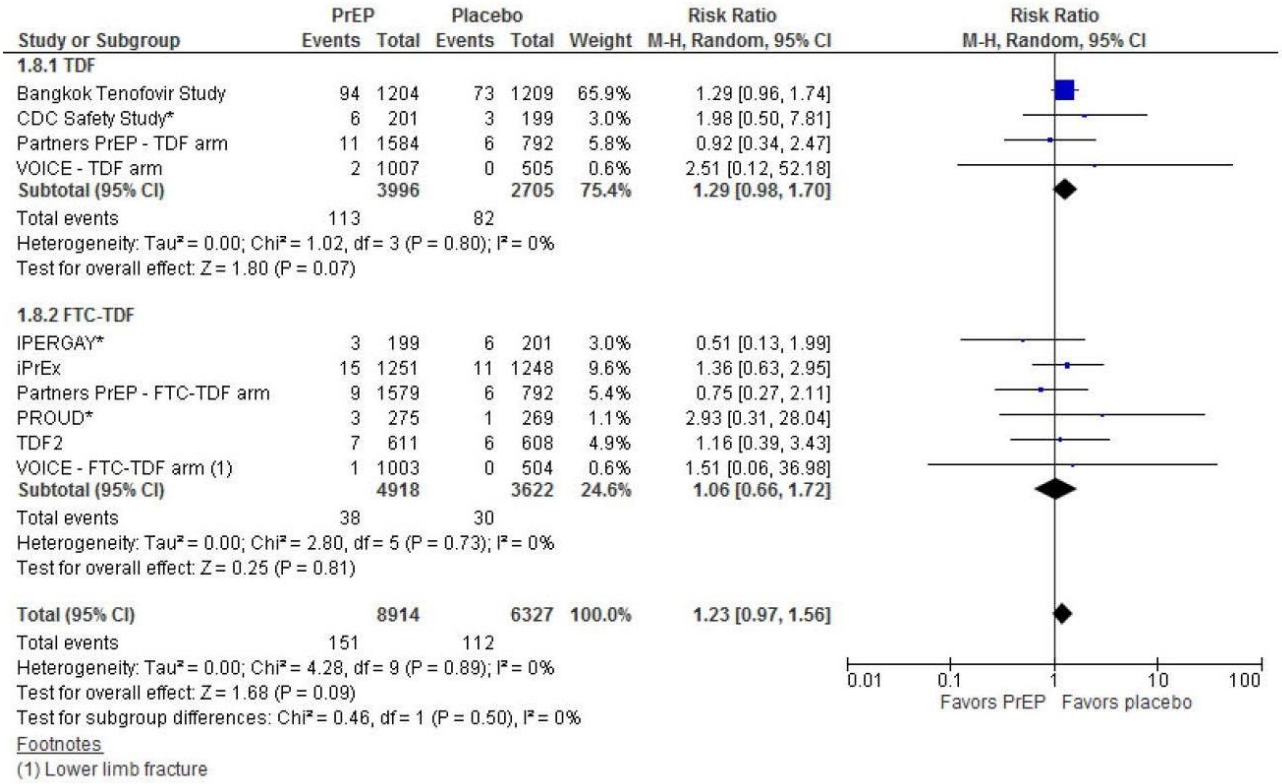
Figure 12. Meta-analysis - Withdrawals Due to Adverse Events Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate.

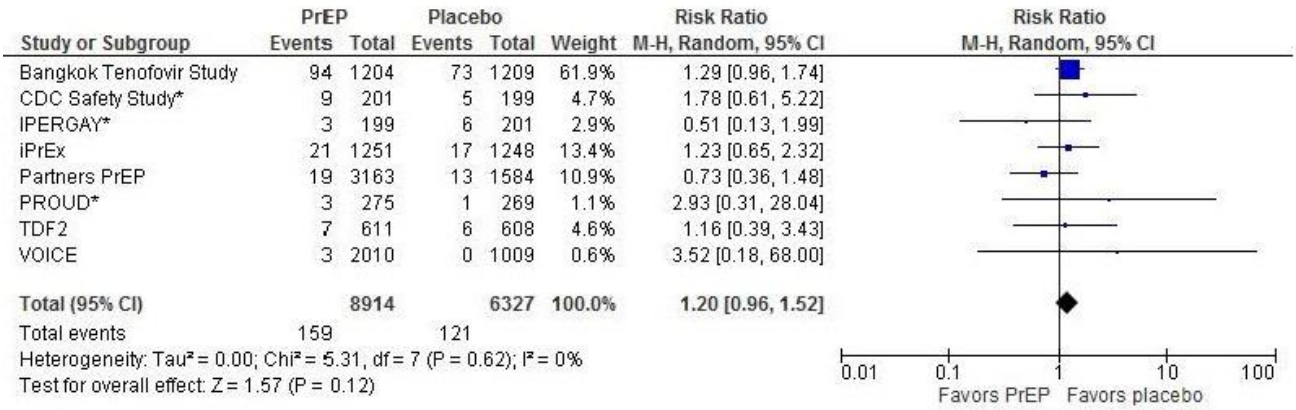
Figure 13. Meta-analysis - Fracture Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate.

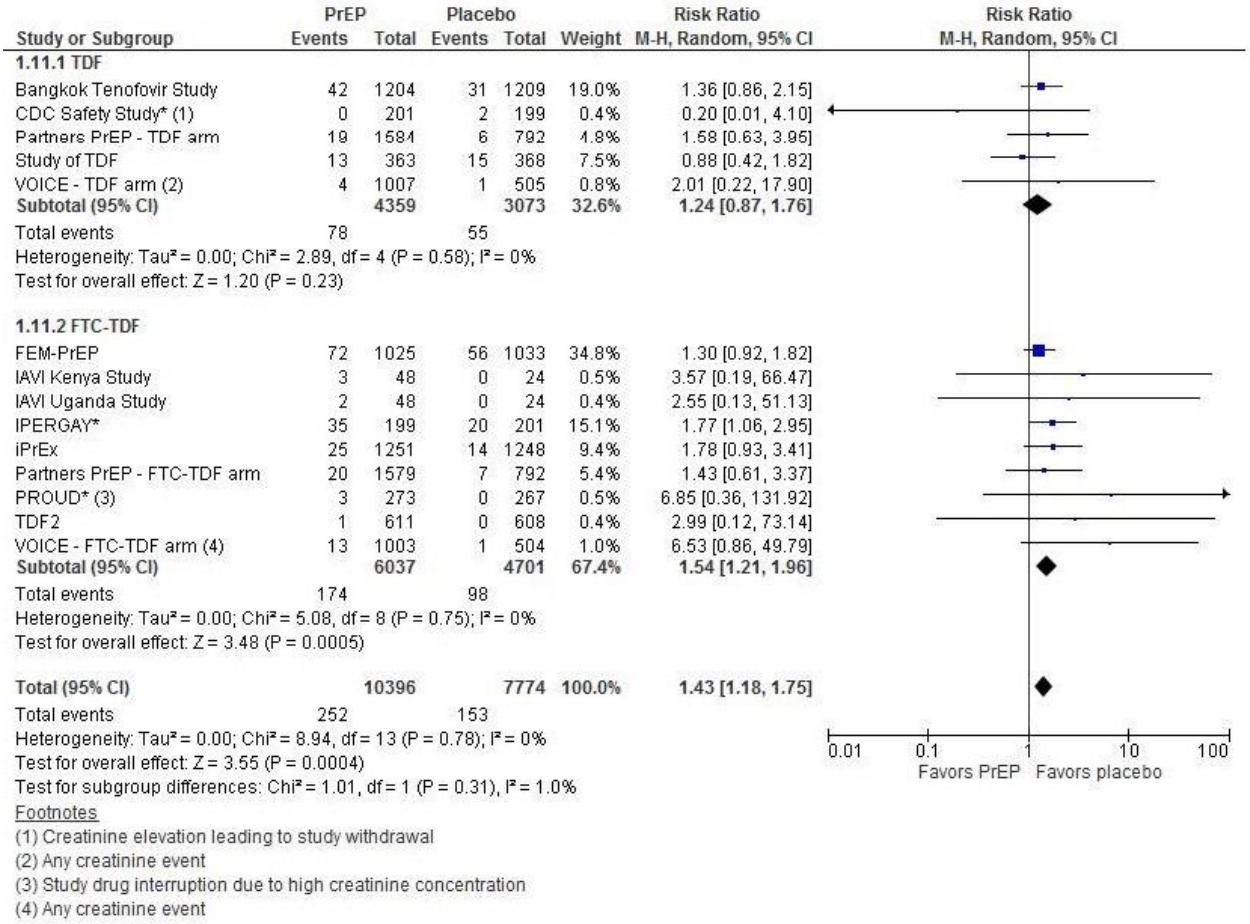
Figure 14. Meta-analysis - Fracture Using FDA Data (iPrEx, Partners PrEP, CDC Safety Study)



*U.S, Canada, or Europe. .

Abbreviations: CI = confidence interval, M-H = Mantel-Haenszel, PrEP = pre-exposure prophylaxis.

Figure 15. Meta-analysis - Renal Adverse Events Stratified by Study Drug

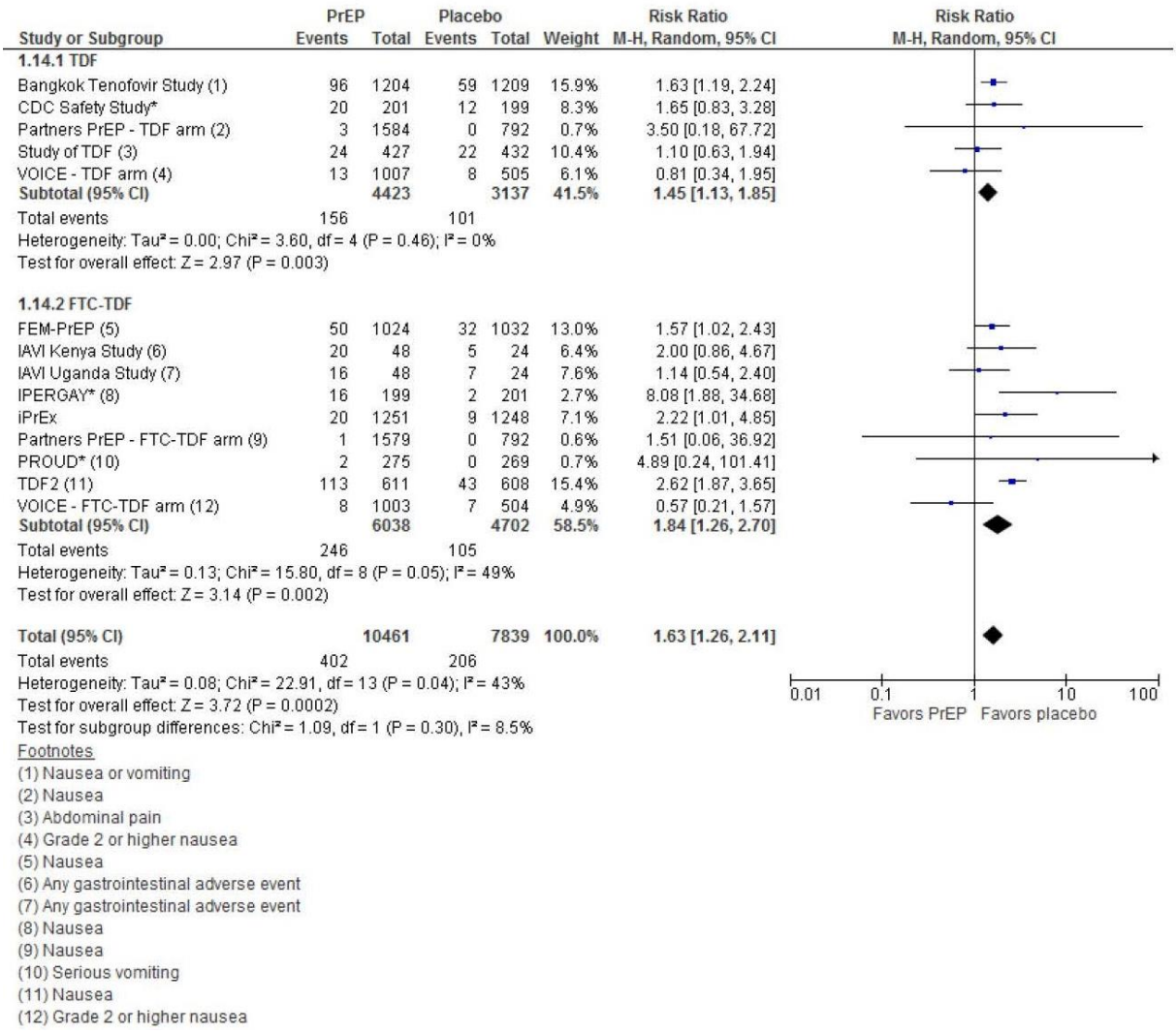


Note: Defined as ≥Grade 1 serum creatinine elevation unless otherwise noted.

*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate.

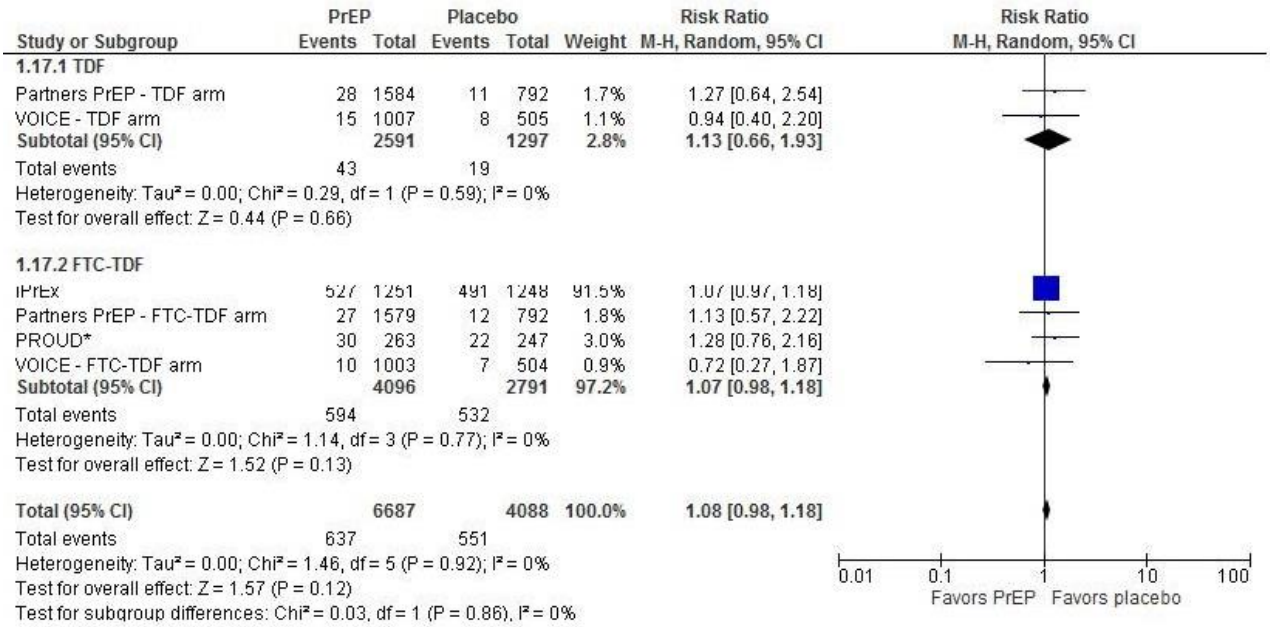
Figure 16. Meta-analysis - Gastrointestinal Adverse Events Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate.

Figure 17. Meta-analysis - Syphilis Stratified by Study Drug

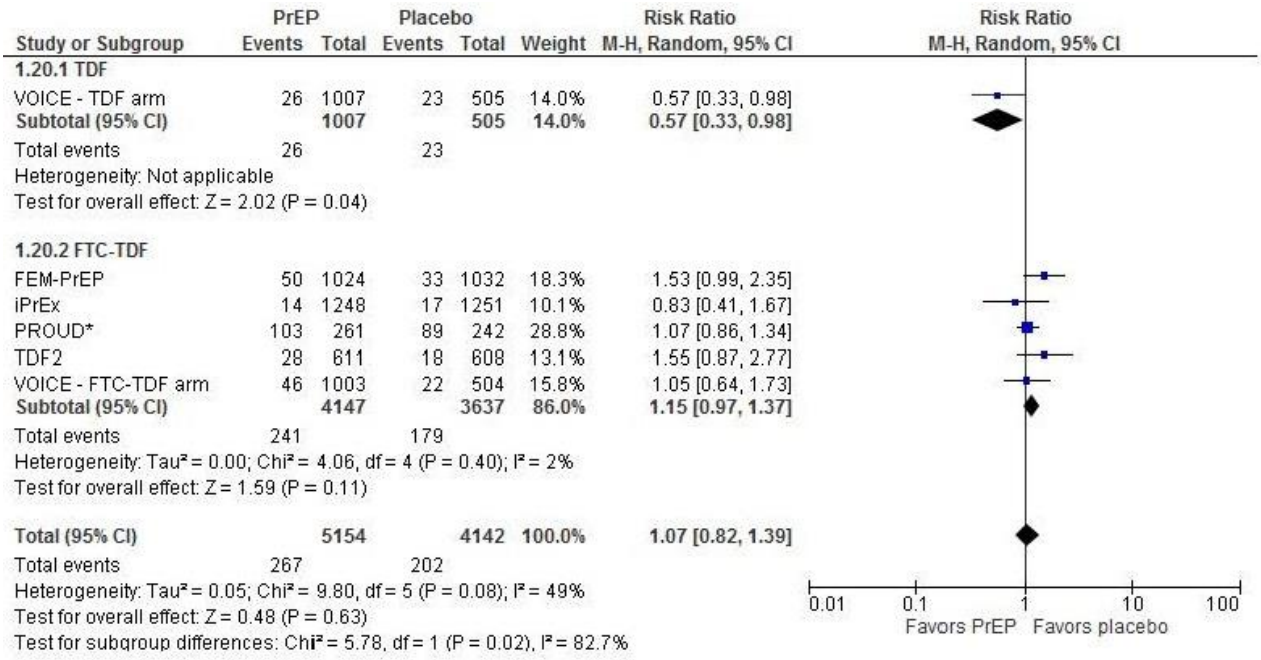


*U.S, Canada, or Europe.

*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate.

Figure 18. Meta-analysis - Gonorrhea Stratified by Study Drug

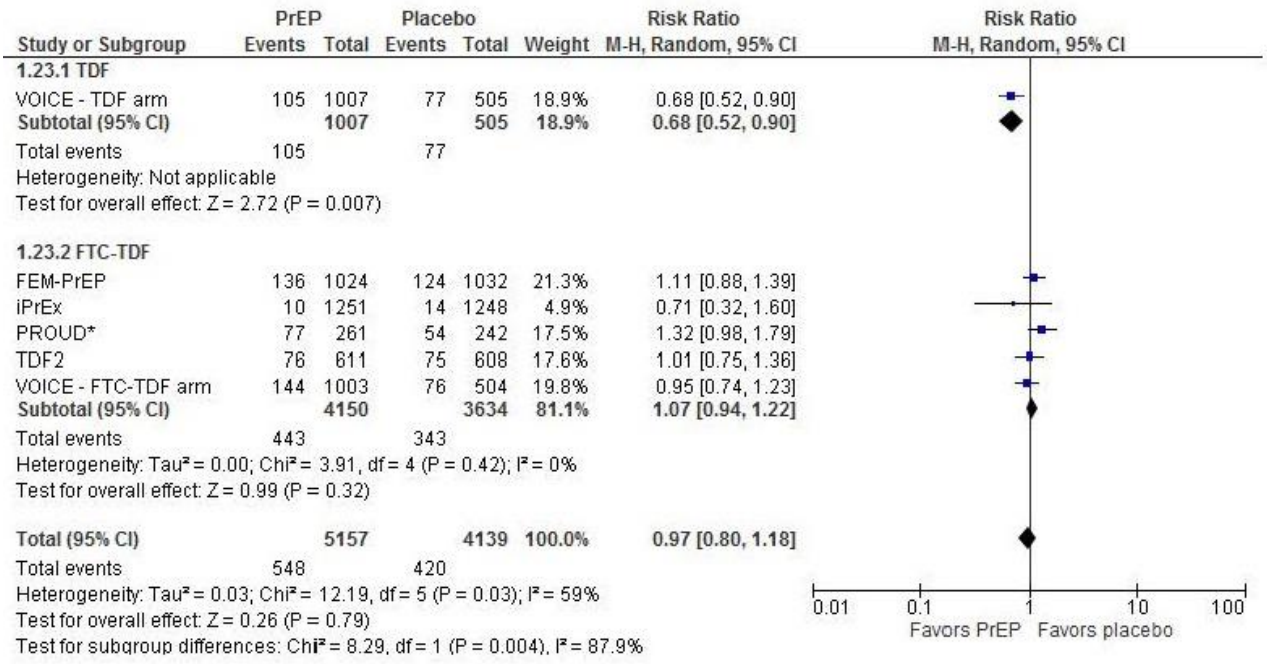


'U.S, Canada, or Europe.

