JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Preexposure Prophylaxis for the Prevention of HIV
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE A 2019 review for the US Preventive Services Task Force (USPSTF) found oral preexposure prophylaxis (PrEP) associated with decreased HIV infection risk vs placebo or no PrEP in adults at increased HIV acquisition risk. Newer PrEP regimens are available.

OBJECTIVE To update the 2019 review on PrEP, to inform the USPSTF.

DATA SOURCES Ovid MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Embase (January 2018 to May 16, 2022); surveillance through March 24, 2023.

STUDY SELECTION Randomized clinical trials of PrEP vs placebo or no PrEP or newer vs older PrEP regimens and diagnostic accuracy studies of instruments for predicting incident HIV infection.

DATA EXTRACTION AND SYNTHESIS Dual review of titles and abstracts, full-text articles, study quality, and data abstraction. Data were pooled using the DerSimonian and Laird random-effects model.

MAIN OUTCOMES AND MEASURES HIV acquisition, mortality, and harms; and diagnostic test accuracy.

RESULTS Thirty-two studies were included in the review (20 randomized clinical trials [N = 36 575] and 12 studies of diagnostic accuracy [N = 5 544 500]). Eleven trials in the 2019 review found oral PrEP associated with decreased HIV infection risk vs placebo or no PrEP (n = 18 172; relative risk [RR], 0.46 [95% CI, 0.33-0.66]). Higher adherence was associated with greater efficacy. One new trial (n = 5387) found oral tenofovir alafenamide/emtricitabine (TAF/FTC) to be noninferior to tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in men who have sex with men (RR, 0.53 [95% CI, 0.23-1.26]). Two new trials found long-acting injectable cabotegravir associated with decreased risk of HIV infection vs oral TDF/FTC (RR, 0.33 [95% CI, 0.18-0.62] in cisgender men who have sex with men and transgender women [n = 4490] and RR, 0.11 [95% CI, 0.04-0.31] in cisgender women [n = 3178]). Discrimination of instruments for predicting incident HIV infection was moderate in men who have sex with men (5 studies; n = 25 488) and moderate to high in general populations of persons without HIV (2 studies; n = 5 477 291).

CONCLUSIONS AND RELEVANCE In adults at increased HIV acquisition risk, oral PrEP was associated with decreased risk of acquiring HIV infection compared with placebo or no PrEP. Oral TAF/FTC was noninferior to oral TDF/FTC, and injectable cabotegravir reduced the risk of HIV infection compared with oral TDF/FTC in the populations studied.

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JAMA. 2023;330(8):746-763. doi:10.1001/jama.2023.9865
Corrected on October 23, 2023.

In 2019, the US Preventive Services Task Force (USPSTF) recommended that clinicians offer preexposure prophylaxis (PrEP) with effective antiretroviral medications to persons at increased HIV acquisition risk (A recommendation),[1] based on evidence showing that oral PrEP with tenofovir disoproxil fumarate alone or in combination with emtricitabine (TDF/FTC) was associated with decreased risk of acquiring HIV infection.[2,3] Subsequently, the US Food and Drug Administration (FDA) approved oral tenofovir alafenamide fumarate/emtricitabine (TAF/FTC) and long-acting injectable cabotegravir for PrEP. Compared with tenofovir disoproxil fumarate, tenofovir alafenamide fumarate achieves higher and more sustained intracellular drug levels at lower tenofovir serum levels, potentially increasing effectiveness and bone and kidney safety. Cabotegravir is administered every 2 months, potentially increasing adherence, which is directly related to PrEP effectiveness. This evidence report was conducted to update the 2019 USPSTF review[2,3] to inform the USPSTF for an updated recommendation statement on use of PrEP, by synthesizing evidence on benefits and harms of PrEP, including newer regimens, and on accuracy of instruments for identifying potential candidates for PrEP.

Methods

Scope of the Review

Detailed methods and evidence tables with additional study details are available in the full evidence report.[4] **Figure 1** shows the analytic framework and key questions (KQs) that guided the review. The full report includes additional evidence on the dapivirine ring (not FDA approved/available in the US), additional outcomes (hepatitis C and hepatitis B virus infection), and findings for contextual questions (not systematically reviewed) on adherence, persistence, utilization, drug resistance, disparities, and tele-PrEP.

Search Strategies

A research librarian searched Ovid MEDLINE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Embase from January 2018 to May 16, 2022 (eMethods 1 in the Supplement). Searches were supplemented by reference list review of applicable articles, and relevant studies from the 2019 USPSTF review were carried forward. Since May 2022, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on March 24, 2023, and identified no eligible randomized trials.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria (eMethods 2 in the Supplement). The populations of interest were adolescents and adults without HIV infection at increased HIV acquisition risk. Randomized clinical trials (RCTs) of PrEP vs placebo or no PrEP, newer (oral TAF/FTC and injectable cabotegravir) vs older (oral tenofovir disoproxil fumarate alone or oral TDF/FTC) PrEP regimens, and intermittent vs event-driven PrEP that assessed risk of HIV infection, mortality, quality of life, or harms of treatment were eligible. For newer vs older PrEP regimens, weight gain and lipid profiles were also evaluated. Diagnostic accuracy studies of instruments to predict HIV acquisition were also included. Inclusion was restricted to English-language articles, and studies published only as abstracts were excluded.

Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, interventions or screening instruments, adherence, and results from each study. A second investigator reviewed abstracted data for accuracy. Two independent investigators assessed the quality of each study as good, fair, or poor using predefined criteria (eMethods 3 in the Supplement[5]). Discrepancies were resolved by consensus.

Data Synthesis

Meta-analyses of oral PrEP vs placebo or no PrEP were conducted for the 2019 USPSTF review using the DerSimonian and Laird random-effects model[3]; there were no new placebo-controlled trials to perform updated meta-analyses. Two trials of injectable cabotegravir vs oral TDF/FTC were not pooled due to heterogeneity in populations and settings.[6,7]

The aggregate internal validity (quality) of the body of evidence was assessed for each KQ using methods developed by the USPSTF,[5] based on the number, quality, and size of studies; consistency of results between studies; and directness of evidence.

Results

Across all KQs, 32 studies (reported in 61 publications) were included (20 RCTs [N = 36 575] and 12 diagnostic accuracy studies [N = 5 544 500]) (**Figure 2**).[6-66]

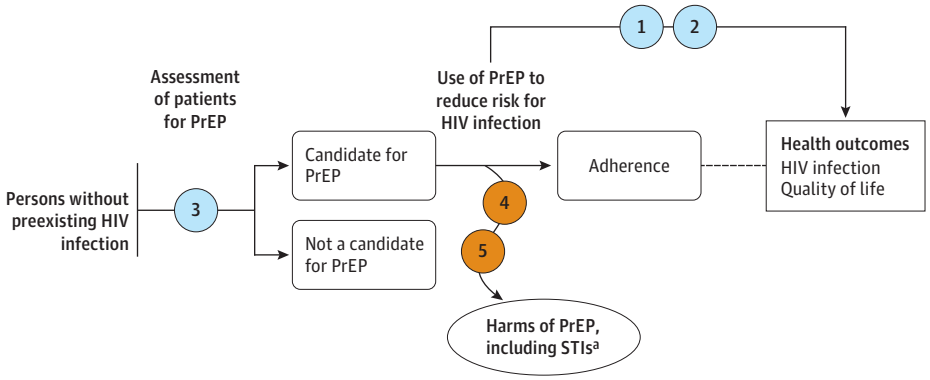
Fourteen RCTs[8,10,12,14,16-24,26,28,32-36,38-41,43,45-52,56,61,63,65,66] and 7 diagnostic accuracy studies[13,25,27,31,44,59,60] (in 45 publications) were carried forward from the 2019 USPSTF review; 6 RCTs[6,7,11,30,42,53-55] (including 2 RCTs of dapivirine[11,53]) and 5 diagnostic accuracy studies[29,37,57,58,64] were new, and 3 new publications reported additional outcome or analyses for previously included trials[9,15,62] (in 16 publications).

Benefits of PrEP

Key Question 1. What are the benefits of preexposure prophylaxis (PrEP) in persons without preexisting HIV infection vs placebo or no PrEP (including deferred PrEP) on the prevention of HIV infection and quality of life?

