JAMA | US Preventive Services Task Force | EVIDENCE REPORT

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

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IMPORTANCE Effective prevention strategies for HIV infection are an important public health priority. Preexposure prophylaxis (PrEP) involves use of antiretroviral therapy (ART) daily or before and after sex to decrease risk of acquiring HIV infection.

OBJECTIVE To synthesize the evidence on the benefits and harms of PrEP, instruments for predicting incident HIV infection, and PrEP adherence to inform the US Preventive Services Task Force.

DATA SOURCES Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and EMBASE through June 2018, with surveillance through January 2019.

STUDY SELECTION English-language placebo-controlled randomized clinical trials of oral PrEP with tenofovir disoproxil fumarate/emtricitabine or tenofovir disoproxil fumarate monotherapy; studies on the diagnostic accuracy of instruments for predicting incident HIV infection; and studies on PrEP adherence.

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 for effects of PrEP on HIV infection, mortality, and harms.

MAIN OUTCOMES AND MEASURES HIV acquisition, mortality, and harms; adherence to PrEP; and diagnostic test accuracy and discrimination.

RESULTS Fourteen RCTs (N = 18 837), 8 observational studies (N = 3884), and 7 studies of diagnostic accuracy (N = 32 279) were included. PrEP was associated with decreased risk of HIV infection vs placebo or no PrEP after 4 months to 4 years (11 trials; relative risk [RR], 0.46 [95% CI, 0.33-0.66]; I^2 = 67%; absolute risk reduction [ARD], −2.0% [95% CI, −2.8% to −1.2%]). Greater adherence was associated with greater efficacy (RR with adherence ≥70%, 0.27 [95% CI, 0.19-0.39]; I^2 = 0%) in 6 trials. PrEP was associated with an increased risk of renal adverse events (12 trials; RR, 1.43 [95% CI, 1.18-1.75]; I^2 = 0%; ARD, 0.56% [95% CI, 0.09%-1.04%]) and gastrointestinal adverse events (12 trials; RR, 1.63 [95% CI, 1.26-2.11]; I^2 = 43%; ARD, 1.95% [95% CI, 0.48%-3.43%]); most adverse events were mild and reversible. Instruments for predicting incident HIV infection had moderate discrimination (area under the receiver operating characteristic curve, 0.49-0.72) and require further validation. Adherence to PrEP in the United States in men who have sex with men varied widely (22%-90%).

CONCLUSIONS AND RELEVANCE In adults at increased risk of HIV infection, PrEP with oral tenofovir disoproxil fumarate monotherapy or tenofovir disoproxil fumarate/emtricitabine was associated with decreased risk of acquiring HIV infection compared with placebo or no PrEP, although effectiveness decreased with suboptimal adherence.

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Preexposure prophylaxis (PrEP) involves use of antiretroviral therapy regularly (eg, daily) or before and after possible HIV exposure events such as sex ("on-demand" or "event-driven") to decrease risk of acquiring HIV infection. The purpose of this report was to synthesize the evidence on effects of PrEP on HIV acquisition risk, mortality, harms, and other clinical outcomes; effects of adherence on PrEP-associated outcomes; and accuracy of methods for identifying potential candidates for PrEP. It was used by the United States Preventive Services Task Force (USPSTF) to develop a new recommendation on PrEP for the prevention of HIV infection.

Methods

Scope of the Review

Detailed methods are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/prevention-of-human-immunodeficiency-virus-hiv-infection-pre-exposure-prophylaxis. **Figure 1** shows the analytic framework and key questions (KQs) that guided the review. The full report also includes contextual questions (not systematically reviewed) that addressed factors associated with PrEP adherence and rates of antiretroviral drug–resistant HIV in PrEP-treated individuals.