*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate.

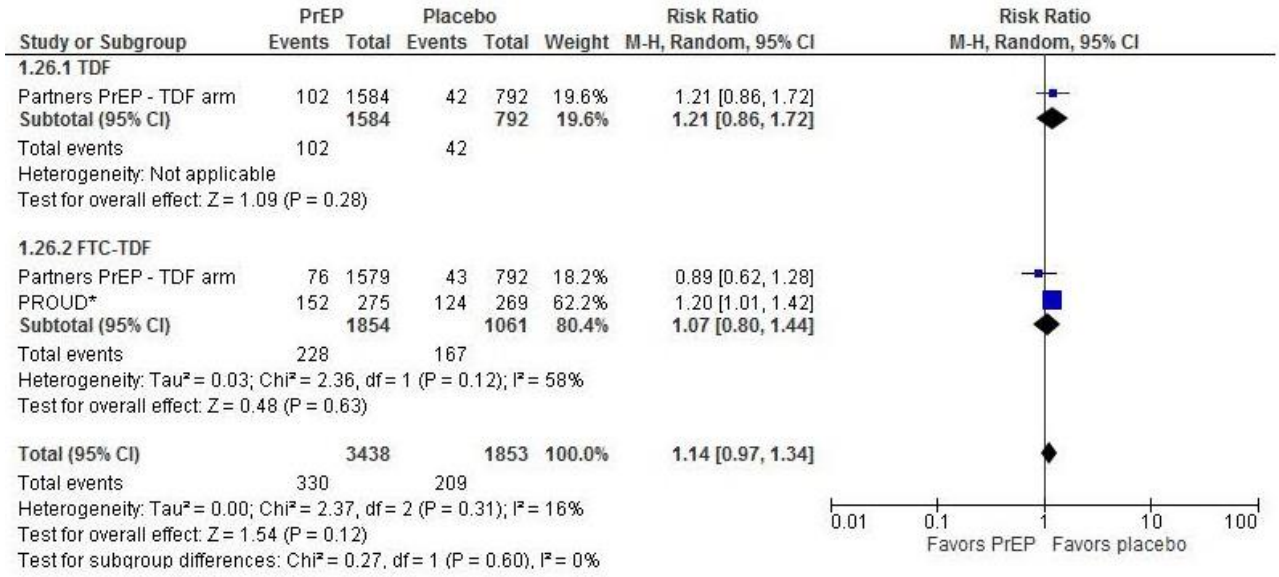
Figure 19. Meta-analysis - Chlamydia Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate.

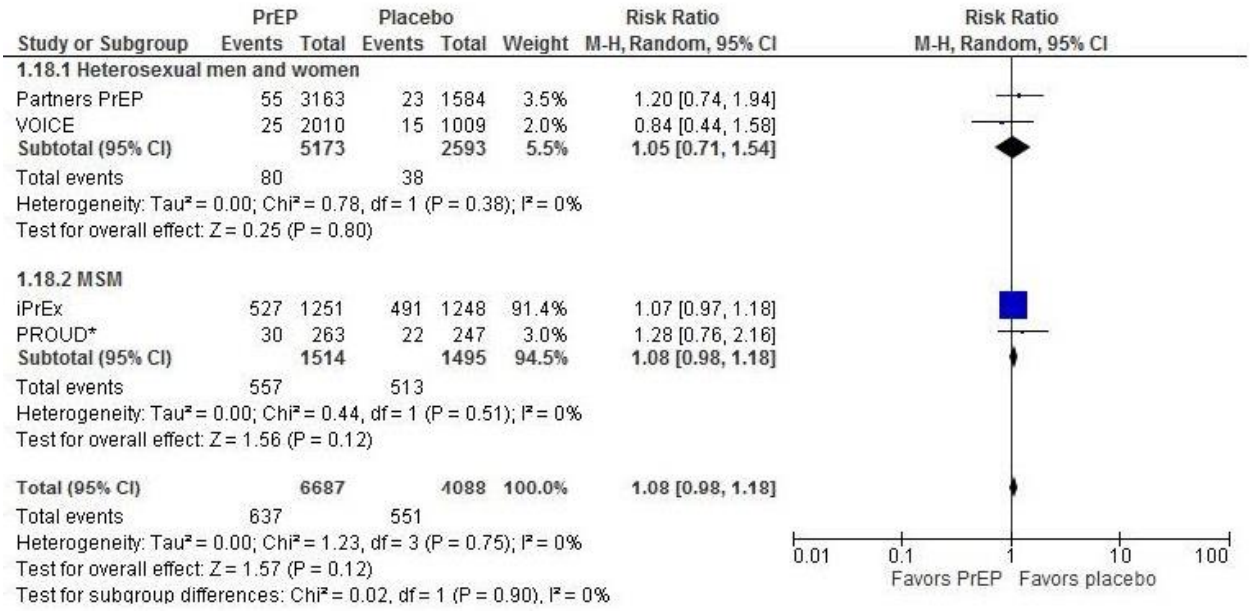
Figure 20. Meta-analysis – Combined Bacterial STIs Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate.

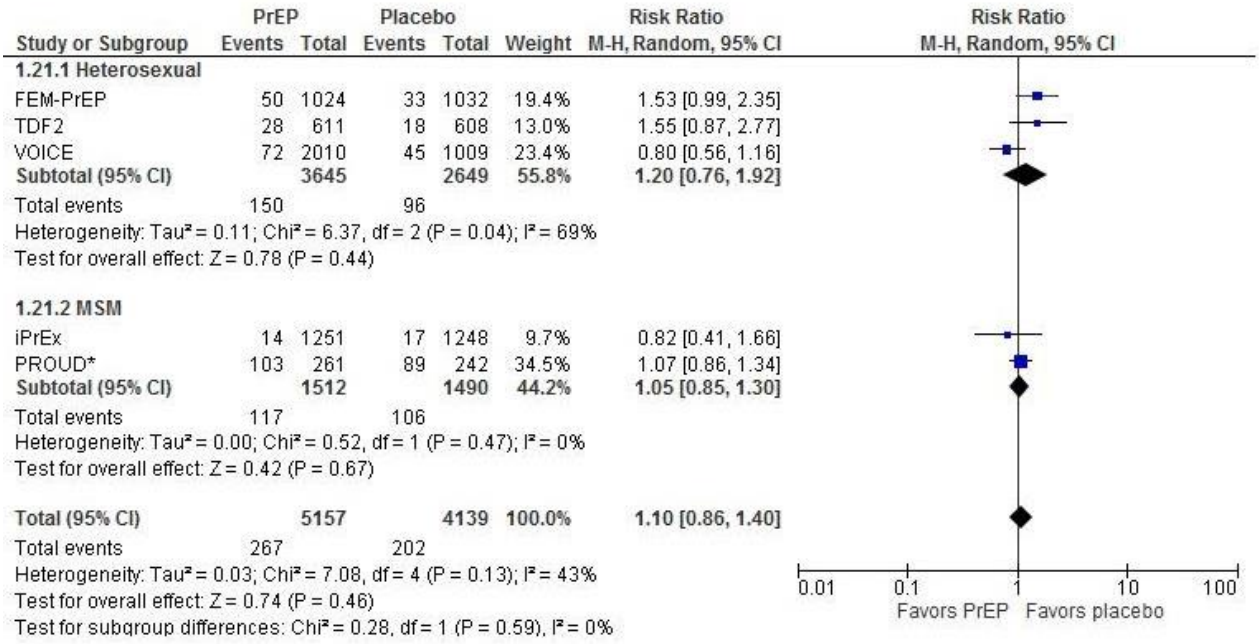
Figure 21. Meta-analysis - Syphilis Stratified by HIV Risk Category



*U.S, Canada, or Europe.

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

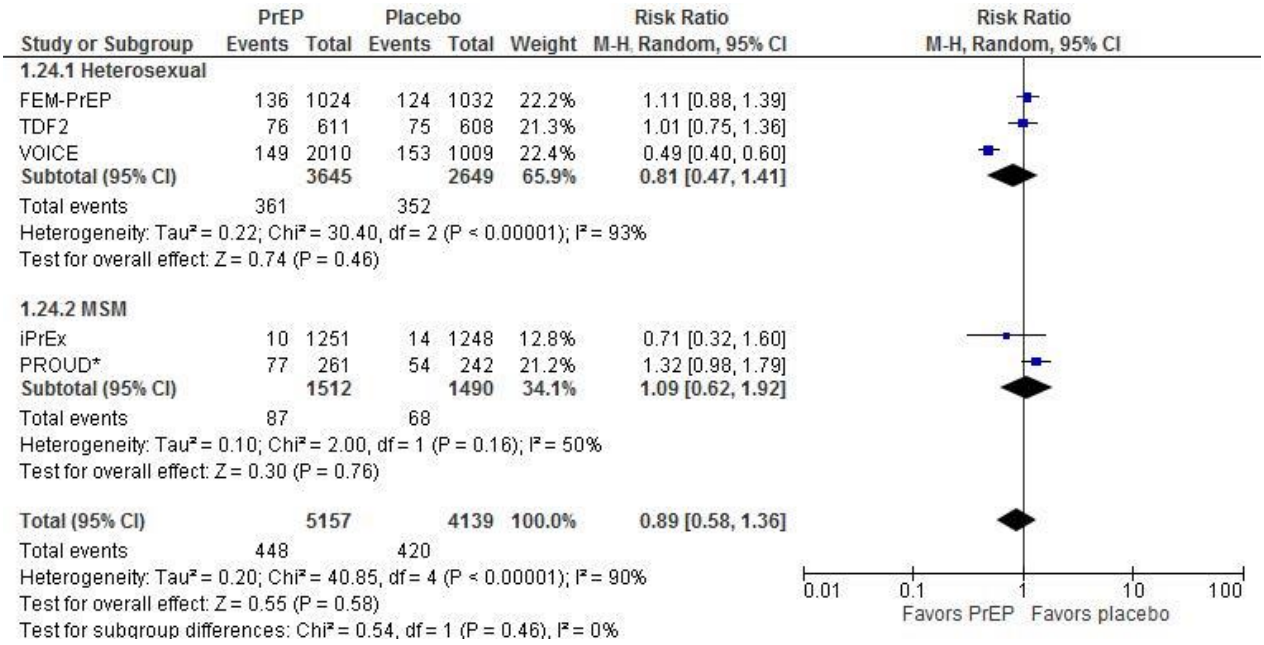
Figure 22. Meta-analysis - Gonorrhea Stratified by HIV Risk Category



U.S, Canada, or Europe.

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

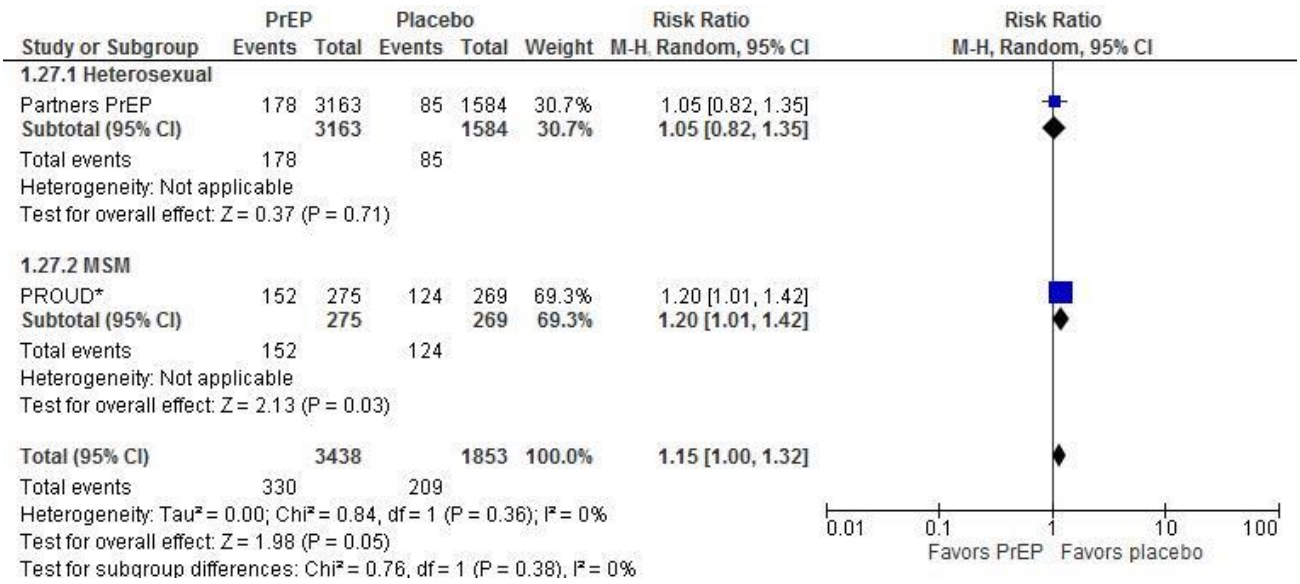
Figure 23. Meta-analysis - Chlamydia Stratified by HIV Risk Category



*U.S, Canada, or Europe.

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

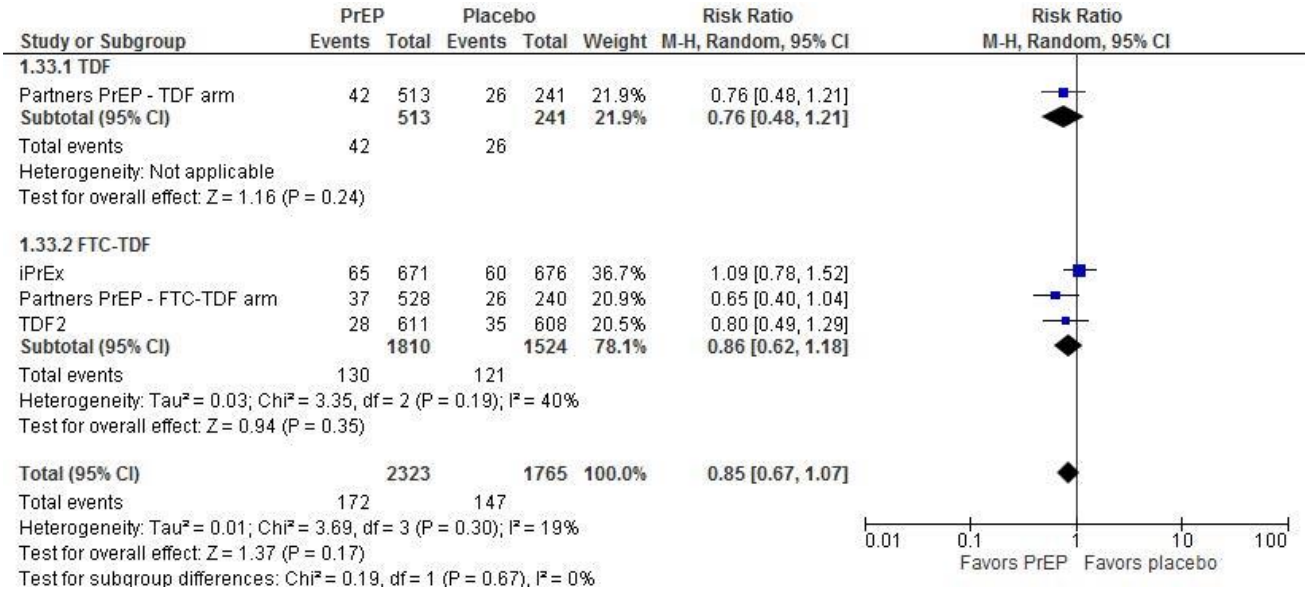
Figure 24. Meta-analysis - Any STI Stratified by HIV Risk Category



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; MSM=men who have sex with men; PrEP=pre-exposure prophylaxis.

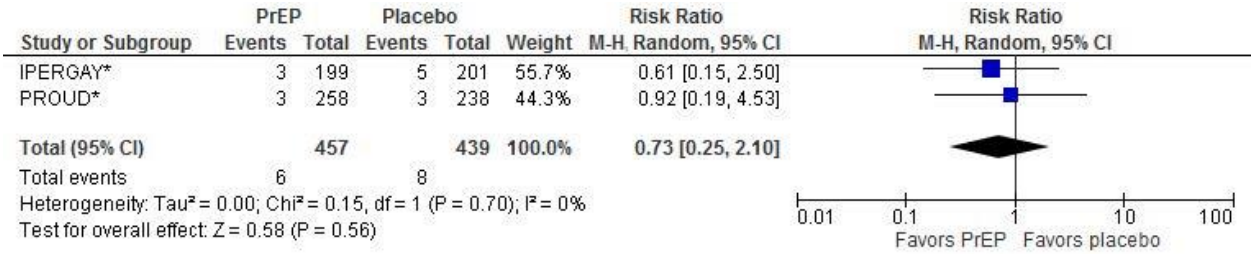
Figure 25. Meta-analysis – Herpes Simplex Virus Infection Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI = confidence interval, M-H = Mantel-Haenszel, PrEP = pre-exposure prophylaxis.

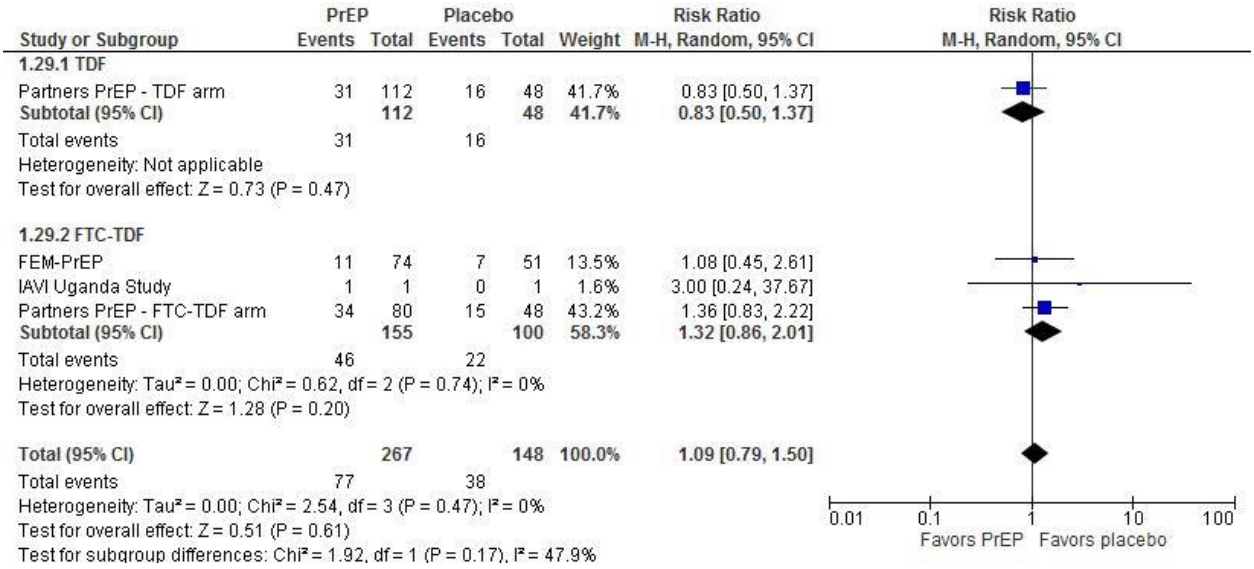
Figure 26. Meta-analysis – Hepatitis C Virus Infection



*U.S, Canada, or Europe.

Abbreviations: CI = confidence interval, M-H = Mantel-Haenszel, PrEP = pre-exposure prophylaxis.

Figure 27. Spontaneous Abortion Stratified by Study Drug



*U.S, Canada, or Europe.

Abbreviations: CI=confidence interval; FTC=emtricitabine; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate.