Twelve RCTs, all in the 2019 USPSTF review, evaluated oral PrEP vs placebo or no PrEP (total N = 18 244) (eTables 1-4 in the Supplement).[10,17,21,22,28,38,43,46,52,56,63,65] Eleven trials randomized patients to PrEP or placebo, and 1 open-label trial[43] randomized patients to immediate vs delayed PrEP. Six trials[10,28,38,56,63,65] conducted in Africa enrolled men and women at increased HIV infection risk due to heterosexual contact; 4 trials[21,22,43,46] conducted in the US, Europe, Canada, or internationally enrolled men who have sex with men or transgender women; 1 trial[52] conducted in Africa enrolled both men who have sex with men and high-risk women; and 1 trial[17] conducted in Thailand enrolled persons who inject drugs. PrEP was prescribed daily in 11 trials,[10,17,21,22,28,38,43,52,56,63,65] and 1 trial[46] reported results for

Figure 1. Analytic Framework and Key Questions: Preexposure Prophylaxis for the Prevention of HIV Infection



Key questions

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

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line depicts a health outcome that follows an intermediate outcome. For additional information, see the USPSTF Procedure Manual.[5] PrEP indicates preexposure prophylaxis; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine; and TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

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

[b] Dapivirine not addressed in this article but results are described in the full report.[4]

event-driven dosing. The mean age in all trials was younger than 40 years. No trial enrolled pregnant persons or persons younger than 18 years. In all trials, HIV risk reduction and adherence counseling was provided to all patients.[43] All trials were rated good quality except for 1 rated fair quality[43] due to unclear allocation concealment methods and open-label design.

PrEP was associated with reduced risk of incident HIV infection vs placebo or no PrEP (11 trials; n = 18 172; relative risk [RR], 0.46 [95% CI, 0.33-0.66]) (eFigure 1 in the Supplement), but statistical heterogeneity was present (I^2 = 67%). The absolute risk reduction was −2.0% (95% CI, −2.8% to −1.2%; I^2 = 58%) after 4 months to 4 years. Funnel plot asymmetry was present on visual inspection, indicating small sample effects, and the Egger test (a quantitative measure of funnel plot asymmetry) was statistically significant (P = .03), indicating potential publication bias (eFigure 2 in the Supplement).[67,68] A stratified analysis eliminated statistical heterogeneity and showed a strong interaction (P < .001) between higher adherence and increased effectiveness of PrEP (adherence, ≥70%: 6 trials (n = 7328); RR, 0.27 [95% CI, 0.19-0.39]; I^2 = 0%) (eFigure 3 and eTable 5 in the Supplement).[10,17,21,22,38,43,46,52,56,63,65] There was also a strong association between adherence analyzed as a continuous variable and effectiveness (P < .001) (eFigure 4 in the Supplement). Results were consistent in stratified analyses based on follow-up duration, receipt of industry support, and geographic setting and in sensitivity analysis excluding 1 fair quality trial[43] (eTable 5 in the Supplement).

Oral PrEP was associated with a modestly decreased risk of mortality that was not statistically significant, due to small numbers of mortality events (9 trials; n = 17 744; RR, 0.81 [95% CI, 0.59-1.11]; I^2 = 0%)[10,17,21,22,38,43,56,63,65] (eFigure 5 in the Supplement). No trial reported effects on quality of life.

Key Question 1a. How do the benefits of PrEP differ by populations of interest (eg, defined by age, sex, gender identity, race and ethnicity, and HIV risk category)?

PrEP was effective across population subgroups defined by HIV risk category (persons at increased risk of HIV infection via heterosexual contact, men who have sex with men or transgender women, or persons who inject drugs) (eTable 6 and eFigure 6 in the Supplement), although evidence in persons who inject drugs was limited to 1 trial.[17]

Based on within-study stratified analyses, 4 trials[10,17,21,65] did not find that PrEP effectiveness differed according to age, and 3 trials[10,17,63] did not find that PrEP effectiveness differed between men and women (eTable 6 in the Supplement). A post hoc analysis of 1 trial[21] found that PrEP was effective in men who have sex with men (hazard ratio [HR], 0.50 [95% CI, 0.34-0.75]) but not in transgender women (HR, 1.1 [95% CI, 0.5-2.7]), although the interaction was not statistically significant (P = .09),[18] indicating no statistically significant difference in treatment effect between subgroups. One trial found that effectiveness of PrEP was similar in Hispanic and non-Hispanic persons.[21] A new post hoc analysis from 1 trial found event-driven PrEP associated with decreased HIV incidence vs placebo

Figure 2. Literature Search Flow Diagram: Preexposure Prophylaxis for the Prevention of HIV Infection

[a] The sum of the number of studies per key question (KQ) exceeds the total number of studies because some studies were applicable to multiple KQs. For some individual KQs, the total number of studies is less than the sum of new and carried forward studies, because some new studies were subsequent publications to studies carried forward.

among those who took 15 or fewer pills per month with high adherence (0 vs 9.2 per 100 person-years, $P = .01$) and those who took more than 15 pills per month (0 vs 8.1 per 100 person-years, $P = .004$).[9]

Key Question 1b. How do the benefits of PrEP differ by dosing strategy or regimen?

Estimates for oral PrEP vs placebo or no PrEP and risk of HIV infection were very similar in stratified analysis according to use of tenofovir disoproxil fumarate alone (5 trials, n = 7546) or TDF/FTC (8 trials; n = 10 626; $P = .79$ for interaction) (eTable 5 and eFigure 1 in the Supplement).[10,21,38,43,46,52,63,65] The estimate from 1 trial (n = 199)[46] of event-driven PrEP in men who have sex with men (RR, 0.14 [95% CI, 0.03-0.63]) was stronger than from 9 trials (n = 17 700) that used daily dosing (RR, 0.47 [95% CI, 0.32-0.71]; $I^2 = 75\%$) (eTable 5 and eFigure 7 in the Supplement),[10,17,21,22,38,43,56,63,65] but the interaction was not statistically significant ($P = .13$) and the estimate for event-driven PrEP was similar to daily dosing with high adherence (5 trials; n = 6928; RR, 0.28 [95% CI, 0.20-0.41]).[10,22,43,52,63] These trials were designed to evaluate event-driven or daily PrEP against placebo or no PrEP; therefore, comparisons of PrEP regimens based on these trials are indirect. Although 2 trials (n = 654 [1 new[30]]) compared event-driven or intermittent vs daily PrEP, they were not designed to assess incident HIV infection and reported few cases (**Table 1** and **Table 2**; eTables 1-4 in the Supplement).[12,20,30]

Benefits of New PrEP Regimens

Key Question 2. What are the benefits of newer PrEP regimens (oral tenofovir alafenamide-emtricitabine [TAF-FTC], or injectable cabotegravir) vs tenofovir disoproxil fumarate-emtricitabine (TDF-FTC)?

Oral TAF/FTC vs TDF/FTC

One new, good-quality trial compared PrEP with oral TAF/FTC vs TDF/FTC[42,54] (Tables 1 and Table 2; eTables 1-4 in the Supplement). The DISCOVER trial (n = 5387) is an ongoing European and North American trial of once-daily TAF/FTC (25-200 mg) or TDF/FTC (300-200 mg) in HIV-negative cisgender adult men (98.6%) or transgender women (1.4%) who have sex with men and had increased HIV acquisition risk.[42] Adherence was high (84% to 96% based on dried blood spot samples, consistent with ≥4 doses/wk).

At 96 weeks, TAF/FTC was associated with a statistically nonsignificant decreased risk of HIV infection vs TDF/FTC (0.3% vs 0.6%; RR, 0.53 [95% CI, 0.23-1.26][54]); this difference was within the prespecified noninferiority margin. There were no statistically significant interactions with age, race, ethnicity, geographical region, recreational drug use, binge alcohol use, or number of unprotected receptive anal intercourse partners.[42] However, stratified estimates were imprecise. No infections occurred in transgender women in either group.

Long-Acting Injectable Cabotegravir vs Daily Oral PrEP

Two new, concurrently conducted trials (HIV Prevention Trials Network [HPTN] trials 083 and 084) compared long-acting injectable cabotegravir (600 mg intramuscularly every 8 weeks, following a 5-week 30-mg daily oral lead-in) vs daily oral TDF/FTC (300 mg/200 mg) (Table 1 and Table 2; eTables 1-4 in the Supplement).[6,7] The studies were designed as 3-year and 3.5-year trials but were discontinued at a median of 1.2 and 1.4 years, based on cabotegravir meeting predefined superiority thresholds. The trials were rated good quality.

HPTN 083 (n = 4566) enrolled cisgender men who have sex with men (87%) or transgender women who have sex with men (12%) in the US (37%), Latin America (43%), Asia (16%), and Africa (3.3%).[6] Among US participants, 50% were Black and 50% were non-Black. Injectable cabotegravir was associated with decreased risk of HIV infection vs oral TDF/FTC (0.6% vs 1.7%; RR, 0.33 [95% CI, 0.18-0.62]). Adherence was 91.5% for cabotegravir (based on injection delay <2 weeks) and 74% with TDF/FTC (based on tenofovir plasma concentration >40 ng/mL). Estimates were similar in men who have sex with men (HR, 0.35 [95% CI, 0.18-0.68]) and transgender women (HR, 0.34 [95% CI, 0.08-1.56]). Among US patients, cabotegravir was associated with decreased risk of HIV acquisition in Black (HR, 0.28 [95% CI, 0.10-0.84]) and non-Black (HR, 0.09 [95% CI, 0.00-2.05]) persons. Findings were also similar when results were stratified by age (≤30 vs >30 years) and geographic region.