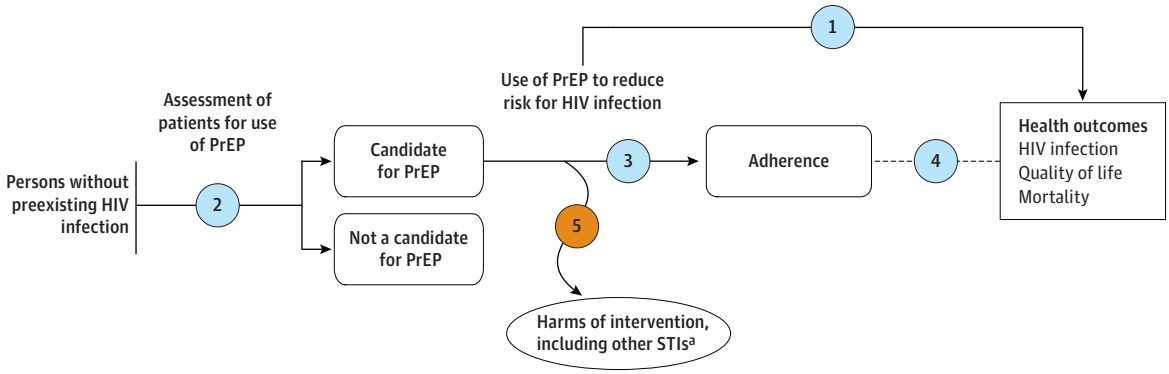
Data Sources and Searches

Ovid MEDLINE, the Cochrane Library, and EMBASE were searched for English-language articles published from inception through June 2018 (eMethods 1 in the Supplement). Searches were supplemented by review of reference lists of included studies. Since June 2018, 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 January 25, 2019, and identified no eligible randomized trials.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria. Randomized

Figure 1. Analytic Framework: HIV Preexposure Prophylaxis



Key questions

1. What are the benefits of PrEP in individuals without preexisting HIV infection vs placebo or no 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 US 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 vs placebo or no PrEP when used for the prevention of HIV infection?

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 indicates a health outcome that immediately follows an intermediate outcome. Refer to the USPSTF Procedure Manual for further details.[1] PrEP indicates preexposure prophylaxis; STI, sexually transmitted infection.

[a] Also includes renal insufficiency, fractures, pregnancy-related outcomes, infection with antiretroviral drug–resistant HIV, gastrointestinal harms, headaches, and discontinuation due to adverse events.

clinical trials (RCTs) of PrEP vs placebo or no PrEP in HIV-uninfected adults and adolescents (13-18 years) at higher risk for acquiring HIV were eligible for KQ1 and KQ5. Trials had to evaluate oral combination tenofovir disoproxil fumarate/emtricitabine or tenofovir disoproxil fumarate monotherapy and report HIV infection, mortality, quality of life, or harms. Tenofovir disoproxil fumarate/emtricitabine is the only medication approved by the US Food and Drug Administration (FDA) and recommended for PrEP; tenofovir disoproxil fumarate monotherapy is an alternate regimen for people who inject drugs (PWID) and in persons at risk because of heterosexual behavior.[2] Studies of the diagnostic accuracy of instruments to predict HIV acquisition in the United States or US-applicable settings were eligible for KQ2. United States–based RCTs and observational studies of PrEP implementation that reported adherence were eligible for KQ3 and KQ4.[3,4]

Data Abstraction and Quality Rating

For each included study, 1 investigator abstracted information on populations, interventions or screening instruments, comparators, adherence, outcomes, study designs, and settings. A second investigator reviewed abstracted information for accuracy. Two independent investigators assessed the quality of each study as good, fair, or poor using predefined criteria developed by the USPSTF (eMethods 2 in the Supplement). Quality ratings for individual studies are provided in eTables 1-3 in the Supplement.

For all KQs, the overall strength of the body of evidence was assessed as high, moderate, low, or insufficient using methods developed for the USPSTF, based on the overall quality of studies, consistency of results between studies, precision of findings, and risk of reporting bias.[1] The applicability of the findings to US primary care populations and settings was also assessed.

Data Synthesis

Meta-analysis was conducted to calculate pooled relative risks (RRs) for effects of PrEP vs placebo or no PrEP on HIV infection, mortality, and harms, using the DerSimonian and Laird random-effects model in Review Manager Version 5.3 (Cochrane Collaboration Nordic Cochrane Centre). Statistical heterogeneity was assessed using the I^2 statistic.[5] When I^2 was greater than 30%, the analysis was also performed with the profile likelihood method using Stata/IC Version 13.1 (StataCorp).[6] Results using the profile likelihood method were similar to those from the DerSimonian and Laird model and are not reported in this article. Sensitivity analyses and stratified analyses were conducted on study quality, PrEP regimen, HIV risk category, dosing schedule, study duration, and country. Stratified analyses were assessed for interactions using a test for heterogeneity across subgroups.