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

Guidance for:	Details
Detecting substantial risk of acquiring HIV infection	**MSM:** HIV-infected sexual partner Recent bacterial STI* High number of sex 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 sex partners History of inconsistent or no condom use Commercial sex work In high-prevalence area or network **PWID:** HIV-positive injecting 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	Follow-up visits at least every 3 months to provide the following: HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment At 3 months and every 6 months thereafter, assess renal function Every 6 months, test for bacterial STIs **MSM:** Do oral/rectal STI testing **Heterosexual women and men:** For women, assess pregnancy intent Pregnancy test every 3 months **PWID:** 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, syphilis for MSM including those who inject drugs.
†Gonorrhea, syphilis for heterosexual women and men including those who inject drugs.
Abbreviations: HIV=human immunodeficiency virus; MSM=men who have sex with men; PrEP=pre-exposure prophylaxis; PWID=people who inject drugs; 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[91] 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[95] 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 US[84] 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)

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[92] Brazil, Ecuador, Peru, Thailand, South Africa, US 1.2 years (median) Good	A. TDF-FTC 300/200mg (n=1,251) B. Placebo (n=1,248)	MSM: Anal sex with ≥4 male partners, a diagnosis of STI, history of transactional sex activity, condomless anal sex with an HIV-infected partner or of unknown infection status in the previous 6 months	A vs. B Age 18 to 24: 47% vs. 53% Age 25 to 29: 22% vs. 19% Age 30 to 39: 20% vs. 18% Age ≥40: 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[69] Kenya, Uganda 2 years (median) Good	A. TDF 300mg + placebo TDF-FTC (n=1,571) B. TDF-FTC 300/200mg + placebo TDF (n=1,565) C. Placebo TDF + placebo TDF-FTC (n=1,570)	High-risk heterosexual men and women: ART-naïve HIV-infected partner	A vs. B vs. C Age 18 to 24: 12% vs. 11% vs. 11% Age 25 to 34: 46% vs. 44% vs. 43% Age 35 to 44: 30% vs. 32% vs. 32% Age ≥45: 13% vs. 14% vs. 13% Male: 62% vs. 64% vs. 61% Race: NR	82% (plasma)
PROUD McCormack 2016[77] England 1 year Fair	A. Immediate TDF-FTC 245/200 mg (n=275) B. TDF-FTC deferred for 1 year (n=269)	MSM: 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[93] 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[94] Botswana 1 year (median) Good	A. TDF-FTC 300/200mg, (n=611) B. Placebo (n=608)	High-risk heterosexual men and women: Sexually active in high-prevalence area	A vs B Age 18 to 20 years: 2% vs. 3% Age 21 to 29 years: 90% vs. 87% Age 30 to 39 years: 8% vs. 10% Female: 46% vs. 46% Race: NR	80% (plasma)
VOICE Marrazzo 2015[75] South Africa, Uganda, Zimbabwe 3 years (maximum) Good	A. TDF 300 mg + placebo (n=1,007) B. TDF-FTC 300/200mg + 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 Female: 100% all groups Race: NR	30% (plasma)

*Primary publication; details on all included publications appear in **Evidence Table B1.**
†Daily, oral dose unless specified.
‡Sample of patient who reported that they were taking PrEP.

Abbreviations: ART=antiretroviral therapy; CI=confidence interval; FTC=emtricitabine; HIV=human immunodeficiency virus; IQR=interquartile range; MEMS= medication event monitoring system; MSM=men who have sex with men; NR=not reported; PrEP=pre-exposure prophylaxis; PWID=people who inject drugs; RR=relative risk; STI=sexually transmitted infection; TDF=tenofovir disoproxil fumarate; US=United States.

Table 3. Risk of HIV Infection in RCTs of PrEP versus Placebo/No PrEP

	Number of trials	RR (95% CI)	I^2
All trials	11[52,53,69,75,77,84,91-95]	0.46 (0.33 to 0.66)	67%
• Restricted to good-quality trials	10[52,53,69,75,84,91-95]	0.48 (0.33 to 0.71)	71%
PrEP drug regimen (p for interaction=0.79)			
• TDF	5[69,75,84,91,93]	0.49 (0.28 to 0.84)	58%
• TDF-FTC	8[52,53,69,75,77,92,93,95]	0.44 (0.27 to 0.72)	67%
Adherence (p for interaction<0.00001))			
• Adherence ≥70%	6[52,53,69,77,84,94]	0.27 (0.19 to 0.39)	0%
• Adherence >40% to <70%	3[91-93]	0.51 (0.38 to 0.70)	0%
• Adherence ≤40%	2[75,95]	0.93 (0.72 to 1.20)	0%
HIV risk category (p for interaction=0.43)			
• Heterosexual men and women	5[69,75,93-95]	0.54 (0.31 to 0.97)	82%
• Men who have sex with men	4[52,77,84,92]	0.23 (0.08 to 0.62)	64%
• People who inject drugs	1[91]	0.52 (0.29 to 0.92)	Not applicable
Dosing schedule (p for interaction=0.13)			
• Daily dosing	9[53,69,75,77,84,91-95]	0.47 (0.32 to 0.71)	75%
• On-demand dosing	1[52]	0.14 (0.03 to 0.63)	Not applicable
Follow-up duration (p for interaction=0.35)			
• Duration of follow-up <1 year	3[52,53,93]	0.21 (0.07 to 0.58)	0%
• Duration of follow-up ≥1 to 2 years	4[77,92,94,95]	0.48 (0.28 to 0.84)	70%
• Duration of follow-up ≥2 years	4[69,75,84,91]	0.47 (0.22 to 1.00)	86%
Industry support (p for interaction=0.38)			
• Study reported industry support	3[53,94,95]	0.58 (0.27 to 1.22)	54%
• Study reported government or not-for-profit funding only	8[52,69,75,77,84,91-93]	0.39 (0.23 to 0.64)	77%
Country setting (p for interaction=0.004)			
• US or other high-income countries	3[52,77,84]	0.13 (0.05 to 0.32)	0%
• Africa, Asia, or international trial	8[53,69,75,91-95]	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; US=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[91]	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% (41.1 to 99.4); p for interaction=NR	Efficacy Female: 78.6% (95% CI 16.8 to 96.7) Male: 37.6% (95% CI -17.8% to 67.9%); p for interaction=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 for interaction=NR *Injected during 12 wks before enrollment* Yes: 44.3% (95% CI -12.5 to 72.4) No: 57.4% (95% CI -17.0 to 86.6); p for interaction=NR
FEM PrEP Van Damme 2012[95]	≥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 for interaction=0.91	NA	NR	NR
iPrEx Grant 2010[92]	<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 for interaction=0.36	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 for interaction=0.09**	Non-Hispanic: HR 0.48 (95% CI 0.14 to 1.60) Hispanic: HR 0.57 (95% CI 0.37 to 0.89); p for interaction=0.79	*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 for interaction=0.01**
Partners PrEP Baeten 2012[69]	*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 for interaction=0.79 *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 for interaction=0.06	*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 for interaction=0.65 *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 for interaction=0.24	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 for interaction=0.05** *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 for interaction=0.77
TDF2 Thigpen 2012[94]	NR	Female: RR 0.49 (95% CI 0.02 to 1.21) Male: RR 0.20 (95% CI 0.4 to 0.91); p for interaction=0.31	NR	NR

Abbreviations: CI=confidence interval; FTC=emtricitabine; HR=hazard ratio; NR=not reported; PrEP=pre-exposure prophylaxis; TDF= tenofovir disoproxil fumarate.

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

Study, year of publication	Study design	N	Population	Years PrEP administered	Drug levels	Self report	Other method of assessing adherence
Chan, 2016[129]	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 or more 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	NR
CDC Safety Study Grohskopf, 2013[84]	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%	20052007	NR	NR	Medication event monitoring system: 79% (range 60 to 92%) Pill count: 93% (range 81 to 98%)
Grant 2018[113]	RCT	179	MSM (97%), transgender women (2%), gender queer (1%) Mean age NR; 30% age 18-24; 18% age 25-29; 21% age 30-39; 32% age ≥40 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%

Study, year of publication	Study design	N	Population	Years PrEP administered	Drug levels	Self report	Other method of assessing adherence
Hosek, 2017a[128]	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, 2017b[127]	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

Study, year of publication	Study design	N	Population	Years PrEP administered	Drug levels	Self report	Other method of assessing adherence
Hosek, 2013[130]	Double-blind medication pilot RCT with third non-medication control group	58	MSM, age 18-22, at least 2 episode 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 43–83%	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[80] 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%
Montgomery, 2016[125]	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 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

Study, year of publication	Study design	N	Population	Years PrEP administered	Drug levels	Self report	Other method of assessing adherence
Van Epps 2018[131]	Retrospective cohort	1,086	Indication for PrEP NR Mean age NR; 39% age <35 years; 35% age 35-49; 21% age 50-64; 6% age 65-79 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: FSM=females who have sex with males; 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.

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[91]* and Martin 2015[105] RCT	1,204	RR 0.52 (95% CI 0.29 to 0.92)	"Adherent" (drug taken on 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) in cases and 67% (93/138) in controls, OR 0.30 (95% CI 0.09 to 0.98)
FEM-PrEP Van Damme, 2012[95]* and Agot 2015[96] RCT	1,062	HR 0.94 (95% CI 0.59 to 1.52)	NR	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)
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[92]* 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[69]*, Donnell 2014[136] 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) in cases vs. 83% (772/945 samples) in controls OR 0.10 (95% CI 0.05 to 0.23) Tenofovir >10 ng/mL in plasma: 41% (9/29) in cases vs. 79% (730/945 samples) in controls, OR 0.13 (95% CI 0.06 to 0.30) Tenofovir >40 ng/mL in plasma: 24% (6/29) in cases vs. 72% (670/945 samples) in controls, OR 0.11 (95% CI 0.04 to 0.27) Tenofovir detected in plasma: 41% (9/29) in cases vs. 83% (772/945) in controls, OR 0.10 (95% CI 0.05 to 0.23)
TDF2 Thigpen, 2012[94]* RCT	611	RR 0.39 (95% CI 0.19 to 0.81)	NR	Detectable tenofovir plasma level: 50% (2/4) in cases vs. 80% (55/69) in controls, OR 0.25 (95% CI 0.03 to 1.97) Detectable emtricitabine plasma level: 50% (2/4) in cases vs. 81% (56/69) in controls, OR 0.23 (95% CI 0.03 to 1.80)

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[75]* 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) among cases and 44% (68/156) among controls, aRR 0.55 (95% CI 0.26 to 1.14) TDF-FTC: 39% (24/61) among cases and 52% (77/148) among controls, aRR 0.83 (95% CI 0.39 to 1.76) for TDF- FTC
Hosek, 2017a[128] Observational	200	--	NR	TDF plasma level not detectable in 4 seroconverters
Hosek 2017b[127] *ATN 113* Observational	78	--	NR	TDF plasma levels consistent with <2 doses of PrEP/week in 3 seroconverters
iPrEx - OLE Grant, 2014[140] 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 (~2-3 tablets/week): HR 0.16 (95% CI 0.01 to 0.79) 700-1249 fmol/punch (~4-6 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
US PrEP Demonstration Project Liu, 2016[80] and Cohen, 2015[141] Observational	383	--	NR	TDF plasma levels consistent with poor adherence in 2 seroconverters

*Main study publication.

Abbreviations: CI=confidence interval; FTC=emtricitabine; HR=hazard ratio; NR=not reported; OR=odds ratio; PrEP=pre-exposure prophylaxis; RR=relative risk; TDF=tenofovir disoproxil fumarate; US=United States.

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 for interaction=0.23)*	12[52-54,69,75,77,84,91-95]	0.93 (0.77 to 1.12)	56%
• TDF	5[69,75,84,91,93]	0.79 (0.56 to 1.12)	72%
• TDF-FTC	9[52-54,69,75,77,92,94,95]	1.02 (0.81 to 1.30)	46%
Withdrawal due to adverse events *PrEP drug regimen (p for interaction=0.67)*	4[52,69,92,95]	1.25 (0.99 to 1.59)	0%
• TDF	1[69]	1.00 (0.34 to 2.92)	Not applicable
• TDF-FTC	4[52,69,92,95]	1.27 (1.00 to 1.59)	0%
Fracture *PrEP drug regimen (p for interaction=0.50)*	8[52,69,75,77,84,91,92,94]	1.23 (0.97 to 1.56)	0%
• TDF	4[69,75,84,91]	1.29 (0.98 to 1.70)	0%
• TDF-FTC	6[52,69,75,77,92,94]	1.06 (0.66 to 1.72)	0%
Renal adverse events *PrEP drug regimen (p for interaction=0.31)*	12[52-54,69,75,77,84,91-95]	1.43 (1.18 to 1.75)	0%
• TDF	5[69,75,84,91,93]	1.24 (0.87 to 1.76)	0%
• TDF-FTC	9[52-54,69,75,77,92,94,95]	1.54 (1.21 to 1.96)	0%
Gastrointestinal adverse events *PrEP drug regimen (p for interaction=0.30)*	12[52-54,69,75,77,84,91-95]	1.63 (1.26 to 2.11)	43%
• TDF	5[69,75,84,91,93]	1.45 (1.13 to 1.85)	0%
• TDF-FTC	9[52-54,69,75,77,92,94,95]	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 for interaction=0.60)* *HIV risk category (p for interaction=0.38)*	2[69,77]	1.14 (0.97 to 1.34)	16%
• TDF	1[69]	1.21 (0.86 to 1.72)	Not applicable
• TDF-FTC	2[69,77]	1.07 (0.80 to 1.44)	58%
• Heterosexual men and women	1[69]	1.05 (0.82 to 1.35)	Not applicable
• MSM	1[77]	1.20 (1.01 to 1.42)	Not applicable
Syphilis *PrEP drug regimen (p for interaction=0.86)* *HIV risk category (p for interaction=0.90)*	4[69,75,77,92]	1.08 (0.98 to 1.18)	0%
• TDF	2[69,75]	1.13 (0.66 to 1.93)	0%
• TDF-FTC	4[69,75,77,92]	1.07 (0.98 to 1.18)	0%
• Heterosexual men and women	2[69,75]	1.05 (0.71 to 1.54)	0%
• MSM	2[77,92]	1.08 (0.98 to 1.18)	0%
Gonorrhea *PrEP drug regimen (p for interaction=0.02)* *HIV risk category (p for interaction=0.59)*	5[75,77,92,94,95]	1.07 (0.82 to 1.39)	49%
• TDF	1[75]	0.57 (0.33 to 0.98)	Not applicable
• TDF-FTC	5[75,77,92,94,95]	1.15 (0.97 to 1.37)	2%
• Heterosexual men and women	3[75,94,95]	1.20 (0.76 to 1.92)	69%
• MSM	2[77,92]	1.05 (0.85 to 1.30)	0%
Chlamydia *PrEP drug regimen (p for interaction=0.004)* *HIV risk category (p for interaction=0.46)*	5[75,77,92,94,95]	0.97 (0.80 to 1.18)	59%
• TDF	1[75]	0.68 (0.52 to 0.90)	Not applicable
• TDF-FTC	5[75,77,92,94,95]	1.07 (0.94 to 1.22)	0%
• Heterosexual men and women	3[75,94,95]	0.81 (0.47 to 1.41)	93%
• MSM	2[77,92]	1.09 (0.62 to 1.92)	50%
Herpes simplex virus infection *PrEP drug regimen (p for interaction=0.67)* *HIV risk category (p for interaction=0.06)*	3[79,94,103]	0.85 (0.67 to 1.07)	19%
• TDF	1[79]	0.76 (0.48 to 1.21)	Not applicable
• TDF-FTC	3[79,94,103]	0.86 (0.62 to 1.18)	40%
• Heterosexual men and women	2 [79,94]	0.73 (0.56 to 0.96)	0%
• MSM	1[103]	1.12 (0.80 to 1.56)	Not applicable
Hepatitis C virus infection†	2[52,77]	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, year Study design	PrEP regimen	Resistance mutations among people with newly diagnosed HIV infection	Resistance mutations among people randomized to PrEP
Bangkok Tenofovir Study Choopanya 2013[91] 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[95] 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[84] 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[92] 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% (2/1251)
Partners PrEP Baeten 2012[69] 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% (3/3140) overall 0.1% (2/1572) TDF 0.06% (1/1,568) TDF-FTC
PROUD McCormack, 2016[77] 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[93] 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[94] 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)

Study, year Study design	PrEP regimen	Resistance mutations among people with newly diagnosed HIV infection	Resistance mutations among people randomized to PrEP
VOICE Marrazzo 2015[75] 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[140] Observational	A: TDF-FTC daily (n=1225)	M184V: 3.6% (1/28)	0.1% (1/1225)
Hosek 2017a[128] Observational	A: TDF-FTC daily (n=200)	Antiretroviral drug resistance (not specified): 0% (0/4)	0% (0/200)
Hosek 2017b[127] Observational	A: TDF-FTC daily (n=78)	Antiretroviral drug resistance to TDF or FTC: 0% (0/3)	0% (0/78)
Liu 2016[80] Observational	A: TDF-FTC daily (n=383)	Antiretroviral drug resistance to TDF or FTC: 0% (0/2)	0% (0/383)
Montgomery 2016[125] Observational	A: TDF-FTC daily (n=35)	M184V, D67N, T215S, and K219Q: 100% (1/1)	2.0% (1/50)

*Includes two individuals in placebo group who were HIV-infected at enrollment.
†Excludes one person on PrEP and four individuals in placebo group who were HIV-infected at enrollment.
‡Includes 2 individuals in TDF-FTC and 8 individuals in placebo group who were HIV-infected at enrollment; all cases of resistance occurred in individuals who were HIV-infected at enrollment.
§ Includes 5 individuals on TDF, 3 individuals on FTC-TDF, and 6 individuals on placebo who had HIV infection at enrollment; K65R and M184V mutations occurred in people with HIV infection at randomization.
‖Includes 2 individuals in TDF group who were HIV-infected at enrollment or at 4 week visit; both mutations occurred in both people.
¶Includes 1 person in TDF-FTC group and 2 people 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 person who were HIV infected at time of enrollment.
Abbreviations: FTC=emtricitabine; HIV=human immunodeficiency virus; NR=not reported; PrEP=pre-exposure prophylaxis; TDF=tenofovir disoproxil fumarate.

Table 10. Summary of Evidence

Key Question	No. of Studies (k) No. of Participants* (n) Study Design	Summary of Findings by Outcome	Consistency/ Precision Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for Key Question	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 for interaction=0.0002) ≥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 follow-up, though results consistent when trials stratified according to follow-up duration. Three trials reported some industry support, but no difference between studies that only reported industry support and those that only reported governmental or not-for-profit funding on estimates.	High	Studies of women and men at increased risk of heterosexual contact conducted in Africa; the only study of PWIDs 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 Key Question 1, HIV infection.	Moderate	See Applicability for Key Question 1, HIV infection.
	Quality of life: k=0	--	--	--	--	--	--
KQ1a. Benefits of PrEP by population subgroups	HIV infection: k=12 RCTs (n=18,244)	Stratified by risk category (p for interaction=0.43) 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 Key Question 1, HIV infection.	Moderate	Studies of women and men at increased risk of heterosexual contact conducted in Africa; the only study of PWIDs conducted in Asia; several studies of MSM conducted in the U.S., Europe, and Canada.

Key Question	No. of Studies (k) No. of Participants* (n) Study Design	Summary of Findings by Outcome	Consistency/ Precision Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for Key Question	Applicability
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 for interaction=0.65) 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 for interaction=0.13) 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 Key Question 1, HIV infection.	High for TDF vs. TDF-FTC, moderate for daily dosing vs. on-demand dosing	5 trials evaluated TDF alone, which is not approved for PrEP in the United States. 1 trial evaluated on-demand dosing of PrEP versus placebo in MSM; no studies on intermittent or on-demand dosing in women or PWID.
KQ2. Diagnostic accuracy of instruments for identifying individuals at risk of incident HIV infection	k=7 studies of risk prediction or diagnostic accuracy (n=32,279)	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. PWIDs: AUROC 0.72 in one study.	Consistent; precise No reporting bias detected	Fair	Retrospective design; each instrument validated in one study or not validated in a cohort independent from the one used to develop the instrument; cutoffs not pre-defined in any study.	Low	All studies conducted in the U.S.; 3 studies used cohorts that included individuals who underwent HIV testing prior to the year 2000; no study evaluated a U.S. applicable instrument for risk prediction in women.