HPTN 084 (n = 3178) enrolled cisgender women in 7 countries in sub-Saharan Africa.[7] Pregnant and breastfeeding women were ineligible. Injectable cabotegravir was associated with decreased risk of HIV acquisition vs oral TDF/FTC (0.3% vs 2.3%; RR, 0.11 [95% CI 0.04-0.31]). Adherence with cabotegravir was 93.0% (based on injection delay <2 weeks) and with TDF/FTC was 41.9% (based on a plasma concentration ≥40 ng/mL) or 18% (based on tenofovir diphosphate level consistent with taking ≥4 doses/wk). Results were similar in stratified analyses based on age (<25 vs ≥25 years), contraception method, and body mass index.

Diagnostic Accuracy of Risk Assessment Tools

Key Question 3. What is the diagnostic accuracy of provider or patient risk assessment tools in identifying persons at increased risk of HIV acquisition who are candidates for PrEP?

Twelve studies (total n = 5 544 500; 5 new [n = 5 512 189][29,37,57,58,64]) evaluated instruments developed and validated in US cohorts for predicting incident HIV infection (eTables 7-9 in the Supplement).[13,25,27,29,31,37,44,57-60,64] Eight studies (2 new)[58,64] evaluated risk prediction instruments in men who have sex with men,[13,25,27,31,44,58,59,64] 1 prior study evaluated persons who inject drugs,[60] 1 new study evaluated cisgender women,[57] and 2 new studies evaluated general populations of HIV-uninfected persons.[29,37] In the studies evaluating risk prediction instruments in general populations[29,37] and cisgender women,[57] HIV risk assessment was based solely on data extracted from electronic health records. Otherwise, risk prediction instruments were based on information obtained from patient interviews, health records, or data previously collected for other research purposes. No instrument was specifically designed to be administered as a self-administered questionnaire. Methodological limitations included evaluation of older (pre-2000) cohorts,[44,58-60] use of previously collected data,[13,25,27,31,44,57-60,64] failure to validate accuracy in a separate (nondevelopment) cohort,[13,60] failure to predefine positive test thresholds,[13,25,29,37,44,58-60] and inadequate or unclear methods for ruling out preexisting HIV infection.[29,37,57]

For men who have sex with men, 5 studies of 5 different instruments (number of criteria ranged from 4 to 12) reported area under the receiver operating characteristic curve (AUROC) values for in-

Table 1. Study Characteristics of Head-to-Head Trials of PrEP

Source, country, duration of follow-up/quality[a]	Interventions	HIV risk group(s), risk-based inclusion criteria	Patient characteristics	Adherence (method for measuring adherence)
Event-driven vs daily oral PrEP[b]				
ADAPT/HPTN 067 Bekker et al,[12] 2018 South Africa 34 wk Fair Included in prior report	A: Daily TDF/FTC (n = 59) B: Time-driven TDF/FTC (1 tablet twice a week, plus a dose after sex; n = 59) C: Event-driven TDF/FTC (1 tablet both before and after sex; n = 60)	High-risk women or transgender men History of an acute STI, transactional sex, intercourse without a condom with someone of unknown or HIV-infected status, or >1 sex partner in 6 mo	A vs B vs C: Age (mean): 25 vs 26 vs 25 y Female: 100% (no transgender men enrolled) Black: 98% vs 100% vs 100%	A vs B vs C (plasma level ≥2.5 ng/mL at week 30 [consistent with ≥2 doses/wk] [daily and time-driven] or when reporting sex in prior wk [event-driven]): 54% vs 36% vs 31%
ADAPT/HPTN 067 Grant et al,[20] 2018 Thailand, US 34 wk Fair Included in prior report	A: Daily TDF/FTC (n = 119) B: Time-driven TDF/FTC (1 tablet twice a week, plus a dose after sex; n = 119) C: Event-driven TDF/FTC (1 tablet both before and after sex; n = 119)	Men who have sex with men Reported anal or neovaginal sex with a man in the past 6 mo and have ≥1 of the following in the past 6 mo: sex with >1 man or transgender woman; history of an acute STI; sex in exchange for money, goods, or favors; or intercourse without a condom with an HIV-infected partner or partner of unknown HIV infection status	A vs B vs C, Bangkok site: Age 18 to 24 y: 13% vs 20% vs 14% Age 25 to 29 y: 22% vs 32% vs 27% Age 30 to 39 y: 60% vs 39% vs 48% Age ≥40 y: 5% vs 9% vs 12% Men who have sex with men: 98% vs 98% vs 100% Transgender: 2% vs 2% vs 0% Race: NR A vs B vs C, Harlem site: Age 18 to 24 y: 32% vs 28% vs 28% Age 25 to 29 y: 22% vs 18% vs 13% Age 30 to 39 y:19% vs 20% vs 23% Age ≥40 y: 27% vs 33% vs 35% Men who have sex with men: 97% vs 98% vs 97% Transgender: 3% vs 0% vs 2% Gender queer: 0% vs 2% vs 2% Asian: 3% Black: 70% Hispanic: 25% Native American: 3% White: 13% Other: 21%	A vs B vs C, Bangkok site (peripheral blood mononuclear cell levels consistent with ≥2 tablets on visits when sex was reported in prior wk): 97.6% vs 98.7% vs 95.7% A vs B vs C, Harlem site (dried blood spot levels consistent with ≥2 tablets on visits when sex was reported in prior wk): 48.5% vs 30.9% vs 16.7%
Kwan et al,[30] 2021 Hong Kong 32 wk Fair	A: Daily TDF/FTC (n=59) B: Event-driven TDF/FTC (n=60)	Men who have sex with men Had condomless anal intercourse in the preceding 6 mo	Age (mean): 29 vs 30 y	Median, 100% vs 93% (self-report, proportion of days with PrEP-covered condomless anal intercourse)
Oral TAF/FTC vs TDF/FTC				
DISCOVER Mayer, 2020[42] Ogbuagu et al,[54] 2021 Europe and North America 96 wk Good	A: TAF/FTC (n = 2694) B: TDF/FTC (n = 2693)	Cisgender men who have sex with men or transgender women who have sex with men Condomless anal sex with ≥2 partners in the previous 12 wk or syphilis, rectal gonorrhea, or rectal chlamydia in the prior 24 wk	A vs B: Age (mean): 34 vs 34 y Cisgender men who have sex with men: 98% vs 99% Transgender women who have sex with men: 2% vs 1% Asian: 4% vs 5% Black: 9% vs 9% White: 84% vs 84% Other race: 3% vs 3% Hispanic or Latinx ethnicity: 24% vs 25%	A vs B: Dried blood spot, random sample consistent with ≥4 doses/wk: 88%-96% vs 84%-93%
Long-acting injectable cabotegravir vs daily oral TDF/FTC				
HPTN 083 Landovitz et al,[6] 2021 International Median, 1.4 y Good	A: Cabotegravir long-acting injectable (600 mg at wk 5, 9, 17, and every 8 wk afterward) and oral placebo (n = 2282) B: Oral TDF/FTC (300 mg/200 mg once daily) and injectable placebo (n = 2284)	Cisgender men who have sex with men and transgender women who have sex with men	Age (median): 26 vs 26 y Men who have sex with men: 88% vs 87% Transgender women who have sex with men: 12% vs 13%	Received injection with no delay ≥2 wk: 91.5% vs 74% (plasma, tenofovir level >40 ng/mL [consistent with ≥4 doses/wk])
HPTN 084 Delany-Moretwle et al,[7] 2022 Sub-Saharan Africa Median, 1.24 y Good	A: Cabotegravir (600 mg in a 3-mL intramuscular injectable every 8 wk) (n = 1592) B: Daily TDF/FTC (300 mg/200 mg) (n = 1586)	High-risk women Reported at least 2 episodes of vaginal intercourse in the previous 30 d at risk of HIV infection based on an HIV risk score	Age (median): 25 vs 25 y Black race: 97.2% vs 96.5% Gender identity: 99.9% vs 99.8% female, 0% vs 0.2% male, and 0.1% vs 0% transgender male	Received injection with no delay ≥2 wk: 93% vs 42% (plasma, tenofovir level ≥40 ng/mL)

Abbreviations: ADAPT, Alternative Dosing to Augment PrEP Pill Taking; HPTN, HIV Prevention Trials Network; NR, not reported; PrEP, preexposure prophylaxis; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide fumarate/emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

[a] For each study, year indicates year of primary publication.

[b] Evidence from an additional study (IPERGAY, Molina et al,[46] 2015) of event-driven PrEP, but vs placebo, is reported in the Supplement.