Sensitivity analyses were also conducted using data from the FDA medical review of PrEP[7] on HIV incidence and fracture rates in place of data reported in journal articles when there were discrepancies. Results were very similar, and this article presents findings based on journal article data. Study-level adherence was assessed as a categorical variable in a stratified analysis (≥70%, >40% to <70%, or ≤40%)[8] and as a continuous variable through meta-regression, and a plot of adherence against effectiveness (log RR) was constructed. For trials that used multiple adherence measurement methods, adherence data were selected using a prioritized list.[9] For analyses with at least 10 trials, funnel plots were constructed and the Egger test conducted for small sample effects.[10]

All significance testing was 2-tailed; *P* values of .05 or less were considered statistically significant.

Results

Across all KQs, 14 RCTs (in 37 articles[11-47]) (N = 18 837), 8 observational studies[48-55] (N = 3884), and 7 studies of diagnostic accuracy of HIV risk prediction instruments[56-62] (N = 32 279) were included (**Figure 2**). The main results for each key question are summarized below.

Benefits of PrEP

Key Question 1. What are the benefits of PrEP in individuals without preexisting HIV infection vs placebo or no PrEP on the prevention of HIV infection and quality of life?

Key Question 1a. How do the benefits of PrEP differ by population subgroups?

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

Twelve RCTs (reported in 33 publications[11-44]) evaluated PrEP vs placebo (11 trials[12,14,17,18,21,27,33,39,40,42,43]) or immediate vs delayed PrEP (1 trial[31]) (**Table 1**; eTables 4-6 in the Supplement). The trials enrolled between 72 and 4726 participants (total n = 18 244). The mean age in all trials was younger than 40 years. No trial enrolled pregnant women or people younger than 18 years. Duration of follow-up ranged from 4 months to 4 years.

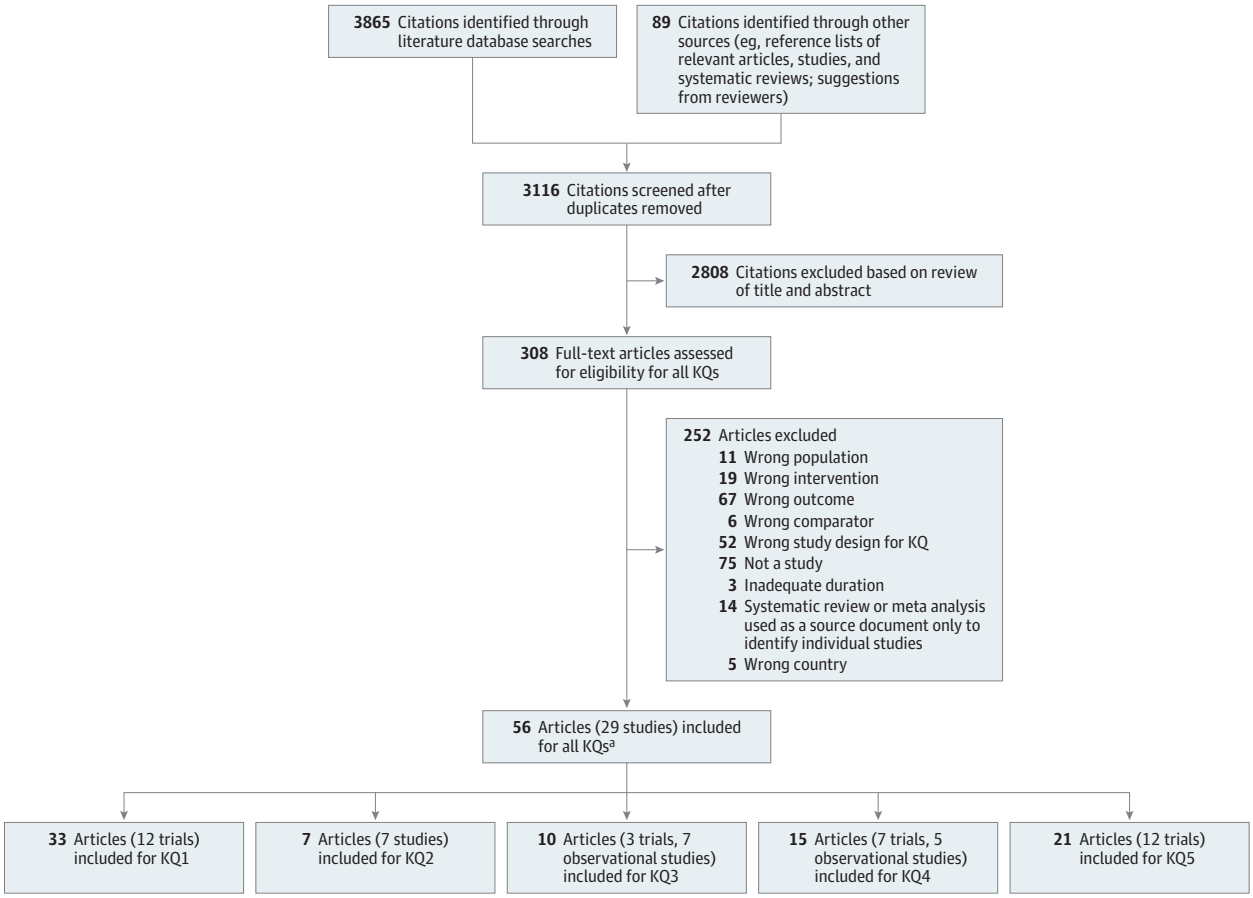
All trials enrolled persons at increased risk for HIV infection. Six trials[12,21,27,40,42,43] enrolled persons at increased risk because of heterosexual contact, 4 trials[17,18,31,33] men who have sex with men or transgender women, 1 trial[39] high-risk women and men who have sex with men, and 1 trial[14] PWID. All trials of persons at increased risk because of heterosexual contact were conducted in Africa and the trial of PWID was conducted in Thailand; all trials conducted in the United States, Canada, and Europe focused on men who have sex with men.