Key Question	No. of Studies (k) No. of Participants* (n) Study Design	Summary of Findings by Outcome	Consistency/ Precision Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for Key Question	Applicability
KQ3. Adherence to PrEP in U.S. primary care–applicable settings	k=10 (3 RCTs and 7 observational studies) (n=3,177)	In five 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. PWIDs or women and men at increased risk of HIV infection due to 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 five RCTs found present 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 PWIDs.
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 Key Question 1, HIV infection.

Key Question	No. of Studies (k) No. of Participants* (n) Study Design	Summary of Findings by Outcome	Consistency/ Precision Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for Key Question	Applicability
KQ5, cont.	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 Key Question 1, 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 Key Question 1, 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 GI adverse events.	High	See Applicability for Key Question 1, 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 th is information. Results heavily weighted by one trial.	Low	See Applicability for Key Question 1, HIV infection.
	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 impact behaviors differently than when patients know they are on PrEP.	Moderate	See Applicability for Key Question 1, 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 impact behaviors differently than when patients know they are on PrEP.	Moderate	See Applicability for Key Question 1, HIV infection.

Key Question	No. of Studies (k) No. of Participants* (n) Study Design	Summary of Findings by Outcome	Consistency/ Precision Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for Key Question	Applicability
KQ5, cont.	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 impact behaviors differently than when patients know they are on PrEP.	Moderate	See Applicability for Key Question 1, 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 impact behaviors differently than when patients know they are on PrEP.	Moderate	See Applicability for Key Question 1, HIV infection.
	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 impact behaviors differently than when patients know they are on PrEP.	Moderate	See Applicability fo Key Question 1, 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 impact behaviors differently than when patients know they are on PrEP.	Low	See Applicability fo Key Question 1, 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 due to heterosexual contact who were taken off PrEP at time of pregnancy

Abbreviations: EPC=Evidence-based Practice Center; HIV=human immunodeficiency virus; NR=not reported; PrEP=pre-exposure prophylaxis; US=United States.
*For Key Questions 1 and 5, number of participants included in analysis.
†In women who became pregnant while on PrEP.

Appendix A1. Search Strategies

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

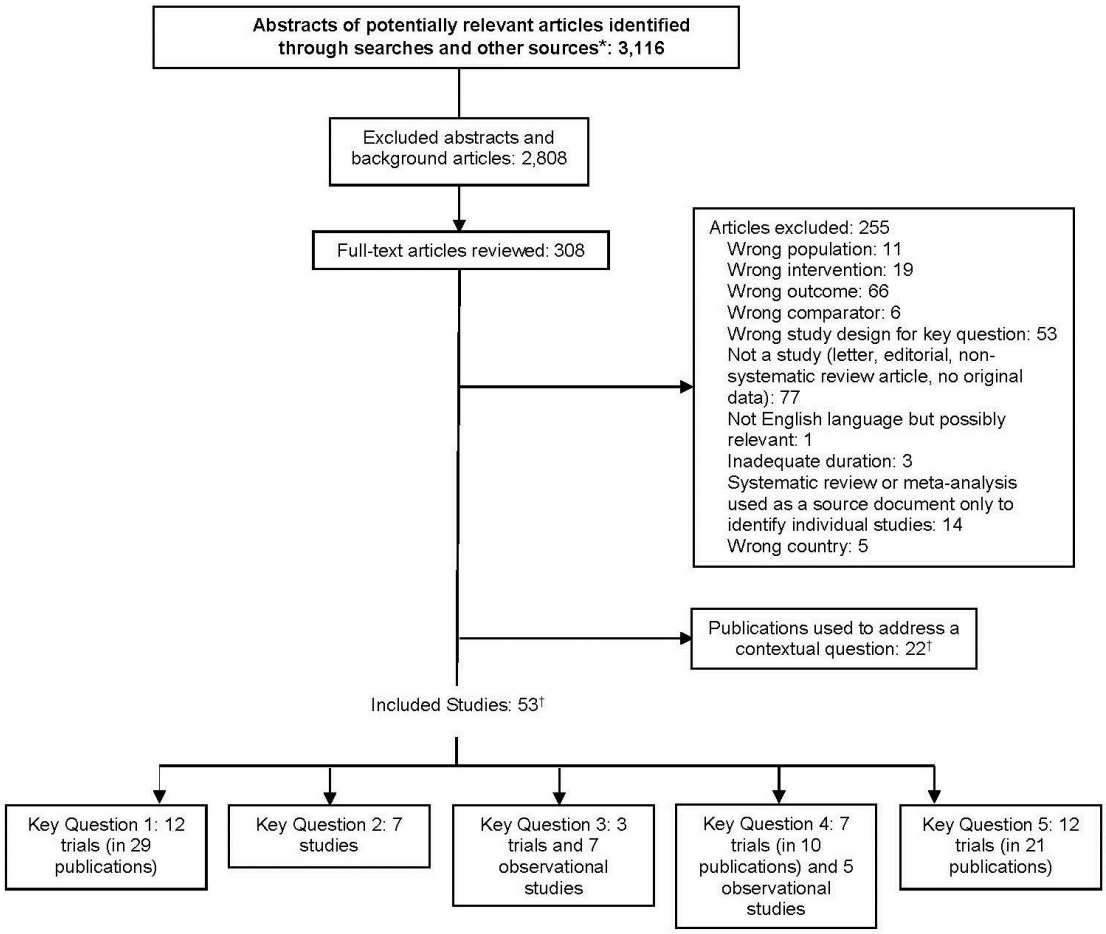
1 exp HIV Infections/
2 (hiv or "human immunodeficiency virus").mp.
3 exp Risk/
4 ("risk assessment" or "risk factors").mp.
5 exp "Sensitivity and Specificity"/
6 (sensitivity or specificity or "diagnostic accuracy").mp.
7 (1 or 2) and (3 or 4) and (5 or 6)
8 limit 7 to yr="2005 - 2018"

Appendix A2. Inclusion and Exclusion Criteria

	Included	Excluded
Populations	Adolescents (13 to <18 years of age) and adults (≥18 years of age) 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 **KQs 3:** U.S. 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: KQs=key questions; 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 prior reports, reference lists of relevant articles, systematic reviews, reviewer suggestions, etc.
†Some papers are included in multiple Key Questions and/or Contextual Questions.

Note: One additional trial[114] evaluated dosing strategies for Key Questions 1 and 5.

Appendix A4. Excluded Studies List

1. Aaron E, Blum C, Seidman D, et al. Optimizing delivery of HIV preexposure prophylaxis for women in the United States. AIDS Patient Care STDS. 2018 Jan;32(1):16-23. doi: 10.1089/apc.2017.0201. PMID: 29323558. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

2. Abbas UL, Glaubius R, Mubayi A, et al. Antiretroviral therapy and pre-exposure prophylaxis: combined impact on HIV transmission and drug resistance in South Africa. J Infect Dis. 2013 Jul 15;208(2):224-34. doi: 10.1093/infdis/jit150. PMID: 23570850. Excluded: wrong study design for Key Question.

3. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010 Sep 03;329(5996):1168-74. doi: 10.1126/science.1193748. PMID: 20643915. Excluded: wrong intervention.

4. Abdool Karim SS. HIV pre-exposure prophylaxis in injecting drug users. Lancet. 2013 Jun 15;381(9883):2060-2. doi: 10.1016/S0140-6736(13)61140-X. PMID: 23769217. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

5. Adams LM, Balderson BH. HIV providers' likelihood to prescribe pre-exposure prophylaxis (PrEP) for HIV prevention differs by patient type: a short report. AIDS Care. 2016 Sep;28(9):1154-8. doi: 10.1080/09540121.2016.1153595. PMID: 26915281. Excluded: wrong outcome.

6. Alistar SS, Owens DK, Brandeau ML. Effectiveness and cost effectiveness of oral pre-exposure prophylaxis in a portfolio of prevention programs for injection drug users in mixed HIV epidemics. PLoS One. 2014;9(1):e86584. doi: 10.1371/journal.pone.0086584. PMID: 24489747. Excluded: wrong study design for Key Question.

7. Allen E, Gordon A, Krakower D, et al. HIV preexposure prophylaxis for adolescents and young adults. Curr Opin Pediatr. 2017 Aug;29(4):399-406. doi: 10.1097/MOP.0000000000000512. PMID: 28598901. Excluded: wrong study design for Key Question.

8. Aloysius I, Savage A, Zdravkov J, et al. InterPrEP. Internet-based pre-exposure prophylaxis with generic tenofovir DF/emtricitabine in London: an analysis of outcomes in 641 patients. J Virus Erad. 2017 Oct 01;3(4):218-22. PMID: 29057086. Excluded: wrong study design for Key Question.

9. Al-Tayyib AA, Thrun MW, Haukoos JS, et al. Knowledge of pre-exposure prophylaxis (PrEP) for HIV prevention among men who have sex with men in Denver, Colorado. AIDS Behav. 2014 Apr;18 Suppl 3:340-7. doi: 10.1007/s10461-013-0553-6. PMID: 23824227. Excluded: wrong outcome.

10. Anderson PL, Garcia-Lerma JG, Heneine W. Nondaily preexposure prophylaxis for HIV prevention. Curr Opin HIV AIDS. 2016 Jan;11(1):94-101. doi: 10.1097/COH.0000000000000213. PMID: 26633641. Excluded: wrong study design for Key Question.

11. Anderson PL, Glidden DV, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med. 2012 Sep 12;4(151):1-8. PMID: 22972843. Excluded: wrong outcome.

12. Anderson PL, Reirden D, Castillo-Mancilla J. Pharmacologic considerations for preexposure prophylaxis in transgender women. J Acquir Immune Defic Syndr. 2016 Aug 15;72 Suppl 3:S230-4. doi: 10.1097/QAI.0000000000001105. PMID: 27429188. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

13. Andersson E, Nordquist A, Esbjornsson J, et al. Increase in transmitted drug resistance in migrants from sub-Saharan Africa diagnosed with HIV-1 in Sweden. AIDS. 2018 Apr 24;32(7):877-84. doi: 10.1097/QAD.0000000000001763. PMID: 29369826. Excluded: wrong outcome.

14. Anglemyer A, Rutherford GW, Horvath T, et al. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. Cochrane Database Syst Rev. 2013;4:CD009153. doi: 10.1002/14651858.CD009153.pub3. PMID: 23633367. Excluded: systematic review of meta-analysis document used as a source document only to identify individual studies.

15. Anonymous. Pre-exposure prophylaxis effective. AIDS Patient Care STDS. 2006 Sep;20(9):660. PMID: 17036415. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

16. 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).

17. Antoni G. On-demand PrEP with TDF/FTC remains highly effective among MSM with infrequent sexual intercourse: a sub-study of the ANRS IPERGAY trial. 2017. http://programme.ias2017.org/Abstract/Abstract/3629. Accessed January 3, 2018. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

18. Arnold T, Brinkley-Rubinstein L, Chan PA, et al. Social, structural, behavioral and clinical factors influencing retention in pre-exposure prophylaxis (PrEP) care in Mississippi. PLoS One. 2017;12(2):e0172354. doi: 10.1371/journal.pone.0172354. PMID: 28222118. Excluded: wrong outcome.

19. 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.

20. 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).

21. Baeten JM. Preexposure prophylaxis reduced HIV-1 spread in serodiscordant heterosexual couples. ANN Intern Med. 2012;157(10):JC5-3. doi: 10.7326/0003-4819-157-10-201211200-02003. PMID: 23165679. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

22. 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.

23. 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.

24. Baker J. Stay current with options for HIV prevention. JAAPA. 2013 Dec;26(12):14-20; quiz 5. doi: 10.1097/01.JAA.0000437820.76526.41. PMID: 24177333. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

25. 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).

26. Balkus JE, Brown E, Palanee T, et al. An empiric HIV risk scoring tool to predict HIV-1 acquisition in African women. J Acquir Immune Defic Syndr. 2016 Jul 1;72(3):333-43. doi: 10.1097/QAI.0000000000000974. PMID: 26918545. Excluded: wrong country.

27. Balkus JE, Brown ER, Palanee-Phillips T, et al. Performance of a validated risk score to predict HIV-1 acquisition among african women participating in a trial of the dapivirine vaginal ring. J Acquir Immune Defic Syndr. 2018 01 01;77(1):e8-e10. doi: 10.1097/QAI.0000000000001556. PMID: 28961677. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

28. Baral SD, Poteat T, Stromdahl S, et al. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. Lancet Infect Dis. 2013 Mar;13(3):214-22. doi: 10.1016/s1473-3099(12)70315-8. PMID: 23260128. Excluded: wrong outcome.

29. Baral SD, Stromdahl S, Beyrer C. The potential uses of preexposure prophylaxis for HIV prevention among people who inject drugs. Curr Opin HIV AIDS. 2012 Nov;7(6):563-8. doi: 10.1097/COH.0b013e328358e49e. PMID: 23076122. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

30. Barash EA, Golden M. Awareness and use of HIV pre-exposure prophylaxis among attendees of a Seattle gay pride event and sexually transmitted disease clinic. AIDS Patient Care STDS. 2010 Nov;24(11):689-91. doi: 10.1089/apc.2010.0173. PMID: 20863247. Excluded: wrong outcome.

31. Barreiro P. Hot news: Sexually transmitted infections on the rise in PrEP users. AIDS Rev. 2018 Jan-Mar;20(1):71. PMID: 29628512. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

32. 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).

33. 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).

34. Baxter C, Abdool Karim S. Combination HIV prevention options for young women in Africa. Afr J AIDS Res. 2016 Jul;15(2):109-21. doi: 10.2989/16085906.2016.1196224. PMID: 27399041. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

35. Bazzi AR. Antiretroviral pre-exposure prophylaxis for HIV prevention is highly effective in community settings. Evid Based Med. 2016 Jun;21(3):99. doi: 10.1136/ebmed-2016-110403. PMID: 27029888. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

36. 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.

37. 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).

38. 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.

39. Bekker LG, Li SS, Tolley B, et al. HPTN 076: TMC278 la safe, tolerable, and acceptable for HIV preexposure prophylaxis. Top Antivir Med. 2017;25(1):172s-3s. Excluded: wrong intervention.

40. Bini EJ, Currie SL, Shen H, et al. National multicenter study of HIV testing and HIV seropositivity in patients with chronic hepatitis C virus infection. J Clin Gastroenterol. 2006 Sep;40(8):732-9. PMID: 16940888. Excluded: wrong intervention.

41. 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.

42. Bird SM. Trial size, HIV pre-exposure prophylaxis, and breastfeeding. Lancet. 2016 May 21;387(10033):2090-1. doi: 10.1016/S0140-6736(16)30539-6. PMID: 27301821. Excluded: wrong population.

43. Blackwell CW. Preexposure prophylaxis: An emerging clinical approach to preventing HIV in high-risk adults. Nurse Pract. 2014 Sep 18;39(9):50-3. doi: 10.1097/01.NPR.0000452976.92052.fa. PMID: 25140852. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

44. Blashill AJ, Ehlinger PP, Mayer KH, et al. Optimizing adherence to preexposure and postexposure prophylaxis: the need for an integrated biobehavioral approach. Clin Infect Dis. 2015 Jun 1;60 Suppl 3:S187-90. doi: 10.1093/cid/civ111. PMID: 25972502. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

45. Blaylock JM, Hakre S, Decker CF, et al. HIV PrEP in the military: Experience at a tertiary care military medical center. Mil Med. 2018 Mar 01;183(suppl_1):445-9. doi: 10.1093/milmed/usx143. PMID: 29635556. Excluded: wrong study design for Key Question.

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Appendix A5. Criteria for Assessing Internal Validity of Individual Studies

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. December 2015. Accessed at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

Appendix A6. Expert Reviewers of the Draft Report

- Christopher J. Graber, MD, MPH, Associate Clinical Professor of Medicine, David Geffen School of Medicine at UCLA, 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, UCSF 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, Food and Drug Aministration
- Brandy Peaker, MD, MPH, CDC Liason, 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 B1a. HIV Pre-Exposure Prophylaxis Randomized Controlled Trials – Study Characteristics

Study name **Author, year**	**Study design**	**No. 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[114]	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 post-sex dose; 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 the hepatitis B virus, history of an acute STI, transactional sex, intercourse without a condom with someone of unknown or HIV-infected status, or self-report of more than one sex partner in 6 months preceding study entry.	A vs B vs C Mean age 25 vs 26 vs 25 years 100% vs 100% vs 100% female (no transgender men enrolled) 98% vs 100% vs 100% Black Mean number of sex partners in past 3 months: 1 vs 1 vs 1 Median number of sex events in the past 3 months: 4 vs 4 vs 4 Median number of condomless sex events in the past 3 months: 2 vs 2 vs 1	Screened: 294 Eligible: 269 Enrolled: 191 Analyzed: 178 Withdrawal: 0 (post-randomization) Loss to followup: 0	Fair	HIV Prevention Trials Network

Study name Author, year	Study design	No. of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
ADAPT/ HPTN 067/ Grant, 2018[113]	Same as Bekker 2018	Two centers Thailand (Bangkok), United States (NY, Harlem)	Two centers Thailand (Bangkok), United States (NY, Harlem)	A. Daily TDF-FTC (n=119) B. Time-driven TDF-FTC (one tablet twice a week, plus a post-sex dose; 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, hepatitis B 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 sexually transmitted infection; sex in an exchange for money, goods, or favors; or intercourse without a condom with an HIV-infected partner or partner of unknown HIV infection status	A vs B vs C Bangkok site (n=178) Mean age NR; 13% vs 20% vs 14% age 18-24; 22% vs 32% vs 27% age 25-29; 60% vs 39% vs 48% age 30-39; 5% vs 9% vs 12% age ≥40 98% vs 98% vs 100% MSM; 2% vs 2% vs 0% transgender Race NR Mean number of sex partners in past 3 months: 28% vs 27% vs 17% 0-1; 32% vs 41% vs 49% 2-4; 27% vs 10% vs 19% 5-9; 13% vs 22% vs 15% ≥10 Condomless anal intercourse in past 6 months: 37% vs 44% vs 29% Harlem site (n=179) Mean age NR; 32% vs 28% vs 28% age 18-24; 22% vs 18% vs 13% age 25-29; 19% vs 20% vs 23% age 30-39; 27% vs 33% vs 35% age ≥40 97% vs 98% vs 97% MSM; 3% vs 0% vs 2% transgender; 0% vs 2% vs 2% gender queer 70% Black; 13% white; 3% Asian; 3% Native American; 21% other; 25% Hispanic (participants could self-identify in more than one category) Mean number of sex partners in past 3 months: 5% vs 7% vs 7% 0-1; 51% vs 35% vs 43% 2-4; 14% vs 30% vs 30% 5-9; 29% vs 25% vs 20% ≥10 Condomless anal intercourse in past 6 months: 80% vs 67% vs 83%	Screened: 608 Eligible: Unclear Enrolled: 431 Analyzed: 357 Withdrawal: 0 (post-randomization) Loss to followup: 19% (81/431)	Same as Bekker 2018	Same as Bekker 2018

Study name **Author, year**	**Study design**	**No. of centers, Country**	**Study duration Mean followup**	**Interventions**	**Inclusion criteria**	**Patient characteristics**	**Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup**	**Quality rating**	**Funding source**
Bangkok Tenofovir Study Choopanya, 2013[91]* and Martin, 2015[105]	Double-blind RCT	17 drug treatment clinics Thailand	9665 person-years (mean 4.0 years, SD 2.1, Maximum 6.9 years)	A. Tenofovir 300mg once daily (n=1204) B. Placebo (n=1209) Participants could choose directly observed therapy or monthly take-home prescriptions, and switch at monthly follow-up appointments	HIV-uninfected, age 20 to 60, reporting PWID in past 12 months Excluded: HBsAg-infected, pregnant or breastfeeding	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% Education ≤6 years: 47% vs. 49%; Education 7 to 12 years: 45% vs. 41%; Education >12 years: 8% vs. 10% Current methadone treatment: 21% vs. 22% Injected in past 12 weeks: 62% vs. 64% Heroin use: 22% vs 22% Methamphetamine use 35% vs. 32% Midazolam use: 23% vs. 24% Shared needles in past 12 weeks: 19% vs. 18% >1 Sexual partner in past 12 weeks: 21% vs. 23% Sex with casual partner in past 12 weeks: 36% vs. 40%.	Screened: 4,094 Eligible: NR Enrolled: 2,413 Analyzed: 2,411 Withdrawals: 0/1,204 vs. 2/1,209 excluded due to newly HIV-infected at enrollment Loss to followup: 34% (409/1,204) vs. 34% (410/1,207)	Good	U.S. Centers for Disease Control and Prevention; Bangkok Metropolitan Administration
Bangkok Tenofovir Study Martin, 2014[104]	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/minute by the Cockcroft-Gault formula	Same as Choopanya 2013	Same as Choopanya 2013	Same as Choopanya 2013	Same as Choopanya 2013