Table 2. Risk of HIV Infection and Adverse Events in Head-to-Head Trials of PrEP

Source[a]	Interventions	Clinical health outcomes	Adverse events
Event-driven vs daily oral PrEP[b]			
ADAPT/HPTN 067 Bekker et al,[12] 2018	A: Daily TDF/FTC (n = 59) B: Time-driven TDF/FTC (1 tablet twice a week, plus a dose after sex; n = 59) C: Event-driven TDF/FTC (1 tablet both before and after sex; n = 60)	HIV infection: A vs B vs C: 0% (0/59) vs 3% (2/59) vs 3% (2/60) A vs B: RR, 0.20 (95% CI, 0.01-4.08) A vs C: RR, 0.20 (95% CI, 0.01-4.15)	Any headache, dizziness, or lightheadedness: A vs B vs C: 12% (43/348) vs 6% (20/331) vs 8% (26/332) A vs B: OR, 2.19 (95% CI, 1.13-4.27) A vs C: OR, 1.66 (95% CI, 0.88-3.13) Any GI symptom: A vs B vs C: 11% (37/348) vs 9% (29/331) vs 5% (18/332) A vs B: OR, 1.24 (95% CI, 0.61-2.51) A vs C: OR, 2.08 (95% CI, 0.98-4.40)
ADAPT/HPTN 067 Grant et al,[20] 2018	A: Daily TDF/FTC (n = 119) B: Time-driven TDF/FTC (1 tablet twice a week, plus a dose after sex; n = 119) C: Event-driven TDF/FTC (1 tablet both before and after sex; n = 119)	HIV infection: A vs B vs C: 0.8% (1/119) vs 0% (0/119) vs 0% (0/119) A vs B: RR, 3.03 (95% CI, 0.12-75) A vs C: RR, 3.03 (95% CI, 0.12-75) South Africa (from Bekker et al,[12] 2017), Bangkok and Harlem sites combined: A vs B vs C: 0.6% (1/178) vs 1.1% (2/178) vs 1.1% (2/179) A vs B: RR, 0.50 (95% CI, 0.04-5.53) A vs C: RR, 1.01 (95% CI, 0.14-7.22)	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% A vs B vs C, Harlem: Proportion of visits when patients reported neurologic events: 6.1% vs 3.3% vs 4.5% Proportion of visits when patients reported GI events: 8.0% vs 5.8% vs 7.1%
Kwan et al,[30] 2021	A: Once-daily TDF/FTC (n = 59) B: On-demand TDF/FTC (n = 60)	NR	Creatinine clearance: no difference between groups
Oral TAF/FTC vs TDF/FTC			
DISCOVER Mayer et al,[42] 2020 Ogbuagu et al,[54] 2021	A: TAF/FTC (n = 2694) B: TDF/FTC (n = 2693)	HIV infection, primary (interim) analysis (for which 100% of patients had completed 48 wk and 50% had completed 96 wk): 0.16 vs 0.34 per 100 person-years; IRR, 0.47 (95% CI, 0.19-1.15) 0.3% (7/2670) vs 0.6% (15/2665) RR, 0.47 (95% CI, 0.19-1.14)[c] HIV infection at 96 wk (all patients had completed 96 wk): 0.16 vs. 0.30 per 100 person-years; IRR, 0.54 (95% CI, 0.23-1.26); 0.3% (8/2694) vs. 0.6% (15/2693); RR, 0.53 (95% CI, 0.23-1.26)[c]	Mortality: 0.01% (3/2694) vs 0.07% (2/2693); RR, 1.50 (95% CI, 0.25-8.97) Serious adverse event: 7.5% (202/2694) vs 6.9% (186/2693); RR, 1.09 (95% CI, 0.90-1.32) Discontinuation of study drug due to adverse event: 1.5% (40/2694) vs 1.9% (51/2693); RR, 0.78 (95% CI, 0.52-1.18) Any adverse event: 94% (2523/2694) vs 94% (2521/2693) Rectal chlamydia: 33% (890/2694) vs 33% (902/2693) Oropharyngeal gonorrhea: 32% (871/2694) vs 31% (838/2693) Rectal gonorrhea: 30% (805/2694) vs 30% (797/2693) Syphilis: 15% (413/2694) vs 15% (392/2693) Urethral chlamydia: 13% (346/2694) vs 12% (314/2693) Any kidney adverse event: 10% (263/2694) vs 10% (266/2693) in primary (interim) analysis Grade ≥3 kidney adverse event: 0.07% (2/2694) vs 0.1% (3/2693); RR, 0.67 (95% CI, 0.11-3.99) in primary (interim) analysis Kidney adverse event leading to discontinuation: 0.07% (2/2694) vs 0.2% (6/2693); RR, 0.33 (95% CI, 0.07-1.65) Creatinine clearance, median percentage change from baseline: −2.3% vs 1.8%, $P < .0001$ in primary (interim) analysis Fracture: 2.2% (60/2694) vs 2.2% (60/2693) Diarrhea: 18% (480/2694) vs 17% (453/2693) Nausea: 4.2% (114/2694) vs 4.6% (123/2693) in primary (interim) analysis Hip bone mineral density, percent change from baseline: +0.6% vs -1.0% in persons aged ≥25 y ($P < .001$) and +1.2% vs -1.7% in persons <25 y ($P = .04$) Spine bone mineral density, percent change from baseline: +0.9% vs -1.4% in persons aged ≥25 y ($P < .001$) and +1.4% vs -1.2% in persons <25 y ($P = .14$) Body weight, change from baseline: +1.7 kg vs +0.5 kg, $P < .0001$ (Outcomes at 96 wk, except where noted as primary [interim] analysis, for which 100% of patients had completed 48 wk and 50% had completed 96 wk)

(continued)

Table 2. Risk of HIV Infection and Adverse Events in Head-to-Head Trials of PrEP (continued)

Source[a]	Interventions	Clinical health outcomes	Adverse events
Long-acting injectable cabotegravir vs daily oral TDF/FTC			
HPTN 083 Landovitz et al,[6] 2021	A: Cabotegravir (600 mg in a 3-mL intramuscular injectable every 8 wk) (n = 2282) B: Daily TDF/FTC (300 mg/200 mg) (n = 2284)	HIV infection: 0.57% (13/2243) vs 1.71% (39/2247) RR, 0.33 (95% CI, 0.18-0.62[c]) Incidence rate per 100 person-years, 0.41 vs 1.22 HR, 0.34 (95% CI, 0.18-0.62)	Serious adverse event: 5.3% (120/2280) vs 5.3% (121/2282) Grade 3 or higher adverse event: 31.9% (727/2280) vs 33.6% (767/2282) Hepatic-related discontinuation: 2.1% (47/2280) vs 2.1% (48/2282) Decreased creatinine clearance: 7.0% (159/2280) vs 8.3% (190/2282) Increased aspartate aminotransferase: 2.3% (53/2280) vs 3.0% (69/2282) Increased alanine aminotransferase: 1.0% (23/2280) vs 1.4% (32/2282) Death: 0.18% (4/2280) vs 0
HPTN 084 Delany-Moretwle et al,[7] 2022	A: Cabotegravir (600 mg in a 3-mL intramuscular injectable every 8 wk) (n = 1592) B: Daily TDF/FTC (300 mg/200 mg) (n = 1586)	HIV infection: 0.3% (4/1592) vs 2.3% (36/1586) RR, 0.11 (95% CI, 0.04-0.31[c]) Incidence rate per 100 person-years, 0.20 (95% CI, 0.06-0.52) vs 1.85 (95% CI, 1.30-2.57) HR, 0.12 (95% CI, 0.05-0.31)	Serious adverse event: 2.0% (33/1614) vs 2.0% (33/1610) Grade 3 or higher adverse event: 17.1% (276/1614) vs 17.4% (280/1610) Hepatic-related discontinuation: 0.9% (15/1614) vs 1.1% (18/1610) Death: 0.2% (3/1614) vs 0 Chlamydia: 16.2% (261/1614) vs 17.8% (287/1610) Gonorrhea: 7.8% (126/1614) vs 7.8% (125/1610) Trichomonas: 7.7% (124/1614) vs 6.8% (109/1610) Grade 3 decreased creatinine clearance: 6.8% (110/1614) vs 7.8% (125/1610)

Abbreviations: ADAPT, Alternative Dosing to Augment PrEP pill Taking; GI, gastrointestinal; HPTN, HIV Prevention Trials Network; HR, hazard ratio; IRR, incidence rate ratio; NR, not reported; OR, odds ratio; PrEP, preexposure prophylaxis; RR, relative risk; TAF/FTC, tenofovir alafenamide fumarate/emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

[a] For each study, year indicates year of primary publication.