Study name Author, year	Study design	No. of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
FEM-PrEP Van Damme, 2012[95]* and Agot, 2015[96]	RCT	4 sites Kenya, South Africa, and Tanzania	1 year	A. Oral TDF-FTC 300/200mg once daily (n=1,062) B. Placebo, once daily (n=1,058)	Age 18 to 35 years; HIV-uninfected; not pregnant/breastfeeding; willing to use an effective non barrier contraceptive method; able to swallow a vitamin table similar to study table; 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% (118/1032) Loss to followup: 14% (148/1,024) vs. 11% (118/1,032)	Good	USAID; Gates Foundation; Gilead Sciences provided study drugs
FEM-PrEP Mandala, 2014[102]	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[84]* (CDC Safety Study)	RCT	3 sites USA	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, 18 to 60 years of age, 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	US Department of Health and Human Services, Centers for Disease Control and Prevention

Study name Author, year	Study design	No. of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
Liu, 2011[101] (companion to Grohskopf, 2013)	Cohort from larger RCT	1 site, San Francisco	Same as Grohskoph 2013	Same as Grohskoph 2013	Same as Grohskoph 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. 8% Heavy alcohol use in past 3 months: 4% vs. 6% Any recreational drug use in past 3 months: 44% vs. 52%	Screened: 359 Enrolled: 200 Analyzed: 184 (94 vs. 90; had at least 1 followup DEXA scan)	Same as Grohskoph 2013	Same as Grohskoph 2013
IAVI Kenya Study Mutua, 2012[53]	RCT	2 sites Kenya	4 months	A. Daily TDF-FTC 300/200mg (n=24) B. Intermittent (Monday, Friday and within 2 hours post- coital, not to exceed 1 dose/day) TDF-FTC (n=24) C. Daily placebo (n=12) D. Intermittent placebo (n=12)	HIV-uninfected MSM and FSW aged 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 hepatitis B infection or with circulation < 80 mL/min and pregnant or lactating mothers	A vs. B vs. C vs. D Age (mean): 26 vs. 26 vs. 27 vs. 28 years Female: 12% vs. 0% vs. 8% vs. 8% Race: NR Illicit drug use: 33% vs. 42% vs. 58% vs. 42% Drank alcohol prior to sex: 38% vs. 58% vs. 42% vs. 50% Genital sore or discharge: 4% vs. 0% vs. 0% vs. 8% Condom use with new male partner: 85% vs. 100% vs. 83% vs. 100% Condom use with new female partner: 100% vs. 100% vs. 100% vs. 100% Gave/received money/gifts for sex: 74% vs. 63% vs. 73% vs. 58% Engaged in group sex: 4% vs. 0% vs. 0% vs. 0% Receptive anal sex: 59% vs. 71% vs. 45% vs. 75% Insertive anal sex: 65% vs. 61% vs. 80% vs. 55% Number of sex partners in past month (median): 3 vs. 3 vs. 3 vs. 3	Screened 107 Eligible: 78 Enrolled: 72 Withdrawals: 0 Lost to follow up: 6% (4/72)	Good	IAVI, study medication provided by Gilead Science

Study name Author, year	Study design	No. of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
IAVI Uganda Study Kibengo, 2013[54]	RCT	Single center Uganda	4 months	A. Daily TDF-FTC 300/200mg (n=24) B. Intermittent (Monday, Friday and within 2 hours post- coital, not to exceed 1 dose/day) TDF-FTC 300/200mg (n=24) C. Daily placebo (n=12) D. Intermittent placebo (n=12)	HIV-uninfected aged 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 not using ART Excluded: chronic hepatitis B infection or with creatinine clearance <80mL/min or pregnant or lactating mothers	A vs. B vs. C vs. D Age (mean): 33 vs. 33 vs. 33 vs. 33 years Female: 50% vs. 46% vs. 67% vs. 42% Race: NR Illicit drug use: 2% vs. 0% vs. 3% vs. 0% Alcohol use prior to sex: 8% vs. 8% vs. 17% vs. 0% Presence of genital sore or discharge: 8% vs. 4% vs. 25% vs. 17% Number of sex partners in previous month: 1: 96% vs. 71% vs. 100% vs. 67% 2: 4% vs. 25% vs. 0% vs. 33% 3: 0% vs. 4% vs. 0% vs. 0% Number of HIV infected partners past month: 0: 0% vs. 0% vs. 0% vs. 8% 1: 100% vs. 96% vs. 100% vs. 92% 2: 0% vs. 4% vs. 0% vs. 0% Condom use with HIV-infected partner: Not applicable: 0% vs. 0% vs. 0% vs. 8% Never: 4% vs. 0% vs. 0% vs. 0% Sometimes: 13% vs. 8% vs. 8% vs. 8% Frequently: 4% vs. 17% vs. 8% vs. 0% Always: 79% vs. 75% vs. 83% vs. 83%	Screened: 133 Eligible: 72 Enrolled: 72 Analyzed: 72 No withdrawals or loss to followup	Good	IAVI, study medication provided by Gilead Science

Study name Author, year	Study design	No. of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
IPERGAY Molina, 2015[52]	RCT	7 sites France and Canada	Median 9 months (IQR 5 to 21 months)	A. On demand TDF- FTC 300/200mg (n=199) B. Placebo (n=201) On demand dosing schedule: 1. Two pills 2-24 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 preexposure 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	HIV-uninfected, at least 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 at least two partners during the past 6 months). Excluded: HBsAg-infected, chronic infection with hepatitis C virus, a creatinine clearance of less than 60 ml per minute, alanine aminotransferase level of more than 2.5 ULN, glycosuria or proteinuria of more than 1+ on urine dipstick testing	A vs. B Age (median): 35 vs. 34 years (IQR 29-43) Female: 0% Race: white 94 vs. 89%; other races NR Relationship status: Not in a couple: 72% vs. 74% In a couple with HIV-1–infected partner: 10% vs. 6% Other: 18% vs. 19% Postsecondary education: 73% vs. 70% >5 Alcoholic drinks per day in past month: 25% vs. 21% Use of recreational drugs:43% vs. 46% Sexual partners in past 2 months (median): 8 vs. 8 Episodes of sexual intercourse in past 4 weeks (median): 10 vs. 10 Circumcised: 19% vs. 20% STI diagnosed at screening: 25% vs. 31% HBsAg status: Susceptible: 23% vs. 19% Immune from natural infection: 9% vs. 15% Immune from vaccination: 68% vs. 66%	Screened: 445 Eligible: 433 Enrolled: 414 Analyzed: 97% (400/414) Withdrawals: 8% (31/414) Loss to followup: 3% (12/414)	Good	ANRS, Canadian HIV Trials Network, Fonds de Dotation Pierre Berge pour la Prevention, Bill and Melinda Gates Foundation

Study name Author, year	Study design	No. of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
iPrEx Grant, 2010[92]*	RCT	11 centers Peru, Ecuador, Brazil, USA, Thailand, and South Africa	Median 1.2 years	A. TDF-FTC 300/200mg (n=1,251) B. Placebo (n=1,248)	Men or transgender women who have sex with men, age of 18 years or older, HIV-uninfected status, and evidence of high risk for acquisition of HIV infection based on: anal sex with ≥4 male partners, a diagnosis of STI, history of transactional sex activity, condomless anal sex with an HIV-infected partner or 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 antiretroviral drugs or anti- HIV vaccine, acute HBV infection (active HBV not enrolled in Brazilian sites)	A vs. B Age 18 to 24: 47% vs. 53% Age 25 to 29: 22% vs. 19% Age 30 to 39: 20% vs. 18% Age ≥40: 11% vs. 10% Born male: 100% vs. 100% Black: 9% vs. 8% White: 18% vs. 17% Mixed race or other: 68% vs. 70% Asian: 5% vs. 5% Hispanic: 72% vs. 73% No. partners in past 12 weeks: 18±35 vs. 18±43 Unprotected receptive anal intercourse in past 12 weeks: 59% vs. 60% Transactional sex in past 6 months: 41% vs. 41% Known partner with HIV in past 6 months: 2% vs. 3% Circumcised: 13% vs. 14% Syphilis seroreactivity: 13% vs. 13% Serum herpes simplex virus type 2: 37% vs. 35% Urine leukocyte esterase positive: 2% vs. 2%	Screened: 4,905 Eligible: 3,341 Enrolled: 2,499 (1,251 vs. 1,248) Analyzed: 3,678 (1,244 vs. 1,217) Withdrawals: 3% (41/1,251) vs. 4% (46/1,225) Loss to followup: 16% (199/1,251) vs. 15% (182/1,225)	Good	National Institutes of Health and Bill and Melinda Gates Foundation
iPrEx Deutsch, 2015[98]	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	*TGW only* A. TDF-FTC 300/200mg (n=170)	TGW 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[189]	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

Study name Author, year	Study design	No. 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[103]	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	*HSV-2 negative substudy only* A. TDF-FTC 300/200mg (n=692) B. Placebo (n=691)	iPrEx participants who were HSV type 2 negative at baseline	A vs. B Age - <25: 60% vs. 65% 25 to 29: 21% vs. 18% 30 to 34: 9% vs. 8% 35 to 39: 4% vs. 5% ≥40: 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[109]	Same as Grant 2010	Same as Grant 2010	Mean 61 weeks + 24 weeks poststop followup	*BMD substudy only* A. TDF-FTC 300/200mg (n=247) B. Placebo (n=251)	iPrEx participants with DEXA scans performed	A vs. B Age (mean): 28 vs. 28 Black/African American: 10% vs. 10% White: 18% vs. 17% Mixed/other: 47% vs. 53% Asian: 20% vs. 20% Hispanic: 50% vs. 54% TGW: 11% vs. 10% Alcohol use: 81% vs. 80% Marijuana use: 15% vs. 13% Cocaine use: 6% vs. 6% Amphetamine use: 3% vs. 3% Spine BMD 1.04 vs. 1.04 gm/cm^2 Hip BMD 1.02 vs. 1.02 gm/cm^2	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010

Study name Author, year	Study design	No. of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
iPrEx Solomon, 2014[111]	See above	8 sites Brazil, Ecuador, Peru, Thailand, South Africa, USA	1.5 years	Renal substudy only A. TDF-FTC 300/200mg (n=563) B. Placebo (n=574)	iPrEx participants with serum creatinine and urine dipstick testing available	A vs. B Age: 18 to 24: 47% vs. 52% 25 to 29: 22% vs. 19% 30 to 39: 21% vs. 19% >40: 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
Partners PrEP Baeten, 2012[69]*	RCT	9 sites in Kenya and Uganda	Study duration: 36 months Median followup: 23 months	A. Once-daily TDF 300mg + placebo TDF- FTC (n=1,571) B. Once-daily TDF- FTC 300mg/200mg + 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 function and hematologic function; no evidence of chronic active hepatitis B 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: antiretroviral therapy; 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 Age 18 to 24: 12% vs. 11% vs. 11% Age 25 to 34: 46% vs. 44% vs. 43% Age 35 to 44: 30% vs. 32% vs. 32% Age ≥45: 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 ID #47674)

Study name Author, year	Study design	No. 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[79]	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	A. Once-daily TDF 300mg + placebo TDF-FTC (n=528) B. Once-daily TDF-FTC 300mg/200mg + placebo TDF (n=513) C. Placebo TDF + placebo TDF-FTC (n=481)	Partners PrEP enrolled, herpes simplex virus type 2 (HSV-2) seronegative at baseline and with HSV-2 testing available from final study visit.	A vs B vs C Median age 30 vs 31 vs 30 years Male: 80% v 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[136]	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[144]	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 55% vs. 53% vs. 52% male Race not reported 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[99]	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	A. TDF or FTC B. Placebo	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Lehman, 2015[100]	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	*Seroconverters only* A. Once-daily TDF 300mg + placebo TDF- FTC (n=39) B. Once-daily TDF- FTC 300/200mg + 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[190]	RCT	9 Kenya and Uganda	36 months; monthly follow-up	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 28-38) 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

Study name **Author, year**	**Study design**	**No. 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 Mugo, 2014[107]	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 300/200mg (n=565) C. Once daily placebo (n=621)	HIV uninfected women enrolled in Partners PrEP	A vs. B. vs. C Mean age 32 vs. 33 vs. 33 100% female Race NR Married 98% vs. 99% vs. 99% Contraception use 44% vs. 49% vs. 48%	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Mugwanya, 2015[108]	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 300/200mg (n=1,545) C. Once daily placebo	Same as Baeten 2012	See above	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Murname, 2013[110]	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 Murname, 2015[191]	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[112]	See above	See above	See above	*HIV-uninfected men only* A. Once-daily TDF 300mg + placebo TDF- FTC (n=986) B. Once-daily TDF- FTC 300/200mg + 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 Age 18 to 24: 10% vs. 11% vs. 10% Age 25 to 29: 21% vs. 19% vs. 18% Age 30 to 34: 24% vs. 24% vs. 23% Age ≥35: 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

Study name **Author, year**	**Study design**	**No. 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 Hosek, 2013[130]	Double-blind medi-cation pilot RCT with third non-medi-cation control group	2 clinics in Chicago, IL	24 weeks	A. PrEP with daily emtricitabine/tenofovir disoproxil fumarate (n=20) + Many Men, Many Voices behavioral HIV prevention intervention (3MV) B. Placebo (daily) + 3MV behavioral intervention (n=19) C. 3MV behavioral intervention, alone (n=19)	MSM, age 18-22, at least 2 episode 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 >= 3.5g/g, normoglycemic glycosuria (≥1+ urine dipstick), serious psychiatric symptoms, active Hep B, use of nephrotoxic drugs, diuretics, NSAIDS, other antretroviral drugs, or drugs that interfer 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 (ATN): NIH (Eunice Kennedy Shriver National Institute on Child Health and Human Development; National Institute on Drug Abuse; National Institute of Mental Health)
PROUD McCormack, 2016[77]	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 tenofovir disoproxil fumarate or emtricitabine; currently being treated for hepatitis B 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 post-exposure 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	MRC Clinical Trials Unit; Public Health England; Gilead Sciences

Study name Author, year	Study design	No. 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[93]	RCT	3 sites Ghana, Cameroo n 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 post-test counseling, and received condoms and risk reduction counseling at every monthly visit.	HIV-antibody-uninfected women aged 18 to 35 years who were at risk of HIV infection by virtue of having an average of 3 or more coital acts per week and 4 or more sexual partners per month. Willing to use the study drug as directed and participate for up to 12 months of follow- up. 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
TDF2 Thigpen, 2012[94]*	RCT	2 sites Botswana	2.5 years	A. Oral TDF-FTC 300/200mg, once daily (n=611) B. Placebo, once daily (n=608)	Age 18-39 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, CDC and Division of AIDS, NIH; one investigator reported royalties from Roche and one investigator reported funding from Gilean

Study name Author, year	Study design	No. 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 Chirwa, 2014[97]	Subset of participants from larger trial (those who sero-converted)	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[75]*	RCT	15 sites South Africa, Uganda, Zimbabwe	Maximum 36 months (5,509 person-years)	A. Oral TDF 300 mg and TDF-FTC placebo (n=1,007) B. Oral TDF-FTC 300/200mg and TDF placebo (n=1,003) C. Oral TDF placebo and oral TDF-FTC placebo (n=1,009) *Interventions outside the scope of this review:* D. Vaginal 1% TFV gel (n=1,007) E. Vaginal placebo gel (n=1,003) (all daily)	Women 18 to 45 years of age who were neither pregnant nor breast-feeding and who reported recent vaginal intercourse, were using effective contraception, and had normal renal, hematologic, and hepatic function	A vs. B vs. C vs. D vs. E Age (mean): 26 vs. 25 vs. 25 vs. 25 vs. 25 Female: 100% all groups Race: NR Currently married: 21% all groups ≥2 male sex partners in past 3 months: 24% vs. 21% vs. 24% vs. 22% vs. 20% Episodes of vaginal intercourse in past 7 days: 2.5 vs. 2.5 vs. 2.5 vs. 2.6 vs. 2.6 Condom use during last vaginal sex: 87% vs. 86% vs. 86% vs. 86% vs. 83% Anal sex in the previous 3 months: 16% vs. 18% vs. 17% vs. 18% vs. 18% Chlamydia trachomatis present: 12% vs. 12% vs. 13% vs. 12% vs. 13% Neisseria gonorrhoeae present: 4% vs. 3% vs. 3% vs. 2% vs. 4% Trichomonas vaginalis present: 7% vs. 5% vs. 7% vs. 6% vs. 5% Syphilis present: 1% vs. 1% vs. 2% vs. 1% vs. 1% HSV-2 present: 48% vs. 45% vs. 45% vs. 44% vs. 47% Bacterial vaginosis present: 42% vs. 41% vs. 40% vs. 40% vs. 39%	Screened: 12,320 Eligible: NR Enrolled: 5,029 Analyzed: 4,969 Withdrawals: Not reported Loss to followup: 0.1% (38/5,029)	Good	National Institutes of Health

Study name Author, year	Study design	No. of centers, Country	Study duration Mean followup	Interventions	Inclusion criteria	Patient characteristics	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Quality rating	Funding source
VOICE Mirembe, 2016[106]	Subset of participants randomized to oral arms of larger RCT (Marrazzo 2015)	Sites in Zimbabw e 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: 24% vs. 25% vs. 22% Ages 25 to 34: 65% vs. 67% vs. 65% Ages 35 to 39: 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: AIDS=acquired immunodeficiency syndrome; ALT=alanine aminotransferase; ART=antiretroviral therapy; AST=aspartate aminotransferase; BMD=bone mineral density; CDC=Centers for Disease Control and Prevention; DEXA=dual energy X-ray absorptiometry; dL=deciliter(s); FTC=emtricitabine; HBsAg=surface antigen of hepatitis B; HBV=hepatitis B; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus-type 1; HSV=herpes simplex virus; HSV-2=herpes simplex virus 2; IAVI=International AIDS Vaccine Initiative; iPrEx=Pre-Exposure Prophylaxis Initiative; IQR=interquartile range; mL=milliliters; MRC=Medical Research Council; MSM=men who have sex with men; NIH=National Institutes of Health; NR=not reported; OR=odds ratio; PrEP=pre-exposure prophylaxis; PWID=people who inject drugs; RCT=randomized controlled trial; SD=standard deviation; STI=sexually transmitted infection; TDF=tenofovir disoproxil fumarate; TDF-FTC=emtricitabine/tenofovir disoproxil fumarate; TGW=transgender women; TH=thoracic vertebra; ULN=upper limit of normal; U.S.=United States; US=United States; USA=United States of America; USAID=Unites States Agency for International Development; vs.=versus.

Appendix B1b. HIV Pre-Exposure Prophylaxis Randomized Controlled Trials – Results

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
ADAPT/ HPTN 067 Bekker 2018[114]	A. Daily TDF-FTC (n=59) B. Time-driven TDF-FTC (one tablet twice a week, plus a post-sex dose; 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[113]	A. Daily TDF-FTC (n=119) B. Time-driven TDF-FTC e tablet twice a week, plus ost-sex dose; 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% 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[91]* and Martin, 2015[105]	A. Tenofovir 300mg once daily (n=1204) B. Placebo (n=1209) Participants could choose directly observed therapy or monthly take-home prescriptions, and switch at monthly follow-up 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 AEs: 19% (227/1,204) vs. 20% (246/1,209); RR 0.93 (95% CI 0.79 to 1.09) Grade 4 AEs:: 2% (28/1,204) vs. 3% (31/1,209) Grade 3 AEs: 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 & vomiting: 7.8% (96/1,204) vs. 4.9% (59/1209), 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

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Bangkok Tenofovir Study Martin, 2014[104]	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 (2.1-3.0 mg/dL): 0.2% (2/1,204) vs. 0% (0/1,209), p=0.25 Creatinine, grade 3-4 (≥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/minute: 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+O10, 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 groups 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 groups p=0.12 GFR (Chronic Kidney Disease Epidemiology Collaboration method): slope -0.06, p<0.01 vs. slope -0.04, p<0.001; between groups p=0.07	Same as Choopanya 2013
FEM-PrEP Van Damme, 2012[95]* and Agot, 2015[96]	A. Oral TDF-FTC 300/200mg once daily (n=1,062) B. Placebo, once daily (n=1,058)	A vs. B HIV infection: 5% (31/1,024) vs. 5% (35/1032); 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 AE: 3.2% (33/1,025) vs. 2.2% (23/1,033); RR 1.43 (95% CI 0.84 to 2.42) Any AE: 74.1% (760/1,025) vs. 72.3% (747/1,033); RR 1.01 (95% CI 0.93 to 1.09) Withdrawals due to AE: 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 AE: 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%

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
FEM-PrEP Mandala, 2014[102]	Same as Van Damme 2012	Not reported	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[84]* (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)	No K65R mutations were noted among any seroconverting participants (n=7; 3 TDF, 4 placebo)
Liu, 2011[101] (companion to Grohskopf, 2013)	Same as Grohskoph 2013	Not reported	A vs. B Fracture: 6.4% (6/94) vs. 4.4% (4/90) , p=0.75 BMD femoral neck: 1.1% mean net decrease in TDF group vs. placebo (95% CI 0.4 to 1.9, p=0.004) BMD total hip: 0.8% mean net decrease in TDF group vs. placebo (95% CI 0.3 to 1.3, p=0.003) BMD L2-L4 spine: 0.7% mean net decrease in TDF group vs. placebo (95% CI -0.1 to 1.5, p=0.11) After adjustment for those taken off study drug due to >5% drop in BMD or low BMD: BMD femoral neck: 1.2% mean net decrease in TDF group vs. placebo (p=0.002) BMD total hip: 0.8% mean net decrease in TDF group vs. placebo (p=0.003) BMD L2-L4 spine: 0.9% mean net decrease in TDF group vs. placebo (p=0.039) A vs. B, % change >3% loss in BMD from baseline at: Femoral neck: 36% vs. 20%, p=0.02 Total hip: 14% vs. 3%, p=0.02 L2-L4 spine: 17% vs. 15%, p=0.69	Same as Grohskoph 2013

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
IAVI Kenya Study Mutua, 2012[53]	A. Daily TDF-FTC 300/200mg (n=24) B. Intermittent (Monday, Friday and within 2 hours post- coital, 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 AE: 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)	Not reported
IAVI Uganda Study Kibengo, 2013[54]	A. Daily TDF-FTC 300/200mg (n=24) B. Intermittent (Monday, Friday and within 2 hours post-coital, not to exceed 1 dose/day) TDF-FTC 300/200mg (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 peptide pool response, week 16: 1 vs. 0 vs. 1 vs. 0 (no other data reported) Positive IFN-y ELISPOT, week 16: 0 vs. 1 vs. 0 vs. 0 (no other data reported) Risk behavior, number of sexual partners: Reported to be 1 (IQR 1-1) for all groups	A vs. B vs. C vs. D Severe or very severe AE: 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) Gastrointestinal 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)	Not reported

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
IPERGAY Molina, 2015[52]	A. On demand TDF- FTC 300/200mg (n=199) B. Placebo (n=201) On demand dosing schedule: 1. Two pills 2-24 hours before sex; 4. Third pill 24 hours after first drug intake; 5. 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 preexposure 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 AEs: 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 AE: 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 Hepatitis C virus 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 not reported
iPrEx Grant, 2010[92]*	A. TDF-FTC 300/200mg (n=1,251) B. Placebo (n=1,248)	A vs. B HIV infection: 3.0% (38/1251) vs 5.8% (72/1248); HR 0.53 (95% CI 0.36 to 0.78); NNT 37	A vs. B Death: 0.1% (1/1251) vs. 0.3% (4/1248); 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)	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)

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
iPrEx Deutsch, 2015[98]	*TGW only* A. TDF-FTC 300/200mg (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 AEs: 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[189]	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010
iPrEx Marcus, 2014[103]	*HSV-2 negative substudy only* A. TDF-FTC 300/200mg (n=692) B. Placebo (n=691)	Same as Grant 2010	A vs. B HSV infection: 9.7% (65/671) vs. 8.9% (60/676); OR 1.09 (95% CI 0.75 to 1.58) HSV ulcer adverse event grade ≥2 : 2.9% vs. 65.9%; p<0.05 Perianal ulcer on STI exam: 4% vs. 5%; p=NS Groin ulcer on STI exam: 3% vs. 2%; p=NS	Same as Grant 2010
iPrEx Mulligan, 2015[109]	*BMD substudy only* A. TDF-FTC 300/200mg (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[111]	Renal substudy only A. TDF-FTC 300/200mg (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[69]*	A. Once-daily TDF 300mg + placebo TDF- FTC (n=1,571) B. Once-daily TDF- FTC 300mg/200mg + 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 antiretroviral therapy: 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 AEs: 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% (0/1584); 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% (85/1584) Syphilis: 2% (28/1,584) vs. 2% (27/1,579) vs. 1% (23/1,584) Fracture data from FDA: 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)

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Partners PrEP Baeten, 2012[69]* (cont'd)				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 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)

Study name Author, year	Interventions	Clinical health outcomes	Adverse events	Resistance
Partners PrEP Baeten, 2012[69]* (cont'd)				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[79]	A. Once-daily TDF 300mg + placebo TDF-FTC (n=528) B. Once-daily TDF-FTC 300mg/200mg + 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: 79/1041 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[136]	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Haberer,	Same as Baeten 2012	NA	NA	NA
Partners PrEP Heffron, 2014[99]	A. TDF or FTC B. Placebo	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Lehman, 2015[100]	*Seroconverters only* A. Once-daily TDF 300mg + placebo TDF- FTC (n=39) B. Once-daily TDF- FTC 300/200mg + placebo TDF (n=25) C. Placebo TDF + placebo TDF-FTC (n=58)	Same as Baeten 2012	Same as Baeten 2012	A vs. B vs. C Total population Resistance frequencies >1%: 5.3% (2/38 vs. 20% (5/25) vs. 3.5% (2/58) HIV infected at time of enrollment Resistance frequencies >1%: 12.5% (1/8) vs. 50% (2/4) vs. 0% (0/6) HIV uninfected at time of enrollment Resistance frequencies >1%: 3.3% (1/30) vs. 14.3% (3/21) vs. 3.8% (2/52)
Partners PrEP Matthews, 2014[190]	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

Study name Author, year	Interventions	Clinical health outcomes	Adverse events	Resistance
Partners PrEP Mugo, 2014[107]	*HIV-uninfected women only* A. Once daily TDF 300 mg (n=595) B. Once daily TDF- FTC 300/200mg (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% -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% (-13.9 to 3.5%) and for B vs. C 1.0% (95% CI -11.3 to 13.3%) Any anomaly (among live births): 4.9% (4/81) vs. 8.5% (4/46) vs. 7.6% (5/65); absolute difference for A vs. C -2.6% (95% CI -12.0 to 6.7%) and for B vs. C 0.9% (95% CI -11.1 to 13.0%) Postpartum infant mortality: 1.2% (1/81) vs. 10.9% (5/46) vs. 6.1% (4/66); RR for A vs. C 0.20 (95% CI 0.02 to 1.8) and for B vs. C 1.4 (95% 0.38 to 5.4) Infant growth: No statistically significant differences in head circumference, length, weight; some estimates indicated slightly faster growth in some measures for PrEP vs. placebo	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Mugwanya, 2015[108]	A. Once daily TDF 300 mg (n=1,548) B. Once daily TDF- FTC 300/200mg (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

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
Partners PrEP Murname, 2013[110]	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Murname, 2015[191]	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Were, 2014[112]	*HIV-uninfected men only* A. Once-daily TDF 300mg + placebo TDF- FTC (n=986) B. Once-daily TDF- FTC 300/200mg + 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	Not reported	Same as Baeten 2012
Project PrEPare ATN Hosek, 2013[130]	A. PrEP with daily emtricitabine/tenofovir disoproxil fumarate (n=20) + Many Men, Many Voices behavioral HIV prevention intervention (3MV) B. Placebo (daily) + 3MV behavioral intervention (n=19). C. 3MV behavioral intervention, alone (n=19)	Not reported	A vs B vs C Serious adverse events: None Nausea at 8 weeks: 24% vs 0% vs 6% Antiretroviral drug resistance: NR	Not reported

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
PROUD McCormack, 2016[77]	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 screens for specific infection) 1.07 (95% CI 0.78 to 1.46) Gonorrhea: 39% (103/261) vs. 37% (89/242); OR 1.12 (95% CI 0.78 to 1.61); aOR 0.86 (95% CI 0.62 to 1.20) Chlamydia: 30% (77/261) vs. 22% (54/242); OR 1.46 (95% CI 0.97 to 2.18); aOR 1.27 (95% CI 0.89 to 1.80) Syphilis: 11% (30/263) vs. 9% (22/247); OR 1.32 (95% CI 0.74 to 2.35); aOR 1.29 (95% CI 0.79 to 2.10) Rectal gonorrhoea or chlamydia: 36% (93/258) vs. 32% (77/238); OR 1.18 (95% CI 0.81 to 1.71); aOR 1.00 (95% CI 0.72 to 1.38) HCV infection: 1.2% (3/258) vs. 1.3% (3/238)	A vs. B <u>Any HIV infection</u> M184I or M184V mutation: 40% (2/5) vs. not assessed K65R or K65E mutation: 0% (0/5) vs. not assessed <u>HIV infected at time of enrollment</u> M184I or M184V mutation: 66.7% (2/3) vs. not assessed <u>HIV uninfected at time of enrollment</u> M184I or M184V mutation: 0% (0/2) vs. not assessed
Study of TDF Peterson, 2007[93]	A. TDF, 300 mg orally daily (n=469) B. Placebo (n=467) All participants received HIV post-test 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 one 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 AEs: 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[94]*	A. Oral TDF-FTC 300/200mg, 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 trachomatisinfection: 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, as 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 at enrollment. M184V, K65R and A62V mutations) vs. 0.2% (1/608; HIV RNA <400 at enrollment. K65R mutation)

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
TDF2 Chirwa, 2014[97]	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 antiretroviral- naive HIV subtype C infections; 1 of the 3 participants that screened falsely negative at study entry and that 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

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
VOICE Marrazzo, 2015[75]*	A. Oral TDF 300 mg and TDF-FTC placebo (n=1,007) B. Oral TDF-FTC 300/200mg and TDF placebo (n=1,003) C. Oral TDF placebo and oral TDF-FTC placebo (n=1,009) *Interventions outside the scope of this review:* D. Vaginal 1% TFV gel (n=1,007) E. Vaginal placebo gel (n=1,003) (all daily)	A vs. B vs. C Number of HIV-1 infections: 5% (52/1,007) vs. 6% (61/1,003) vs. 6% (60/1,009); A vs. C: RR 0.87 (95% CI 0.61 to 1.25); B vs. C: RR 1.02 (95% CI 0.72 to 1.44) Effectiveness: TDF (group A): -49%, HR for infection 1.49 (95% CI 0.97 to 2.29) TDF-FTC (group B): -4.4%, HR for infection 1.04 (95% CI 0.73 to 1.49) TFV gel (group D): 14.5%, HR for infection 0.85 (95% CI 0.61 to 1.21) HIV-1 incidence (cases per 100 person years): 6.3 (95% CI 4.7 to 8.3) vs. 4.7 (95% CI 3.6 to 6.1) vs. 4.6 (95% CI 3.5 to 5.9) vs. 6.0 (95% CI 4.6 to 7.6) vs. 6.8 (95% CI 5.3 to 8.6)	A vs. B vs. C Mortality: 0% (0/1,007) vs. 0% (0/1,003) vs. 0.3% (3/1,009) Serious AEs: 8.6% (87/1,007) vs. 12.2% (123/1,003) vs. 11.3% (114/1,009) Grade 4 events: 0.4% (4/1,007) vs. 1.4% (14/1,003) vs. 1.7% (17/1,009) Lower limb fracture: 0.2% (2/1,007) vs. 0.1% (1/1,003) vs. 0% (0/1,009) Creatinine event: 0.4% (4/1,007) vs. 1.3% (13/1,003) vs. 0.2% (2/1,009) Nausea grade 2 or higher: 1.3% (13/1,007) vs. 0.8% (8/1,003) vs. 1.5% (15/1,009) Vomiting grade 2 or higher: 0.1% (6/1,007) vs. 0.1% (6/1,003) vs. 0.1% (9/1,009) Diarrhea grade 2 or higher: 1.2% (12/1,007) vs. 1.8% (18/1,003) vs. 2.1% (21/1,009) Any Grade 3 or 4 GI event: 0% (0/1,007 vs. 0.3% (3/1,003) vs. 0.7% (7/1,009) Chlamydia infection: 10.4% (105/1,007) vs. 14.4% (144/1,003) vs. 15.2% (153/1,009) Gonococccal infection: 2.6% (26/1,007) vs. 4.6% (46/1,003) vs. 4.5% (45/1,009) Syphilis infection: 1.5% (15/1,007) vs. 1.0% (10/1,003) vs. 1.5% (15/1,009)	A vs. B vs. C <u>Total population</u> K65R mutation (TDF resistance): 0% (0/70) vs. 0% (0/71) vs. 0% (0/69) K70E mutation (TDF resistance): 0% (0/70) vs. 0% (0/71) vs. 0% (0/69) M184V mutation (FTC resistance): 0% (0/70) vs. 4.2% (3/71) vs. 0% (0/69) M184I mutation (FTC resistance): 0% (0/70) vs. 1.4% (1/71) vs. 0% (0/69) <u>HIV infected at time of enrollment</u> K65R mutation: 0% (0/5) vs. 0% (0/9) vs. 0% (0/1) K70E mutation: 0% (0/5) vs .0% (0/9) vs. 0% (0/1) M184V mutation: 0% (0/5) vs. 22% (2/9) vs. 0% (0/1) M184I mutation: 0% (0.5) vs. 11% (1/9) vs. 0% (0/1) <u>HIV uninfected at time of enrollment</u> K65R mutation: 0% (0/65) vs. 0% (0/62) vs. 0% (0/68) K70E mutation: 0% (0/65) vs. 0% (0/62) vs. 0% (0/68) M184V mutation: 0% (0/65) vs. 1.6% (1/62) vs. 0% (0/68) M184I mutation: 0% (0/65) vs. 0% (0/62) vs. 0% (0/68)

Study name **Author, year**	**Interventions**	**Clinical health outcomes**	**Adverse events**	**Resistance**
VOICE Mirembe, 2016[106]	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: A62V=A62V accessory mutation; AE=adverse event; ALT=alanine aminotransferase; aOR=adjusted odds ratio; AST=aspartate aminotransferase; BMD=bone mineral density; CDC=Centers for Disease Control and Prevention; CI=confidence interval; DEXA=dual energy X-ray absorptiometry; dL=deciliter(s); eGFR=estimated glomerular filtration rate; ELISPOT=Enzyme-Linked ImmunoSpot assay; Env=Env peptide pool; FTC=emtricitabine; GFR=glomerular filtration rate; GI=gastrointestinal; HBV=hepatitis B; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus-type 1; HR=hazard ratio; HSV=herpes simplex virus; HSV-2=herpes simplex virus 2; IAVI=International AIDS Vaccine Initiative; IFN-y=interferon gamma; iPrEx=Pre-Exposure Prophylaxis Initiative; IQR=interquartile range; ISCD=International Society for Clinical Densiometry; K103N=K103N mutation; K65R=K65R mutation; K70E=K70E mutation; L2=second lumbar vertebra; L4=fourth lumbar vertebra; LS=lumbosacral spine; M184I=M184I mutation; M184V=M184V mutation; mL=milliliters; NA=not applicable; NNT=number needed to treat; NR=not reported; OR=odds ratio; PPV=positive predictive value; PrEP=pre-exposure prophylaxis; RNA=ribonucleic acid; RR=relative risk; STI=sexually transmitted infection; T215Y=T215Y mutation; TDF=tenofovir disoproxil fumarate; TDF-FTC=emtricitabine/tenofovir disoproxil fumarate; TFV=tenofovir; TGW=transgender women; TH=thoracic vertebra; vs.=versus; WHO=World Health Organization.

Appendix B1c. 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 (US applicable)**	**Adherence and effectiveness**	**Subgroups**
ADAPT/ HPTN 067 Bekker 2018[114]	A. Daily TDF-FTC (n=59) B. Time-driven TDF-FTC (one tablet twice a week, plus a post-sex dose; n=59) C. Event-driven TDF-FTC (one tablet both before and after sex; n=60)	Pill count (electronic drug monitoring) defined as having at least one PrEP dose within 4 days (96 h) before and within 1 day (24 h) after sex events, adjusted according to patient self report Plasma tenofovir (TDF) Peripheral blood mononuclear cell (PBMC) measure of tenofovir diphosphate (TDF-DP)	Not applicable	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% (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)

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
ADAPT/ HPTN 067/ Grant, 2018[113]	A. Daily TDF-FTC (n=119) B. Time-driven TDF-FTC (one tablet twice a week, plus a post-sex dose; 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; 1 table every 4 days + an additional tablet taken within 24 hours after sex; event-driven arm: 1 tablet within 48 hours before sex and another one 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
Bangkok Tenofovir Study Choopanya, 2013[91]* and Martin, 2015[105]	A. Tenofovir 300mg once daily (n=1204) B. Placebo (n=1209) Participants could choose directly observed therapy or monthly take-home prescriptions, and switch at monthly follow-up 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 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 non-directly 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 non-DOT: 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

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
Bangkok Tenofovir Study Martin, 2014[104]	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 Age 20 to 29 years: 101.2 vs. 107.9 mL/min Age 30 to 39 years: 92.7 vs. 97.9 mL/min Age 40 to 59 years: 76.9 vs. 80.4 mL/min Among those on tenofovir, clearance was lower among those aged ≥30 years than those 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

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
FEM-PrEP Van Damme, 2012[95]* and Agot, 2015[96]	A. Oral TDF-FTC 300/200mg 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) 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 fmoles TFVdp/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 femtomoles TFVdp/mL in ULPCs among visits where participants report usually or always taking pills: PPV 28.7 (329/1,146)	Not applicable	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 Age HIV infection ≥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 for interaction=0.91 Unclear if subgroup analysis prespecified

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
FEM-PrEP Mandala, 2014[102]	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 [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[84]* (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%) Medication Event Monitoring System 77% (range 57 to 92%); sensitivity analysis removing participants with temporary drug interruptions 79% (range 60 to 92%) Adherence by group was not reported	Not reported	<u>Safety - grade 3 or 4 AE</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)	Not reported
Liu, 2011[101] (companion to Grohskopf, 2013)	Same as Grohskoph 2013	Same as Grohskoph 2013	Same as Grohskoph 2013	Same as Grohskoph 2013	Same as Grohskoph 2013

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
IAVI Kenya Study Mutua, 2012[53]	A. Daily TDF-FTC 300/200mg (n=24) B. Intermittent (Monday, Friday and within 2 hours post- coital, 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 (Mon, Fri doses only): 91% (IQR 78-102) vs. 88% (IQR 69-94); p=0.25 B vs. D (MEMS + text reporting, post-coital doses only): 40% (IQR 23 to 58) vs. 53% (IQR 15-79); p=0.45 B vs. D (timeline followback + text, post-coital doses with 2 hours only): 39% (IQR 29-58) vs. 31% (IQR 21-59); p=0.58 Adherence rates did not differ by gender	Not applicable	Not reported	Not reported

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
IAVI Uganda Study Kibengo, 2013[54]	A. Daily TDF-FTC 300/200mg (n=24) B. Intermittent (Monday, Friday and within 2 hours post- coital, not to exceed 1 dose/day) TDF-FTC 300/200mg (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, post-coital doses only): 40% (IQR 23 to 58) vs. 53% (IQR 15-79); p=0.45 Adherence rates did not differ by gender	Not applicable	Not reported	Not reported

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
IPERGAY Molina, 2015[52]	A. On demand TDF- FTC 300/200mg (n=199) B. Placebo (n=201) On demand dosing schedule: 1. Two pills 2-24 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 preexposure 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	Not reported	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)	Not reported