[b] Evidence from an additional study (IPERGAY, Molina et al,[46] 2015) of event-driven PrEP, but vs placebo, is reported in the Supplement.

[c] Relative risk calculated from data provided in the trial.

cident HIV infection that ranged from 0.60 to 0.73 in validation cohorts (n = 25 488).[25,44,58,59,64] In general populations of HIV-uninfected persons, 2 studies evaluated instruments that applied computerized algorithms to electronic medical record data (number of items, 23 and 44). The instruments had AUROC values of 0.77 (95% CI, 0.74-0.79) and 0.84 (95% CI 0.80-0.89) in validation cohorts (n, = 33 404 and n = 606 701).[29,37] One study of persons who inject drugs (n = 1904)[60] found a 7-item instrument associated with an AUROC value of 0.72 (CI not reported), and 1 small study (21 cases)[57] of cisgender women found a 6-item instrument associated with sensitivity of 95% for new HIV infection, but both studies had important methodological limitations.

Harms of PrEP

Key Question 4. What are the harms of PrEP vs placebo or no PrEP when used for the prevention of HIV infection?

Oral PrEP vs Placebo or No PrEP

There was no difference between oral PrEP with tenofovir disoproxil fumarate alone or TDF/FTC vs placebo in risk of serious adverse events (12 trials; n = 18 292; RR, 0.93 [95% CI, 0.77-1.12]; I^2 = 56%) (eFigure 8 in the Supplement)[10,17,21,22,28,38,43,46,52,56,63,65] and a small, statistically nonsignificant increased risk of withdrawal due to adverse events (4 trials; n = 9704 [1 additional trial[56] with 859 patients had no events and did not contribute to the analysis]; RR, 1.25 [95% CI, 0.99-1.59]; I^2 = 0%) (eFigure 9 in the Supplement).[10,21,46,65]

Oral PrEP was associated with increased risk of kidney (primarily ≥grade 1 elevation in serum creatinine level) adverse events (12 trials; n = 18 170; RR, 1.43 [95% CI, 1.18-1.75]; I^2 = 0%; absolute risk difference [ARD], 0.56% [95% CI, 0.09%-1.04%]) (eFigure 10 in the Supplement)[10,17,21,22,28,38,43,46,52,56,63,65] and gastrointestinal (primarily nausea) adverse events (12 trials; n =18 300; RR, 1.63 [95% CI, 1.26-2.11]; I^2 = 43%; ARD, 1.95% [95% CI, 0.48%-3.43%]) (eFigure 11 in the Supplement).[10,17,21,22,28,38,43,46,52,56,63,65] Serious kidney or gastrointestinal events were rare. There was no interaction between PrEP regimen (tenofovir disoproxil fumarate alone or TDF/FTC) and kidney or gastrointestinal events. Six trials[10,28,35,39,52,61] found that serum creatinine levels returned to normal with or without PrEP cessation and 3 trials reported diminished risk of gastrointestinal events over time.[17,21,63] Oral PrEP was associated with a small, statistically nonsignificant increased risk of fracture vs placebo (7 trials; n = 15 241; RR, 1.23 [95% CI, 0.97-1.56]; I^2 = 0%; ARD, 0.21% [95% CI, −0.21% to 0.62%]) (eFigure 12 in the Supplement)[10,17,21,22,38,46,63] that was heavily weighted (64%) by a trial of persons who inject drugs with a relatively high fracture rate (7.8% vs 6.0%; RR, 1.29 [95% CI, 0.96-1.74]).[17]

There were no differences between oral PrEP vs placebo or no PrEP in risk of syphilis (4 trials; n = 10 775; RR, 1.08 [95% CI, 0.98-1.18]; I^2 = 0%) (eFigure 13 in the Supplement), gonorrhea (5 trials; n = 9296; RR, 1.07 [95% CI, 0.82-1.39]; I^2 = 49%) (eFigure 14 in the Supplement), chlamydia (5 trials; n = 9296; RR, 0.97 [95% CI, 0.80-1.18]; I^2 = 59%) (eFigure 15 in the Supplement), or combined bacterial sexually transmitted infections (STIs) (2 trials; n = 5291; RR, 1.14 [95% CI, 0.97-1.34]; I^2 = 16%) (eFigure 16 in the Supplement).[10,21,43,63,65] All the trials except for 1 were blinded. The open-label trial,[43] which enrolled men who have sex with men, reported imprecise estimates for PrEP vs no PrEP that suggested increased risk of syphilis (RR, 1.28 [95% CI, 0.76-2.16]) and chlamydia (RR, 1.32 [95% CI, 0.98-1.79]); risk of gonorrhea was similar (RR, 1.07 [95% CI, 0.86-1.34]). PrEP was not associated with in-

creased risk of herpes simplex virus infection (3 trials; n = 4088; RR, 0.85 [95% CI, 0.67-1.07]; I^2 = 19%).[14,36,63]

No trial of PrEP enrolled pregnant persons. Among persons who became pregnant during the trials, PrEP was not associated with increased risk of spontaneous abortion (3 trials; n = 415, RR, 1.09 [95% CI, 0.79-1.50]; I^2 = 0%).[28,47,65] Two trials (n = 4706 and n = 2120) found no differences between PrEP vs placebo in risk of adverse pregnancy outcomes.[47]

Event-Driven vs Daily Oral PrEP

One small, new, crossover trial (n = 119) found event-driven oral PrEP associated with decreased risk of any adverse event vs daily oral PrEP (8% [10/119] vs 31% [37/119]; RR, 0.27 [95% CI, 0.14-0.52])[30] (eTables 1 and 2 in the Supplement). All adverse events were grade 1 except in 1 patient with grade 2 symptoms.

Harms of Newer PrEP Regimens

Key Question 5. What are the harms of newer PrEP regimens (oral TAF-FTC, or injectable cabotegravir) vs TDF-FTC?

Daily Oral TAF/FTC vs TDF/FTC

The DISCOVER trial (n = 5387)[42,54] found no difference between TAF/FTC vs TDF/FTC in risk of serious adverse events (7.5% vs 6.9%) or study drug discontinuation due to adverse events (1.5% vs 1.9%). Rates of any adverse event (94% vs 94%) were very similar (Table 2; eTables 1-4 in the Supplement). There were also no differences between TAF/FTC vs TDF/FTC in rates of any kidney adverse event (10% vs 10%), kidney adverse events leading to discontinuation (0.07% vs 0.2%), or fracture (2.2% vs 2.2%). Among persons 25 years or older, TAF/FTC was associated with greater percent change from baseline than TDF/FTC in hip (0.6% vs −1.0%, P < .001) and spine (0.9% vs −1.4%, P < .001) bone mineral density. TAF/FTC, compared with TDF/FTC, was associated with smaller reduction from baseline in low-density lipoprotein cholesterol levels (median, −0.05 vs −0.18 mmol/L; P < .001) and with greater weight gain from baseline (median, 1.7 vs 0.5 kg; P < .001).

Long-Acting Injectable Cabotegravir vs Daily Oral TDF/FTC

In HPTN 083 and 084 (n = 7786), long-acting injectable cabotegravir and daily oral TDF/FTC were associated with very similar risk of serious adverse events or grade 3 or higher adverse events (Table 2; eTables 1-4 in the Supplement).[6,7] There were also no differences in risk of grade 2 or 3 kidney or liver events, discontinuation due to liver-related adverse events, or STIs. In both trials, cabotegravir was associated with increased weight gain vs TDF/FTC (mean differences, 0.86 and 0.4 kg). Injection site reactions (most commonly, pain) were more frequent with cabotegravir than TDF/FTC (81.4% vs 31.3% and 38.0% vs 10.8%); the reactions were usually mild and occurred most commonly with the first injection. In the trial of cisgender women, no congenital abnormalities were observed in infants of those who became pregnant.[7]

Discussion

The findings in this evidence report are summarized in **Table 3**. As described in the 2019 USPSTF review,[2,3] oral PrEP with tenofovir disoproxil fumarate alone or TDF/FTC was associated with decreased risk of acquiring HIV infection compared with placebo or no PrEP; effectiveness increased with higher adherence. Findings were robust in subgroup and stratified analyses based on HIV risk category, study duration, study quality, age, and sex. Evidence in persons who inject drugs remains limited to 1 trial[17] conducted in Thailand, in which most patients received directly observed therapy; all trials of persons at risk via heterosexual contact were conducted in Africa. Although effects on HIV infection risk appeared similar for tenofovir disoproxil fumarate alone and TDF/FTC, tenofovir disoproxil fumarate is not approved by the FDA for use as PrEP and is no longer recommended as an alternative regimen.[69] No randomized trial enrolled adolescents, but in 2018 TDF/FTC was approved by the FDA for PrEP in adolescents weighing at least 35 kg (77.2 lb), based on it having a similar safety profile in this age group compared with adults.[70] No trial reported effects of PrEP on quality of life, including anxiety or worry about getting HIV.[71-73]

Compared with placebo or no PrEP, taking PrEP was associated with increased risk of gastrointestinal and kidney adverse events. However, most events were mild and decreased over time or resolved, with or without PrEP cessation. PrEP was associated with a statistically nonsignificant increase in risk of fracture that was heavily weighted by a trial enrolling persons who inject drugs,[17] with findings limited by relatively short-term follow-up (up to 4 years). There was no association between PrEP and increased risk of bacterial STIs, based primarily on blinded trials.[10,21,43,63,65]

A large new trial found oral daily TAF/FTC to be noninferior to TDF/FTC for incident HIV infection in primarily men who have sex with men (2% transgender women), and potentially associated with increased efficacy.[42,54] TAF/FTC was associated with positive short-term effects on bone mineral density and negative effects on lipid parameters and weight gain, without differences in clinical adverse events, which require longer-term study. TAF/FTC has not been studied in women at risk for acquiring HIV infection from receptive vaginal sex and is not approved in this population.[69]

Alternative PrEP regimens that do not require daily administration could improve utilization and adherence. In 2 new trials, long-acting injectable cabotegravir was associated with greater reduction in risk of HIV infection than oral TDF/FTC in men who have sex with men and transgender women[6] and in African women at increased risk of HIV infection.[7] Cabotegravir was associated with weight gain (<1 kg) and increased risk of injection site reactions that were usually mild and decreased after the initial injection.

Data on effects of PrEP in pregnancy remains limited. Trials excluded pregnant persons and discontinued PrEP in persons who became pregnant, although available evidence suggests no increased risk of adverse pregnancy outcomes among trial participants who became pregnant while taking PrEP.[28,47,65] FDA labeling information and perinatal antiretroviral treatment guidelines permit use of TDF/FTC during pregnancy (pregnancy category B).[69] Evidence on safety of cabotegravir for PrEP during pregnancy is very sparse, although 1 trial[7] reported no congenital abnormalities in infants with in utero exposure to PrEP.

For predicting incident HIV infection, which could help inform decisions regarding eligibility for PrEP, several instruments in men who have sex with men[25,44,58,59,64] and 2 instruments in general populations of HIV-uninfected persons[29,37] were associated with moderate to high discrimination. Both studies of instruments for general populations of HIV-infected persons applied automated algorithms to data extracted from electronic medical records. All instruments

Table 3. Summary of Evidence

PrEP type	No. of studies (No. of participants[a])	Summary of findings by outcome	Consistency/precision/ reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ1: Benefits of PrEP							
Oral PrEP with TDF/FTC or tenofovir disoproxil fumarate alone vs placebo or no PrEP	HIV infection: 12 RCTs (n = 18 244) All RCTs in prior USPSTF review	11 Trials; RR, 0.46 (95% CI, 0.33-0.66); I^2 = 67% ARD, −2.0% (95% CI, −2.8% to −1.2%) after 4 mo to 4 y Stratified by adherence (P < .001 for interaction): Adherence ≥70%: 6 trials; RR, 0.27 (95% CI, 0.19-0.39); I^2 = 0% Adherence >40% to <70%: 3 trials; RR, 0.51 (95% CI, 0.38-0.70); I^2 = 0% Adherence ≤40%: 2 trials; RR, 0.93 (95% CI, 0.72-1.20); I^2 = 0%	Some inconsistency explained by level of adherence; precise Funnel plot asymmetry and Egger test statistically significant (P = .03), but no unpublished studies identified	Good	Variability in duration of follow-up, although 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 nonprofit funding on estimates	High for benefit of oral PrEP	All trials evaluated daily oral PrEP with tenofovir disoproxil fumarate alone or TDF/FTC, except for 1 trial of event-driven PrEP with TDF/FTC Studies of women and men at increased risk via heterosexual contact conducted in Africa; the only study of persons who inject drugs was conducted in Asia; several studies of men who have sex with men were conducted in the US, Europe, and Canada PrEP was more effective in trials conducted in the US, Europe, and Canada (all of these trials reported high adherence and enrolled men who have sex with men)
	Mortality: 9 RCTs (n = 17 744) All RCTs in prior USPSTF review	RR, 0.81 (95% CI, 0.59-1.11); I^2 = 0%	Consistent; imprecise No reporting bias detected	Good	See body of evidence limitations for KQ1, HIV infection Trials not designed to assess mortality and results were heavily weighted (73%) by a single trial of PrEP in persons who inject drugs conducted in Thailand	Low for benefit of oral PrEP	See applicability for KQ1, HIV infection
	Quality of life: 0 studies	NA	NA	NA	NA	NA	NA
Dapivirine vaginal ring vs placebo	HIV infection: 2 RCTs (n = 4564) Both RCTs added for update	RR, 0.71 (95% CI, 0.57-0.89); I^2 = 0% ARD, −2.23% (95% CI, −3.75% to −0.74%) after 1.4 y to 1.6 y	Consistent and precise No reporting bias detected	Good	Relatively short duration of follow-up	High for benefit of dapivirine vaginal ring	Dapivirine vaginal ring not FDA-approved and withdrawn from FDA review Trials were conducted in women at increased risk of HIV infection in Africa
1a: Benefits of PrEP in populations of interest	HIV infection: 12 RCTs (n = 18 244) All RCTs in prior USPSTF review	Stratified by risk category (P = .43 for interaction): Men who have sex with men: 4 trials; RR, 0.23 (95% CI, 0.08-0.62); I^2 = 64% Persons who inject drugs: 1 trial: RR, 0.52 (95% CI, 0.29-0.92) Heterosexual contact: 5 trials; RR, 0.54 (95% CI, 0.31-0.97); I^2 = 82% No differences in within-study subgroup analyses on age (4 trials) or sex (3 trials)	Some inconsistency within risk category subgroups; precise No reporting bias detected	Good	See body of evidence limitations for KQ1, HIV infection	Moderate for benefit of oral PrEP in populations of interest	Studies of women and men at increased risk via heterosexual contact conducted in Africa; the only study of persons who inject drugs conducted in Asia; several studies of men who have sex with men conducted in the US, Europe, and Canada

(continued)

Table 3. Summary of Evidence (continued)

PrEP type	No. of studies (No. of participants[a])	Summary of findings by outcome	Consistency/precision/ reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
1b: Benefits of oral PrEP by dosing strategy or regimen	HIV infection: 12 RCTs of PrEP vs placebo or no PrEP (n = 18 172); 1 RCT of daily vs intermittent or event-driven PrEP (n = 535); 1 RCT of daily vs event-driven PrEP (n = 119) 1 New study of daily vs event-driven PrEP; otherwise, all other studies in prior USPSTF review	PrEP vs placebo or no PrEP Stratified by tenofovir disoproxil fumarate alone or TDF/FTC (P = .65 for interaction): Tenofovir disoproxil fumarate alone: 5 trials; RR, 0.49 (95% CI, 0.28-0.84); I^2 = 58% TDF/FTC: 8 trials; RR, 0.44 (95% CI, 0.27-0.72); I^2 = 74% Stratified by daily or on-demand dosing (P = .13 for interaction): Daily dosing: 9 trials; RR, 0.47 (95% CI, 0.32-0.71); I^2 = 75% On-demand dosing: 1 trial; RR, 0.14 (95% CI, 0.03-0.63) One head-to-head trial found no difference between daily vs intermittent or on-demand PrEP and 1 head-to-head trial of daily vs event-driven PrEP were not powered to assess effects on HIV acquisition and reported few cases	Some inconsistency in stratified analyses (may be explained by level of adherence); precise for tenofovir disoproxil fumarate alone vs TDF/FTC; imprecise for daily vs event-driven PrEP No reporting bias detected	Fair	See body of evidence limitations for KQ1, HIV infection	High for tenofovir disoproxil fumarate alone vs TDF/FTC; moderate for daily vs event-driven PrEP	Five trials evaluated tenofovir disoproxil fumarate alone, which is not approved for PrEP in the US One trial evaluated event-driven PrEP vs placebo and 2 trials evaluated daily vs event-driven or intermittent PrEP in men who have sex with men; no studies on event-driven or intermittent dosing in women or persons who inject drugs
KQ2: Benefits of newer vs older PrEP regimens							
Oral TAF/FTC vs TDF/FTC	HIV infection: 1 new RCT (n = 5387)	TAF/FTC vs TDF/FTC: 1 trial, 0.3% vs 0.6%; RR, 0.53 (95% CI, 0.23-1.26); results within prespecified noninferiority margin	Unable to assess consistency (1 trial); some imprecision No reporting bias detected	Good	Single trial	Moderate for noninferiority of TAF/FTC (with potential benefit)	Trial was conducted in cisgender adult men and transgender women who have sex with men in Europe and North America
Long-acting injectable cabotegravir vs daily oral TDF/FTC	HIV infection: 2 new RCTs (n = 7744)	Cabotegravir vs TDF/FTC: 1 Trial in men who have sex with men and transgender women (n = 4490): 0.6% vs 1.7%; RR, 0.33 (95% CI, 0.18-0.62) 1 Trial in women (n = 3178): 0.3% vs 2.3%; RR, 0.11 (95% CI, 0.04-0.31)	Consistent; precise No reporting bias detected	Good	Single trials conducted in different populations; both trials stopped early for meeting prespecified efficacy threshold	High for reduced risk with cabotegravir	One trial conducted in men who have sex with men and transgender men in the US, Latin America, Asia, and Africa and 1 trial conducted in women at increased risk of HIV infection in Africa Cabotegravir has been FDA approved for PrEP to prevent sexually acquired HIV infection