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
iPrEx Grant, 2010[92]*	A. TDF-FTC 300/200mg (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; Weeks 9-study completion: mean 95% in both groups Pill use, estimated according to pill count in returned bottles, ≥8 weeks: range 89-95% Pill dispensation date/quantity, year 1: decreased from 99% to 91%	Not reported	Efficacy ≥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	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 for interaction=0.36 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 for interaction=0.79 Risk behaviors, unprotected receptive anal intercourse (URAI) - HIV incidence URAI: 3.1% (23/732) vs. 7.4% (56/753); HR 0.42 (95% CI 0.26 to 0.68) No URAI: 2.5% (13/519) vs. 1.6% (8/495); HR 1.59 (95% CI 0.66 to 3.84); p for interaction=0.01 Subgroup analyses pre-specified
iPrEx Deutsch, 2015[98]	*TGW only* A. TDF-FTC 300/200mg (n=170) B. Placebo (n=169)	Same as Grant 2010	Same as Grant 2010	Same as Grant 2010	A vs. B TGW 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% CI 0.34 to 0.75) TGW vs. MSM, p for interaction=0.09 Subgroup analysis not prespecified

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
iPrEx Liu, 2014[189]	Same as Grant 2010	PBMC sampling - random set of total sample (n- 2,499; no stratification by randomization group): Proportion with detectable drug, week 8: 55% (95% CI 49 to 60%); Proportion with drug never detected during longitudinal followup: 31% Proportion with drug inconsistently detected during longitudinal followup: 39% Proportion with drug always detected, longitudinal followup: 30% -San Francisco site only (n=140; 6% of total sample): Proportion with detectable drug, week 8: 90% (95% CI 76 to 96%) Proportion with drug never detected during longitudinal followup: 1% Proportion with drug inconsistently detected during longitudinal followup: 27% Proportion with drug always detected, longitudinal followup: 67% -Boston site only (n=87; 3% of total sample): Proportion with detectable drug, week 8: 72% (95% CI 56 to 84%)	Factors associated with drug detection at week 8: Age ≤20 vs. 21 to 25: OR 2.44 (95% CI 1.24 to 4.77) Age ≤20 vs. 26 to 30: OR 2.18 (95% CI 1.06 to 4.49) Age ≤20 vs. >30: OR 2.86 (95% CI 1.36 to 6.03) No significant association for other factors Factors associated with some drug detection during longitudinal followup vs. no drug detection: Age ≤20 vs. 21 to 25: OR 4.04 (95% CI 1.66 to 9.85) Age ≤20 vs. 26 to 30: OR 3.42 (95% CI 1.21 to 9.67) Age ≤20 vs. >30: 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: OR 6.32 (95% CI 2.09 to 19.09) Age ≤20 vs. 26 to 30: OR 4.74 (95% CI 1.26 to 17.76) Age ≤20 vs. >30: 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)	Same as Grant 2010	Same as Grant 2010
iPrEx Marcus, 2014[103]	*HSV-2 negative substudy only* *A.* TDF-FTC 300/200mg (n=692) B. Placebo (n=691)	Same as Grant 2010	Same as Grant 2010	A vs. B HSV-2 infection, TFV-DP ≤16: HR 1.0 (95% CI 0.4 to 2.5) HSV-2 infection, TFV-DP >16: HR 1.0 (95% CI 0.3 to 3.5)	Same as Grant 2010
iPrEx Mulligan, 2015[109]	*BMD substudy only* A. TDF-FTC 300/200mg (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 peripheral blood mononuclear cells (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

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
iPrEx Solomon, 2014[111]	Renal substudy only A. TDF-FTC 300/200mg (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[69]*	A. Once-daily TDF 300mg + placebo TDF- FTC (n=1,571) B. Once-daily TDF-FTC 300mg/200mg + 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%	Not reported	Detectable vs. non-detectable 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 for interaction=0.65 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 for interaction=0.24 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 for interaction=0.79 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 for interaction=0.06 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 for interaction=0.05 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 for interaction=0.77 Unclear if subgroup analyses prespecified
Partners PrEP Celum 2014[79]	A. Once-daily TDF 300mg + placebo TDF-FTC (n=528) B. Once-daily TDF-FTC 300mg/200mg + placebo TDF (n=513)	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
Partners PrEP Donnell, 2014[136]	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% COI 0.01 to 0.17) Combined PrEP arms HIV seroconverters (39 samples, n=39) vs. HIV uninfected (945 samples, n=196) - Tenofovir >0.3 ng/mL: 41% (9/29) vs. 83% (772/945); aRR 82% (95% CI 46 to 94%), OR 0.10 (95% CI 0.05 to 0.23) Tenofovir >10 ng/mL: 41% (9/29) vs. 79% (730/945); aRR 77% (95% CI 31 to 92%), OR 0.13 (95% CI 0.06 to 0.30) Tenofovir >40 ng/mL: 24% (6/29) vs. 72% (670/945); aRR 87% (95% CI 59 to 96%), OR 0.11 (95% CI 0.04 to 0.27) Tenofovir detected: 41% (9/29) vs. 83% (772/945), OR 0.10 (95% CI 0.05 to 0.23) Pill count coverage >80%: 71% (19/29) vs. 95% (905/945), OR 0.08 (95% CI 0.04 to 0.19)	Same as Baeten 2012

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
Partners PrEP Haberer, 2013[144]	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[99]	A. TDF or FTC B. Placebo	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	A vs. B HIV infection Women using hormonal contraception (DMPA), HIV-1 infection: aHR 0.35 (95% CI 0.12 to 1.05) Women not using hormonal contraception, HIV-1 infection: aHR 0.25 (95% CI 0.07 to 0.84) Men with female partners using hormonal contraception, HIV-1 infection: aOR 0.10 (95% CI 0.00 to 0.77) Men with female partners not using hormonal contraception, HIV-1 infection: aOR 0.18 (95% CI 0.08 to 0.62)
Partners PrEP Lehman, 2015[100]	*Seroconverters only* A. Once-daily TDF 300mg + placebo TDF- FTC (n=39) B. Once-daily TDF-FTC 300/200mg + 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[190]	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 (0.43 to 1.52) Pill count - -Pregnant: 97% -Not pregnant: 98% aRR 0.99 (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

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
Partners PrEP Mugo, 2014[107]	*HIV-uninfected women only* A. Once daily TDF 300 mg (n=595) B. Once daily TDF-FTC 300/200mg (n=565) C. Once daily placebo (n=621)	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012	Same as Baeten 2012
Partners PrEP Mugwanya, 2015[108]	A. Once daily TDF 300 mg (n=1,548) B. Once daily TDF-FTC 300/200mg (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) 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, 0.21) B vs. C -1.67 (95% CI -2.88 to -0.46) 35-44 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) ≥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, 0.34) B vs. C -0.49 (95% CI -2.56 to 1.58) Serum GFR decline ≥25% from baseline Male: adjusted HR: 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: adjusted HR: 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 18-34 years: adjusted HR: A vs. C 1.54 (95% CI 0.60 to 3.98) B vs. C 1.37 (95% CI 0.50 to 3.67) 35-44 years: adjusted HR: A vs. C 1.07 (0.42 to 2.69) B vs. C 1.56 (95% CI 0.67 to 3.67) ≥45 years: adjusted HR: 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

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
Partners PrEP Murname, 2013[110]	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 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
Partners PrEP Murname, 2015[191]	Same as Baeten 2012	*TDF or TDF-FTC arm only* Proportion patients with pill coverage 80-107%: 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

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
Partners PrEP Were, 2014[112]	*HIV-uninfected men only* A. Once-daily TDF 300mg + placebo TDF- FTC (n=986) B. Once-daily TDF-FTC 300/200mg + placebo TDF (n=1,013) C. Placebo TDF + placebo TDF-FTC (n=963)	Not reported	Not applicable	Not reported	Not reported
Project PrEPare ATN Hosek, 2013[130]	A. PrEP with daily emtricitabine/tenofovir disoproxil fumarate (n=20) + Many Men, Many Voices behavioral HIV prevention intervention (3MV) B. Placebo (daily) + 3MV behavioral intervention (n=19). C. 3MV behavioral intervention, alone (n=19)	Self-reported medication adherence: mean 62% (range 43–83%) across arms. Detectable plasma TDF in TDF/FTC arm: Week 4: 63.2% Week 24: 20%	Not reported	Not reported	Not reported
PROUD McCormack, 2016[77]	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 AEs: 8% (21/275) Sufficient study drug (defined as adequate prescription to last one month beyond next scheduled appointment) prescribed 88% of total follow-up time	Not reported	Not reported	Not reported

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
Study of TDF Peterson, 2007[93]	A. TDF, 300 mg orally daily (n=469) B. Placebo (n=467) All participants received HIV post-test counseling, and received condoms and risk reduction counseling at every monthly visit	No between group data reported; maximum overall adherence was 69% based pill counts	Not applicable	Not reported	Not reported
TDF2 Thigpen, 2012[94]*	A. Oral TDF-FTC 300/200mg, once daily (n=611) B. Placebo, once daily (n=608)	Plasma tenofovir level detectable in 50% (2/4) seroconverters and 80% (55/69) non-seroconverters in TDF-FTC group Plasma emtricitabine level detectable in 50% (2/4) seroconverters and 81% (56/69) non-seroconverters in TDF-FTC group Estimated pill counts: 84% vs. 83%; Self-reported adherence for previous 3 days: 94% vs. 94%	Not applicable	Detectable tenofovir level: 50% (2/4) vs. 80% (55/69), OR 0.25 (95% CI 0.03 to 1.97) Detectable emtricitabine level: 50% (2/4) vs. 81% (56/69), OR 0.23 (95% CI 0.03 to 1.80)	A vs. B <u>Sex: HIV infection</u> 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 for interaction=NS (value not reported) Unclear if subgroup analysis prespecified
TDF2 Chirwa, 2014[97]	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 antiretroviral-naive HIV subtype C infections; 1 of the 3 participants that screened falsely negative at study entry and that 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

Study name **Author, year**	**Interventions**	**Adherence method of assessment and rate**	**Factors associated with adherence (US applicable)**	**Adherence and effectiveness**	**Subgroups**
VOICE Marrazzo, 2015[75]*	A. Oral TDF 300 mg and TDF-FTC placebo (n=1,007) B. Oral TDF-FTC 300/200mg 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%	Not applicable	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[106]	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 from 5%, and from 1 to 3 quarterly followup visits for 23%	Same as Marrazzo 2015	For active arm participants with drug detection at 75%-100% of visits (n=81 for active arms combined) at week 48: Net change in BMD, LS: 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, TH: 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% or greater detection, BMD results were similar to those at 48 weeks active discontinuation	Same as Marrazzo 2015

* Main study publication.

Abbreviations: A62V=A62V accessory mutation; AE=adverse event; aHR=adjusted hazard ratio; ALT=alanine aminotransferase; aOR=adjusted odds ratio; aRR=adjusted risk ratio; AST=aspartate aminotransferase; BMD=bone mineral density; CDC=Centers for Disease Control and Prevention; CI=confidence interval; DMPA=depot medroxyprogesterone acetate; eGFR=estimated glomerular filtration rate; FTC=emtricitabine; GFR=glomerular filtration rate; HBV=hepatitis B; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus-type 1; HR=hazard ratio; HSV=herpes simplex virus; HSV-2=herpes simplex virus 2; IAVI=International AIDS Vaccine Initiative; i.e.=for example; iPrEx=Pre-Exposure Prophylaxis Initiative; IQR=interquartile range; K65R=K65R mutation; M184V=M184V mutation; MEMS=Medication event monitoring system; mL=milliliters; 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; RNA=ribonucleic acid; RR=relative risk; SD=standard deviation; STI=sexually transmitted infection; TDF=tenofovir disoproxil fumarate; TDF-FTC=emtricitabine/tenofovir disoproxil fumarate; TFV=tenofovir; TFV-DP=tenofovir-diphosphate; TGW=transgender women; ULPCs=upper layer packed cells; vs.=versus.

Appendix B2. 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 people in the groups in which they were randomized?	Quality
ADAPT Bekker 2018[114], Grant, 2018[113]	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Fair
Bangkok Tenofovir Study Choopanya, 2013[91]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
FEM-PREP Van Damme, 2012[95]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Grohskoph, 2013[84]	Yes, see Liu 2011	Yes, see Liu 2011	Race differed (>% 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[92]	Yes	Yes	Yes	Yes	Yes	Yes, see protocol	Yes	Yes	No	Yes	Good
Partners PrEP Baeten, 2012[69]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Project PrEPare ATN 082 Hosek 2013[130]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Yes	Fair
PROUD McCormack, 2016[77]	Yes	Unclear	Yes	Yes	No	No	No	Yes	No	Yes	Fair
Study of TDF Peterson, 2007[93]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
TDF2 Thigpen, 2012[94]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
VOICE Marrazzo, 2015[75]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good

Abbreviations: IAVI=International AIDS Vaccine Initiative; PrEP=Pre-Exposure Prophylaxis; TDF=tenofovir disoproxil fumarate.

Appendix B3a. 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	Cutoff	Proportion meeting cutoff
Beymer, 2017[115]	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% Age 25 to 29 years: 26% Age 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) No. 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	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%
Hoenigl, 2015[116] San Diego Early Test (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)	A: ≥3 B: ≥5 C: ≥6 D: ≥8 E: ≥10	Derivation cohort Not reported Validation cohort A: 38% B: 24% C: 8.7% D: 4.6% E: 1.2%
Jones, 2017[120] 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)	A: ≥10 B: ≥1 C: ≥5	A: 47.1% B: 62.6% C: 17.5%

Study, Year	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items	Cutoff	Proportion meeting cutoff
Lancki, 2018[119] A: ARCH-MSM B: CDC criteria C: Gilead indications	Cohort Self-identiified as African-American or black, 16 to 29 years of age, 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): Not reported 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 sexually transmitted infection 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 sexually transmitted infections 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	A: ≥10 B: Met criteria C: One or more criteria	A: 72% B: 49% C: 86%
Menza, 2009[117]	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 re-testing every 6 months	MSM	Derivation cohort: Public Health-Seattle and King County STD 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% Validation cohort: Project EXPLORE (1999 to 2001) RCT, control arm (behavioral intervention trial) Age <40 years: 76% Age ≥40 years: 24% White, Asian, or Pacific Islander: 75% Other race: 25%	Derivation cohort: 1,903 Validation cohort: 2,081	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)	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%

Study, Year	Study design	Target population	Population characteristics	Sample size	Acquired HIV infection	Screening instrument items	Cutoff	Proportion meeting cutoff
Smith, 2012[118] HIV Incidence Risk Index for Men who have Sex with Men (HIRI-MSM) (now Assessing the Risk of Contracting HIV in Men who have Sex with Men [ARCH-MSM])	Retrospective cohort In derivation and validation cohorts, MSM were HIV-negative at baseline and underwent re-testing every 6 months	MSM	Derivation cohort: VAXGEN 004 (1998 to 1999) RCT (HIV vaccine trial) Age 18 to 28 years: 19% Age 29 to 49 years: 48% Age 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% Age 26 to 30 years: 22% Age 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 HVI 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)	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%
Smith, 2015[121] Assessing the Risk of Contracting HIV in Injection Drug Users (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% Age 30 to <40 years: 46% Age 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	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%

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; HIRI-MSM=HIV Incidence Risk Index for Men who have Sex with Men; HIV=human immunodeficiency virus; LGBT=lesbian, gay, bisexual, and transgender; MSM=men who have sex with men; PWID=people who inject drugs; RCT=randomized controlled trial; SDET=San Diego Early Test; STD=sexually transmitted disease; STI=sexually transmitted infection; VAXGEN 004=phase 3 clinical trial; vs.=versus.

Appendix B3b. Diagnostic Accuracy of HIV Risk Assessment Tools – Results

Study, Year	Sensitivity	Specificity	AUROC	Comments
Beymer, 2017[115]	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%	Not reported	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[116] San Diego Early Test (SDET) score	Derivation cohort Not reported Validation cohort A: 70% B: 60% C: 37% D: 25% E: 10%	Derivation cohort Not reported Validation cohort A: 63% B: 77% C: 92% D: 96% E: 99%	Derivation cohort Not reported Validation cohort 0.70 (95% CI 0.62 to 0.78)	None
Jones, 2017[120] A: ARCH-MSM B: Menza C: SDET	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[119] A: ARCH-MSM B: CDC criteria C: Gilead indications	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
Menza, 2009[117]	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

Study, Year	Sensitivity	Specificity	AUROC	Comments
Smith, 2012[118] HIV Incidence Risk Index for Men who have Sex with Men (HIRI-MSM) (now Assessing the Risk of contracting HIV in Men who have Sex with Men [ARCH- MSM])	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[121] Assessing the Risk of contracting HIV in Injection Drug Users (ARCH-IDUs)	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; CDC=Centers for Disease Control and Prevention; HIRI-MSM=HIV Incidence Risk Index for Men who have Sex with Men; HIV=human immunodeficiency virus; MSM=men who have sex with men; SDET=San Diego Early Test; vs.=versus.

Appendix B4. Diagnostic Accuracy of HIV Risk Assessment Tools Quality Assessment

Study, Year	Consecutive or random sample?	Pre-specified 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[115]	Yes	No	Unclear	Yes	No	Fair
Hoenigl, 2015[116] San Diego Early Test (SDET) score	Yes	No	Unclear	Unclear	Yes	Fair
Jones, 2017[120] A: ARCH-MSM B: Menza C: SDET	Yes	Yes	Unclear	Yes	Yes	Fair
Lancki, 2018[119] A: ARCH-MSM B: CDC criteria C: Gilead indications	Yes	Yes	No	Yes	No (for CDC and Gilead criteria)	Fair
Menza, 2009[117]	Yes	No	Unclear	Yes	Yes	Fair
Smith, 2012[118] HIV Incidence Risk Index for Men who have Sex with Men (HIRI-MSM) (now Assessing the Risk of contracting HIV in Men who have Sex with Men [ARCH-MSM])	Yes	No	Unclear	Yes	Yes	Fair
Smith, 2015[121] Assessing the Risk of contracting HIV in Injection Drug Users (ARCH-IDUs)	Yes	No	Unclear	Yes	No	Fair

Appendix B5a. HIV Pre-Exposure Prophylaxis Cohort Studies – Study Characteristics

Study Author, year	Study design	No. 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[129]	Cohort	3 USA (Providence RI, Jackson MS, St. Louis MO)	20 months	Oral emtricitabine and tenofovir disoproxil fumarate	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 Lost to followup: 19	Fair	Gilead Sciences, Inc.
Hosek, 2017[128]	Open-label PrEP demonstration project and safety study	12 USA	48 weeks	TDF-FTC	HIV-uninfected YMSM, 18 to 22 years at time of signed informed consent	Mean age 20 years (SD 1.3; median 20) 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 follow up: 34	Fair	Gilead
Hosek 2017[127] (ATN 1130, adolescents)	Cohort	14 USA	48 weeks	TDF-FTC	Age 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 or 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	National Institute of Child Health and Human Development; National Institutes on Drug Abuse and Mental Health; Gilead
iPrEx - OLE Grant, 2014[140]	Cohort	Multi-site USA, 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; age 18 to 24: 20%; 25 to 29: 26%; 30 to 39: 32%; ≥40: 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. US NIH HIV Prevention Trial Network

Study Author, year	Study design	No. 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[135]	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 US	48 weeks	TDF/FTC PrEP (n=278) Study also included a postexposure prophylaxis group (PEP; n=23)	Self-identified MSM, MSM/W, and transgender women (TGW) age 18 years or older, HIV uninfected at study entry by rapid enzyme-linked immunosorbent assay 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, UCLA Center for AIDS Research; National Center for Advancing Translational Sciences
Montgomery, 2016[125]	Retrospective cohort	1 site USA	6 months	Oral tenofovir disproxil fumarate and emtricitabine	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
US PrEP Demonstration Project Liu, 2016[80] and Cohen, 2015[141]	Cohort	3 sites USA	16 months	TDF-FTC	Male at birth, ≥18 years old, MSM or transgender, fluent in English or Spanish, negative HIVAb result at screening and enrollment, negative 4th gen antibody-antigen test at screening	Mean age NR; age 18 to 25: 20%; 26 to 35: 38%; 36 to 45: 24%; ≥45: 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% ED 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	NIAID; NIMH; NIH; Gilead (study drug)

Study Author, year	Study design	No. 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
van Epps, 2018[131]	Retrospective cohort	Database (VHA Corporate Data Warehouse) US	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 antiretroviral medications 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% age <35 years; 35% age 35-49; 21% age 50-64; 6% age 65-79 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	VA; VHA Office of Rural Health; VA HSR&D

Abbreviations: ATN=Adolescent Trials Network for HIV/AIDS Interventions; ED=erectile dysfunction; FSM=females who have sex with males; FTC-TP=emtricitabine triphosphate; HIV=human immunodeficiency virus; HIV+=human immunodeficiency virus infected; HIVAB=human immunodeficiency virus antibody; HSV2=herpes simplex virus 2; MO=Missouri; MS=Mississippi; 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; NIAID=National Institute of Allergy and Infectious Diseases; NIH=National Institutes of Health; NIMH=National Institute of Mental Health; NR=not reported; PrEP=pre-exposure prophylaxis; PWID=people who inject drugs; RI=Rhode Island; SD=standard deviation; STI=sexually transmitted infection; TDF=tenofovir disoproxil; US=United States; USA=United States of America; WSM=women who have sex with men; YMSM=young men who have sex with men.