(continued)

Table 3. Summary of Evidence (continued)

PrEP type	No. of studies (No. of participants[a])	Summary of findings by outcome	Consistency/precision/ reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ3: Diagnostic accuracy of instruments for identifying persons at risk of incident HIV infection							
	12 Studies of risk prediction or diagnostic accuracy (n = 5 544 500) 7 Studies in prior USPSTF review and 5 studies added	Men who have sex with men: 5 studies (n = 25 488 in validation cohorts); AUROC, 0.60-0.73 for different instruments in 5 studies; a sixth study reported better goodness of fit than with instruments evaluated in other studies (AUROC, NR) AUROC, 0.49-0.75 for different instruments in 2 studies of Black men who have sex with men Persons who inject drugs: AUROC, 0.72 in 1 study (n = 1904) Women: sensitivity, 95% (21 cases) General populations: AUROC, 0.77 and 0.84 in 2 studies (n = 33 404 and 606 701 in validation cohorts)	Consistent; precise (for men who have sex with men and general populations of HIV-uninfected persons) No reporting bias detected	Fair	Retrospective design; some instruments validated in 1 study or not validated in a cohort independent from the one used to develop the instrument; cutoffs not predefined in some studies	Moderate for men who have sex with men and general populations; low for persons who inject drugs and women	All studies conducted in the US; some studies used cohorts that included persons who underwent HIV testing prior to year 2000

(continued)

Table 3. Summary of Evidence (continued)

PrEP type	No. of studies (No. of participants[a])	Summary of findings by outcome	Consistency/precision/ reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
KQ4: Harms of PrEP							
Oral PrEP vs placebo	Serious adverse events: 12 RCTs (n = 18 282) All RCTs in prior USPSTF review	RR, 0.93 (95% CI, 0.77-1.12); I^2 = 56%	Some inconsistency; some imprecision No reporting bias detected	Good	Small number of serious adverse events in most trials Composite outcome, some trials had limited details on serious adverse events	Moderate for no difference	See applicability for KQ1, oral PrEP vs placebo
	Withdrawals due to adverse events: 4 RCTs (n = 10 563) All RCTs in prior USPSTF review	RR, 1.25 (95% CI, 0.99-1.59); I^2 = 0%	Consistent; some imprecision No reporting bias detected, but most trials did not report withdrawals due to adverse events	Good	Most trials did not report withdrawals due to adverse events Composite outcome, with variability in cause of withdrawal (clinical or laboratory adverse event) and whether adverse event temporary or permanent	Moderate for increased risk with oral PrEP	See applicability for KQ1, oral PrEP vs placebo
	Kidney adverse events: 12 RCTs (n = 18 170) All RCTs in prior USPSTF review	RR, 1.43 (95% CI, 1.18-1.75); I^2 = 0% ARD, 0.56% (95% CI, 0.09%-1.04%)	Consistent; precise No reporting bias detected	Good	Variability in definition of adverse kidney events (most trials defined as ≥1 grade 1 elevations in serum creatinine level)	High for increased risk with oral PrEP	See applicability for KQ1, oral PrEP vs placebo Most events were mild and reversible
	Gastrointestinal adverse events: 12 RCTs (n = 18 300) All RCTs in prior USPSTF review	RR, 1.63 (95% CI, 1.26-2.11); I^2 = 43% ARD, 1.95% (95% CI, 0.48%-3.43%)	Some inconsistency; precise No reporting bias detected	Good	Composite outcome, with no difference for specific gastrointestinal adverse events	High for increased risk with oral PrEP	See applicability for KQ1, oral PrEP vs placebo Most events were mild and reversible
	Fracture: 7 RCTs (n = 15 241) All RCTs in prior USPSTF review	RR, 1.23 (95% CI, 0.97-1.56); I^2 = 0%	Consistent; precise No reporting bias detected	Moderate	Limited details on fracture site; most fractures traumatic in studies that provided this information Results heavily weighted by 1 trial	Low for increased risk with oral PrEP	See applicability for KQ1, oral PrEP vs placebo
	Syphilis: 4 RCTs (n = 10 775) All RCTs in prior USPSTF review	RR, 1.08 (95% CI, 0.98-1.18); I^2 = 0%	Consistent; precise No reporting bias detected, but NR in most trials	Good	Most trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP	Moderate for no difference	See applicability for KQ1, oral PrEP vs placebo
	Gonorrhea: 5 RCTs (n = 9296) All RCTs in prior USPSTF review	RR, 1.07 (95% CI, 0.82-1.39); I^2 = 49%	Some inconsistency; some imprecision No reporting bias detected, but NR in most trials	Good	Most trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP	Moderate for no difference	See applicability for KQ1, oral PrEP vs placebo
	Chlamydia: 5 RCTs (n = 9296) All RCTs in prior USPSTF review	RR, 0.97 (95% CI, 0.80-1.18); I^2 = 59%	Consistent; precise No reporting bias detected, but NR in most trials	Good	Most trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP	Moderate for no difference	See applicability for KQ1, oral PrEP vs placebo
	Combined bacterial STIs: 2 RCTs (n = 5291) All RCTs in prior USPSTF review	RR, 1.14 (95% CI, 0.97-1.34); I^2 = 0%	Consistent; some imprecision No reporting bias detected, but NR in most trials	Good	Most trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP	Moderate for no difference	See applicability for KQ1, oral PrEP vs placebo
	Herpes simplex virus infection: 3 RCTs (n = 4088) All RCTs in prior USPSTF review	RR, 0.85 (95% CI, 0.67-1.07); I^2 = 19%	Some inconsistency; some imprecision No reporting bias detected, but NR in most trials	Good	Trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP	Moderate for no difference	See applicability for KQ1, oral PrEP vs placebo
	Hepatitis C virus infection: 2 RCTs (n = 896) All RCTs in prior USPSTF review	RR, 0.73 (95% CI, 0.25-2.10); I^2 = 0%	Some inconsistency; imprecise No reporting bias detected, but NR in most trials	Good	One trial was blinded, which might affect behaviors differently than when patients know they are receiving PrEP	Low for decreased risk with oral PrEP	See applicability for KQ1, oral PrEP vs placebo
	Spontaneous abortion[b]: 3 RCTs (n = 415) All RCTs in prior USPSTF review	RR, 1.09 (95% CI, 0.79-1.50); I^2 = 0%	Consistent; some imprecision No reporting bias detected	Good	Analysis restricted to women who became pregnant in trials of PrEP and who discontinued PrEP	Moderate for no difference	Analyses of women at high risk of HIV acquisition via heterosexual contact who discontinued PrEP at time of pregnancy

(continued)

Table 3. Summary of Evidence (continued)