Appendix B5b. HIV Pre-Exposure Prophylaxis Cohort Studies - Results

Study Author, year	Interventions	Clinical health outcomes	Adverse events
Chan, 2016[129]	Oral emtricitabine and tenofovir disoproxil fumarate	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 non- adherent to PrEP)	Adverse effects, 3 months: 1% (3/267) Adverse effects, 6 months: 0.4% (1/267)
Hosek, 2017[128]	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 (1x/week at 4, 32, 40, and 48 weeks) for an incidence rate of 3.29/100 person-years (95% CI: 0.07-6.52)	Grade 3 AE (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[127] (ATN 1130, adolescents)	TDF-FTC	HIV infection: 3/78; annualized incidence 6.4 (95% CI 1.3 to 18.7) infections/100 person- years STI rate, 0-24 weeks: 18.1/100 person-years (95% CI 9.7 to 34) STI rate, week 24 to 48: 9.4/100 person-years (95% CI 3.4 to 26)	Grade 3 or higher AE: 13% (10/78)
iPrEx - OLE Grant, 2014[140]	TDF-FTC	28 HIV infections	PrEP interruption due to side effects: 8% (93/1225) Grade 1 serum creatinine concentration: 0.2% (3/1225)
iPrEx - OLE Glidden, 2016[135]	Same as Grant 2014	NR	PrEP interruption due to AE: 5% (56/1,225) Withdrawal due to AE: 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)

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 (PEP; 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[125]	Oral tenofovir disproxil fumarate and emtricitabine	1 HIV seroconversion found at 3 month follow up; HIV mutations D67N, M 184 V, T21S, K219 L10I.	NR
US PrEP Demonstration Project Liu, 2016[80] and Cohen, 2015[141]	TDF-FTC	HIV infection: 2/557; incidence 0.43/100 person-years (0.05 to 1.54) STI incidence, per 100 person-years- - Chlamydia: 48 (42-55) -Gonorrhea: 43 (37-49) -Syphillis12 (9-16) -Any STI: 90 (81-99)	Serious AE: 3% (19/557) Psychiatric AE: 1% (8/557) Elevation in serum creatinine: 4% (23/557) Bone fracture: 2% (12/557)
van Epps, 2018[131]	TDF/FTC PrEP (n=1,086)	NR	NR

Abbreviations: AE=adverse event; ATN=Adolescent Trials Network for HIV/AIDS Interventions; BMD=bone mineral density; CI=confidence interval; D67N=D67N mutation; GI=gastrointestinal; HIV=human immunodeficiency virus; K219 L 10I=K219 L 10I mutation; M 184 V=M184V mutation; NR=not reported; PrEP=pre-exposure prophylaxis; STI=sexually transmitted infection; T21S=T21S mutation; TDF=tenofovir disoproxil; US=United States.

Appendix B5c. 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[129]	Oral emtricitabine and tenofovir disoproxil fumarate	Self-report: Patients were asked whether they had missed any doses in the previous seven and thirty days: Past week adherence: taking four or more pills or 100% adherence in the past seven days Past-month adherence: having missed five or fewer 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 (0.96 to 1.03); aOR 0.97 (0.93 to 1.02) Black vs. all others: OR 1.24 (0.54 to 2.82); aOR 1.32 (0.42 to 4.15) MSM vs. all others: OR 1.18 (0.36 to 3.83); aOR: NA No insurance vs. any insurance: OR 1.36 (0.57 to 3.25); aOR 1.42 (0.44 to 4.51) MSM, 3 month retention to care Age (per year): OR 1.05 (0.99 to 1.12); aOR 1.03 (0.93 to 1.14) Black vs. all others: OR 0.24 (0.08 to 0.74); aOR 0.13 (0.02 to 0.77) MSM vs. all others: OR 2.33 (0.58 to 9.45); aOR: NA No insurance vs. any insurance: OR 2.64 (0.86 to 8.11); aOR 1.48 (0.33 to 6.55) MSM, 6 month retention to care Age (per year): OR 1.02 (0.98 to 1.05); aOR 1.00 (0.95 to 1.05) Black vs. all others: OR 0.66 (0.30 to 1.42); aOR 0.74 (0.25 to 2.16) MSM vs. all others: OR 2.00 (0.66 to 6.07); aOR: NA No insurance vs. any insurance: OR 1.17 (0.48 to 2.84); aOR 0.87 (0.27 to 2.75)
Hosek, 2017[128]	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 antiretroviral drug 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%

Study Author, year	Interventions	Methods for reporting/ measuring adherence	Association between adherence and effectiveness	Adherence rates	Factors associated with adherence
Hosek 2017[127] (ATN 1130, adolescents)	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%)
iPrEx - OLE Grant, 2014[140]	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 (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 (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 (0.00 to 2.50), HR 0.16 (95% CI 0.01 to 0.79) vs. concurrent off-PrEP 700-1249 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, adjusted OR (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) 1-3 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) Age 18 to 24 years vs. 25-29 years: 1.19 (0.92 to 1.55); vs. 30-39 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)

Study Author, year	Interventions	Methods for reporting/ measuring adherence	Association between adherence and effectiveness	Adherence rates	Factors associated with adherence
iPrEx - OLE Glidden, 2016[135]	Same as Grant 2014	Same as Grant 2014	NR	Same as Grant 2014	Adherence and symptoms - GI symptoms and DB ≥700 fmol/punch: range 0 to 94% No GI symptoms and DB ≥700 fmol/punch: range 37 to 91% Non-GI symptoms, by DBS (dried blood spots) stratum, week 4: aOR 1.2 (0.40 to 3.7) GI symptoms, by DBS stratum, week 4: aOR 0.47 (0.23 to 0.96) Estimated 7% (4 to 11) of use at <4 pills/week (<700 fmol/punch) associated with GI symptoms Relationship between adherence, symptoms and age: GI symptoms and age <30: 23% DB ≥700 fmol/punch No GI symptoms and age <30: 47% DB ≥700 fmol/punch GI symptoms and age ≥30: 57% DB ≥700 fmol/punch No GI symptoms and age ≥30: 64% DB ≥700 fmol/punch; p for interaction=0.09 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 post-exposure prophylaxis group (PEP; n=23)	Dried blood spot (DBS)	One HIV seroconversion: occurred in a participant attended study visits per protocol through week 24 and then was lost to follow-up. Despite initially good adherence (weeks 4 and 12), his week 24 DBS specimen suggested adherence on average of fewer than 2 doses per week over the previous 4–8 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% By race/ethnicity 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%	Adherence, ≥4 doses/week 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% 1.68 to 13.47); ≥46: 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 noncondom-protected receptive anal intercourse within 3 months, binge drinking within 12 months, substance or methamphetamine use within 30 days (comparisons, yes vs no)

Study Author, year	Interventions	Methods for reporting/ measuring adherence	Association between adherence and effectiveness	Adherence rates	Factors associated with adherence
Montgomery, 2016[125]	Oral tenofovir disproxil fumarate and emtricitabine	Dried blood spot (DBS) 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)	DBS, 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) DBS, mean TFV-DP (n=21): 1493.5 fmol/punch (range 31.9 to 4141.1) DBS, 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
US PrEP Demonstration Project Liu, 2016[80] and Cohen, 2015[141]	TDF-FTC	Dried blood spot (DBS) samples: collected at all scheduled follow-up 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 (0.17 to 0.60) African-American vs. white (ref): aOR 0.28 (0.12 to 0.64) Living situation, rent or own vs. other (with friends, family, public housing or homeless; ref): aOR 2.02 (1.14 to 3.55) Condomless receptive anal sex, ≥2 partners vs. 0 to 1 partner (ref): aOR 1.82 (1.14 to 2.89) Health insurance, yes or no (ref): unadjusted OR 1.71 (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
van Epps, 2018[131]	TDF/FTC PrEP (n=1,086)	Prescription refill data	NR	Proportion of days covered (PDC) by PrEP prescription: median 0.74 (IQR 0.40 to 0.92) PDC >0.8: 40%	<u>Adherence, PDC >0.8</u> Age <35 vs 35-49: aOR 1.36 (95% CI 1.00 to 1.85); vs 50-64: aOR 2.00 (95% CI 1.37 to 2.92); vs 65-79: 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 ve 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)

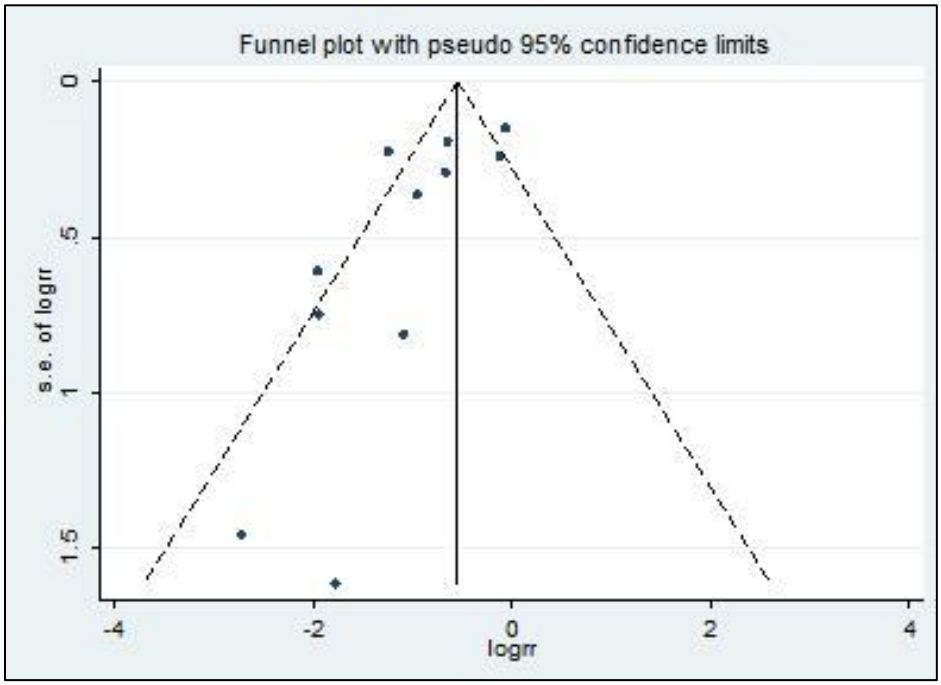
Abbreviations: aOR=adjusted odds ratio; ATN=Adolescent Trials Network for HIV/AIDS Interventions; BLQ=below the level of quantification; CI=confidence interval; D67N=D67N mutation; DB=dried blood; DBS=dried blood spots; fmol=femtomole; GI=gastrointestinal; HIV=human immunodeficiency virus; HR=hazard ratio; 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; US=United States; vs.=versus.

Appendix B6. HIV Pre-Exposure Prophylaxis Cohort Studies Quality Assessment

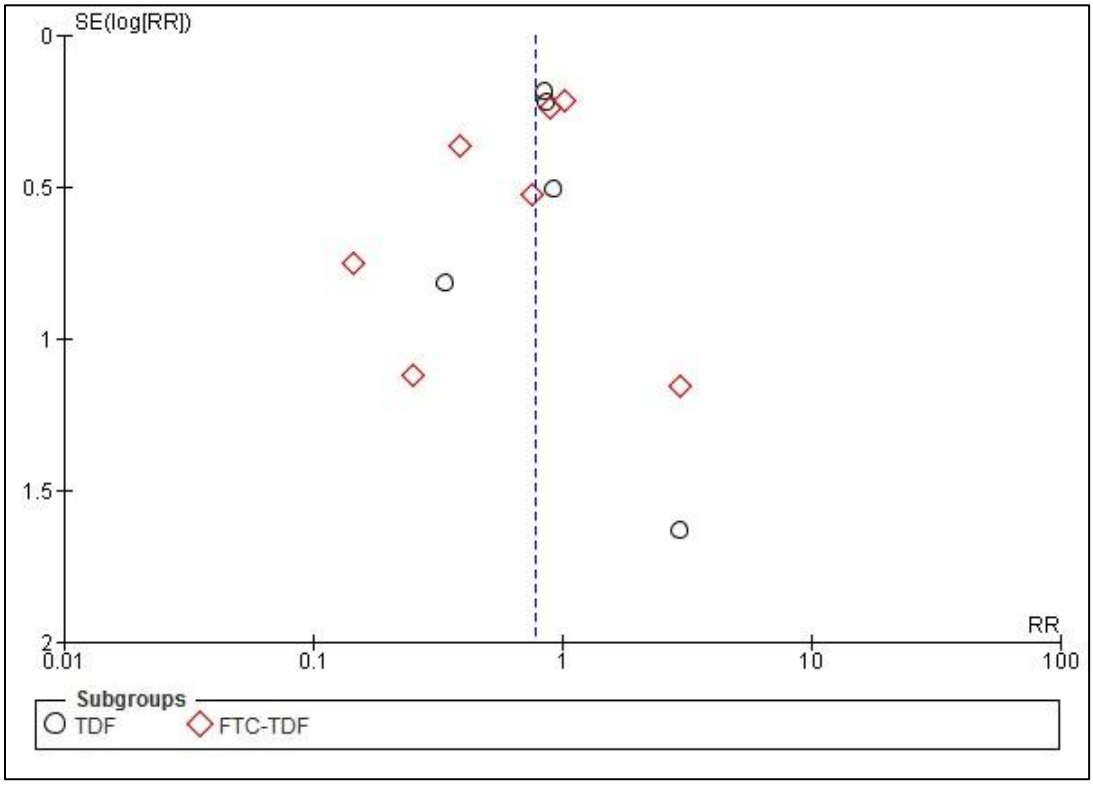
Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Is there high attrition?	Were outcomes pre-specified and defined, and ascertained using accurate	Quality rating
Chan, 2016[129]	Yes	Yes	Unclear	Yes	Yes; 27% at 3 months and 40% at 6 months	Yes	Fair
Hosek, 2017[128]	Unclear	Yes	No	Yes	No	Yes	Fair
Hosek, 2017[127] (ATN 113 adolescents)	Unclear	Yes	No	Yes	Yes; 44% discontinued	Yes	Fair
iPrEx-OLE Grant, 2014[140], Glidden, 2016[135]	Yes	Yes	No	Yes	No	Yes	Good
Landovitz, 2017[126]	Unclear	Yes	No	Yes	Yes	Yes	Fair
Montgomery, 2016[125]	Yes; consecutive	Yes	No	Yes	Yes; 30%	Yes	Fair
US PrEP Demonstration Project	Unclear; likely yes	Yes	No	Yes	No	Yes	Fair
van Epps, 2018[131]	Yes	Yes	Unclear	Yes	Yes, 44%	Yes	Fair

Abbreviations: ATN=Adolescent Medicine Trials Network for HIV/AIDS Interventions.
Note: Standard cohort quality criteria modified for single-arm studies.

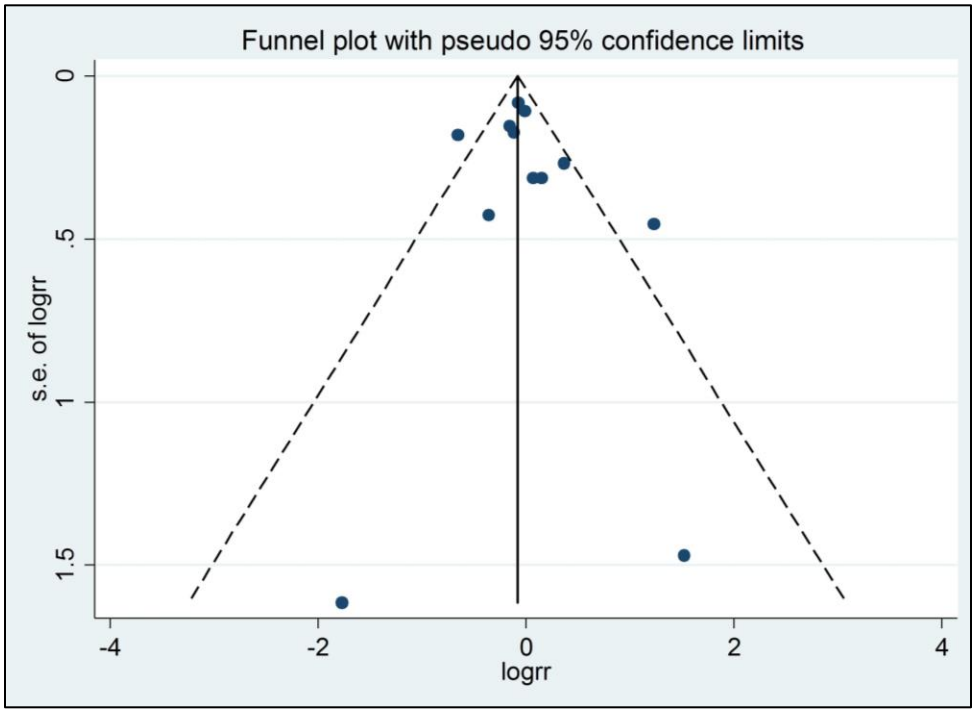
Appendix C1. Funnel Plot - HIV Infection



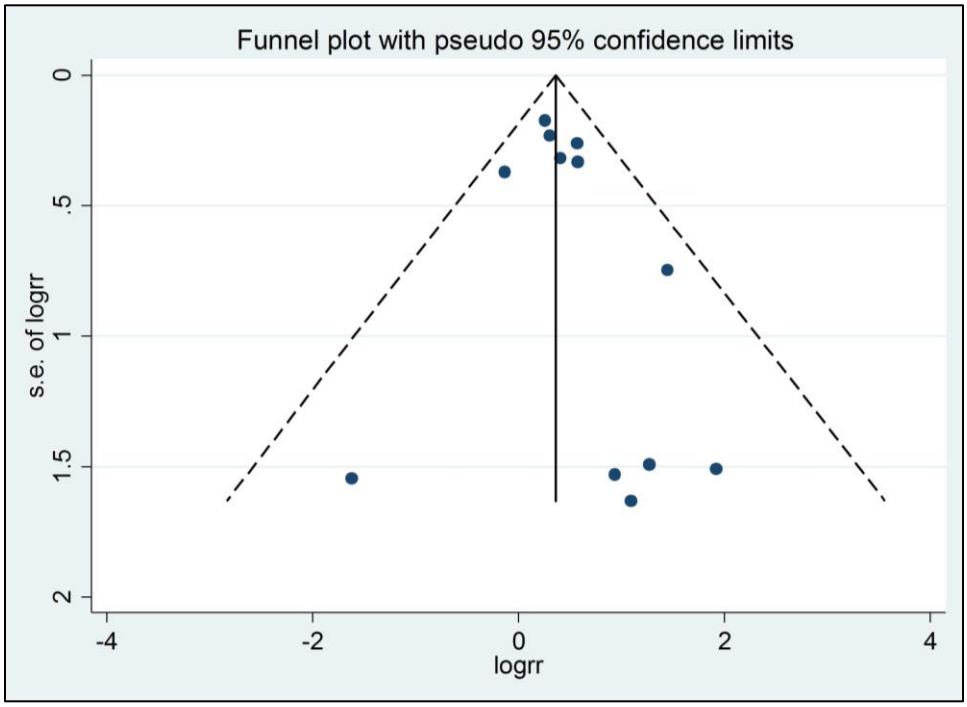
Appendix C2. Funnel Plot - Mortality



Appendix C3. Funnel Plot - Serious Adverse Events



Appendix C4. Funnel Plot - Renal Adverse Events



Appendix C5. Funnel Plot - Gastrointestinal Adverse Events