PrEP type	No. of studies (No. of participants[a])	Summary of findings by outcome	Consistency/precision/ reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
Dapivirine vaginal ring vs placebo	Serious adverse events: 2 RCTs (n = 4587) Both RCTs added for update	RR, 1.73 (95% CI, 0.60-4.94); I^2 = 80%	Inconsistent; very imprecise No reporting bias detected	Good	Substantial heterogeneity; events varied widely and did not appear related to PrEP	Insufficient	See applicability for KQ2, dapivirine vs placebo
	Syphilis: 1 RCT (n = 1959) Added for update	1.3% vs 0.8%	Unable to assess consistency; some imprecision No reporting bias detected	Good	Trial was blinded, which might affect behaviors differently than when patients know they are receiving PrEP	Low for similar risk	See applicability for KQ1, oral PrEP vs placebo
	Gonorrhea: 2 RCTs (n = 4587) Both RCTs added for update	RR, 1.01 (95% CI, 0.80-1.27); I^2 = 63%	Some inconsistency; precise No reporting bias detected	Good	Trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP	Moderate for no difference	See applicability for KQ1, oral PrEP vs placebo
	Chlamydia: 2 RCTs (n = 4587) Both RCTs added for update	RR, 0.98 (95% CI, 0.89-1.07); I^2 = 0%	Consistent; precise No reporting bias detected	Good	Trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP	High for no difference	See applicability for KQ1, oral PrEP vs placebo
	Any STI: 1 RCT (n = 1959) Added for update	RR, 1.06 (95% CI, 0.96-1.16)	Unable to assess consistency; precise No reporting bias detected	Good	Trial was blinded, which might affect behaviors differently than when patients know they are receiving PrEP	Moderate for no difference	See applicability for KQ1, oral PrEP vs placebo
	Pregnancy: 2 RCTs (n = 4587) Both RCTs added for update	3.9 vs 4.0 per 100 person-years and 1.6 vs 2.0 per 100 person-years	Consistent, precise No reporting bias detected	Good	Trial was blinded, which might affect behaviors differently than when patients know they are receiving PrEP	High for no difference	See applicability for KQ1, oral PrEP vs placebo
KQ5: Harms of PrEP							
TAF/FTC vs TDF/FTC	Serious adverse events, discontinuation due to adverse events, or any adverse event: 1 new RCT (n = 5387)	Serious adverse events: 7% vs 7% Discontinuation due to adverse events: 1% vs 2% Any adverse event: 94% vs 94%	Unable to assess consistency; some imprecision No reporting bias detected	Good	Adverse events varied and most did not appear related to PrEP	Moderate for no difference	See applicability for KQ2, TAF/FTC vs TDF/FTC
	Kidney adverse events: 1 new RCT (n = 5387)	Any kidney adverse event: 10% vs 10% Kidney adverse event leading to discontinuation: 0.07% vs 0.2%	Unable to assess consistency; some imprecision No reporting bias detected	Good	Adverse events leading to discontinuation rare	Moderate for no difference	See applicability for KQ2, TAF/FTC vs TDF/FTC
	Fracture, bone mineral density: 1 new RCT (n = 5387)	Fracture: 2% vs 2% Hip bone mineral density (change from baseline): 0.6% vs −1.0% (P < .001) Spine bone mineral density (change from baseline): 0.9% vs −1.4% (P < .001)	Unable to assess consistency; precise No reporting bias detected	Good	Duration may be insufficient to evaluate fracture risk	Moderate for increased bone mineral density with TAF/FTC	See applicability for KQ2, TAF/FTC vs TDF/FTC
	Lipid parameters, weight gain: 1 new RCT (n = 5387)	Low-density lipoprotein cholesterol (change from baseline): median, −0.05 vs −0.18 mmol/L (P < .001) Weight gain (change from baseline): median, 1.7 vs 0.5 kg (P < .001)	Unable to assess consistency; precise No reporting bias detected	Good	No additional limitations noted	Moderate for negative effects of lipids and weight gain with TAF/FTC	See applicability for KQ2, TAF/FTC vs TDF/FTC Clinical significance of differences uncertain

(continued)

Table 3. Summary of Evidence (continued)

PrEP type	No. of studies (No. of participants[a])	Summary of findings by outcome	Consistency/precision/ reporting bias	Overall quality	Body of evidence limitations	Strength of evidence	Applicability
Injectable cabotegravir vs oral TDF/FTC	Serious adverse events: 2 new RCTs (n = 7786)	5.3% vs 5.3% and 2.0% vs 2.0%	Consistent; precise No reporting bias detected	Good	No additional limitations noted	High for no difference	See applicability for KQ1, cabotegravir vs TDF/FTC
	Kidney events, liver events, STIs: 2 new RCTs (n = 7786)	No differences in kidney events, liver events, or STIs	Consistent; precise No reporting bias detected	Good	Trial was blinded, which might affect sexual risk behaviors differently than when patients know they are receiving PrEP	High for no difference	See applicability for KQ1, cabotegravir vs TDF/FTC
	Weight gain: 2 new RCTs (n = 7786)	Mean differences, 0.86 kg and 0.4 kg	Consistent; precise No reporting bias detected	Good	No additional limitations noted	High for increased weight gain with cabotegravir	See applicability for KQ1, cabotegravir vs TDF/FTC
	Injection site reactions: 2 new RCTs (n = 7786)	81.4% vs 31.3% and 38.0% vs 10.8%	Consistent; precise No reporting bias detected	Good	No additional limitations noted	High for increased risk with cabotegravir	See applicability for KQ1, cabotegravir vs TDF/FTC Injection site reactions were usually mild and occurred most commonly with the first injection, with diminishing frequency over time
	Pregnancy: 1 new RCT (n = 3178)	1.5 vs 1.0 per 100 person-years	Unable to assess consistency; some imprecision No reporting bias detected	Good	No additional limitations noted	Moderate for similar risk	See applicability for KQ1, cabotegravir vs TDF/FTC One trial evaluated pregnancy incidence among women in Africa

Abbreviations: ARD, adjusted risk difference; AUROC, area under the receiver operating characteristics curve; FDA, US Food and Drug Administration; KQ, key question; NA, not applicable; NR, not reported; OR, odds ratio; PrEP, preexposure prophylaxis; RCT, randomized clinical trial; RR, relative risk; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide fumarate/emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; USPSTF, US Preventive Services Task Force.

[a] For KQ1 and KQ5, number of participants included in analysis.

[b] In women who became pregnant while taking PrEP.

require further validation. Evidence on risk prediction instruments in persons who inject drugs[60] and cisgender women[57] is limited to single studies with important limitations.

Research is needed to clarify whether TAF/FTC is superior to TDF/FTC for preventing HIV infection; to determine whether short-term differences between newer vs older PrEP regimens in intermediate outcomes (weight gain, lipid parameters, or bone mineral density) are associated with differences in long-term clinical outcomes; to determine whether TAF/FTC is effective in populations other than men who have sex with men; to clarify long-term outcomes of long-acting injectable cabotegravir, including the incidence and clinical consequences of integrase strand transfer inhibitor resistance variants; to confirm the safety and effectiveness of PrEP during pregnancy and in gender-nonconforming persons; and to further validate incident HIV risk prediction instruments.

Limitations

This review had some limitations. First, the DerSimonian and Laird random-effects model was used to pool studies, which may result in overly precise confidence intervals when heterogeneity is present.[74] However, repeated analyses using the profile likelihood method resulted in similar findings. Second, non–English-language articles were excluded; however, large non-English PrEP trials were not identified. Third, the findings were based on analyses of study-level data, limiting the ability to evaluate subgroup effects. Fourth, in the pooled analysis of HIV infection, a statistical test indicated small sample effects, potentially indicating publication bias. However, no unpublished PrEP trials were identified in searches of a clinical trials registry (ClinicalTrials.gov).

Conclusions

In adults at increased HIV acquisition risk, oral PrEP was associated with decreased risk of acquiring HIV infection compared with placebo or no PrEP. Oral TAF/FTC was noninferior to oral TDF/FTC, and injectable cabotegravir reduced the risk of HIV infection compared with oral TDF/FTC in the populations studied.

ARTICLE INFORMATION

Accepted for Publication: June 6, 2023.

Correction: This article was corrected on October 23, 2023, for incorrect data in the text, Tables 1-3, and Supplement.

Author Contributions: Dr Chou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Chou.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Chou, Bougatsos, Ahmed.
Critical revision of the manuscript for important intellectual content: Chou, Spencer, Blazina, Selph.
Statistical analysis: Chou, Selph.
Obtained funding: Chou, Bougatsos.
Administrative, technical, or material support: Spencer, Bougatsos, Blazina.
Supervision: Chou, Bougatsos.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was funded under AHRQ contract 75Q80 120D00006, Task Order 75Q80121F32009, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, under a contract to support the USPSTF.

Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

Additional Contributions: We gratefully acknowledge the AHRQ medical officer (Howard Tracer, MD). The USPSTF members, expert consultants, peer reviewers, and federal partner reviewers did not receive financial compensation for their contributions.

Additional Information: A draft version of this evidence report underwent external peer review from 5 content experts (Susan Buchbinder, MD [HIV Prevention Research, San Francisco Department of Public Health; Departments of Medicine and Epidemiology and Biostatistics, University of California San Francisco]; Jessica Haberer, MD, MS [Global Health Research, Massachusetts General Hospital; Harvard Medical School]; Sybil Hosek, PhD [Stroger Hospital of Cook County; Division of Infectious Diseases, Rush University]; Douglas Krakower, MD [Division of Infectious Diseases at Beth Israel Deaconess Medical Center; The Fenway Institute; Departments of Medicine and Population Medicine, Harvard Medical School]; and 1 anonymous reviewer) and 5 federal partner reviewers from the Centers for Disease Control and Prevention, National Institutes of Health Sexual & Gender Minority Research Office, National Institute of Allergy and Infectious Diseases, and National Institute of Child Health and Human Development. Comments from reviewers were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF recommendation statement. It did not undergo additional review after submission to *JAMA*.

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