Five trials[12,14,18,27,40] evaluated tenofovir disoproxil fumarate monotherapy (300 mg), 8 trials[12,17,21,27,33,39,42,43] tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg), and 1 trial[31] tenofovir disoproxil fumarate (245 mg)/emtricitabine (200 mg). Eleven trials evaluated daily PrEP.[12,14,17,18,21,27,31,39,40,42,43] Dosing was intermittent or event-driven in 3 trials,[21,33,39] but only 1 reported results for event-driven (before and after sex) PrEP.[33] In the other 2 trials, there were no HIV infections or results were combined with daily PrEP.[21,39] In all trials, all patients received HIV risk reduction and adherence counseling. All trials provided free condoms, except for 1 trial[31] that did not require it.

The adherence level, method for measuring adherence, and funding source of each trial are reported in Table 1. All trials were rated good quality except for 1 trial[31] rated fair quality because of unclear allocation concealment methods and open-label design.

PrEP was associated with reduced risk of HIV infection vs placebo or no PrEP (11 trials [n = 18 172]; RR, 0.46 [95% CI, 0.33-0.66]), but statistical heterogeneity was present (I^2 = 67%) (**Figure 3**).[12,14,17,18,27,31,33,39,40,42,43] The absolute risk difference (ARD) was −2.0% (95% CI, −2.8% to −1.2%). Estimates were very similar

Figure 2. Literature Search Flow Diagram: HIV Preexposure Prophylaxis



KQ indicates key question.

[a] Some articles are included in multiple KQs. Twenty-two articles addressed the contextual questions in the larger Agency for Healthcare Research and Quality report, of which 19 overlap with the articles that addressed KQs.

(P = .79 for interaction) for PrEP with tenofovir disoproxil fumarate monotherapy (5 trials [n = 7546]; RR, 0.49 [95% CI, 0.28-0.84]; I^2 = 58%)[12,14,18,27,40] or tenofovir disoproxil fumarate/emtricitabine (8 trials [n = 10 626]; RR, 0.44 [95% CI, 0.27-0.72]; I^2 = 74%).[12,17,27,31,33,39,42,43] Funnel plot asymmetry was present (P = .03 by Egger test) (eFigure 1 in the Supplement).

A stratified analysis found a significant interaction (P < .001) between level of adherence (≤40%, >40 to <70%, or ≥70%) and effectiveness of PrEP; stratification by adherence eliminated statistical heterogeneity (**Table 2**, **Figure 4**). In 6 trials (n = 7328) with adherence 70% or greater, the RR was 0.27 (95% CI, 0.19-0.39; I^2 = 0%).[12,18,31,33,39,42] There was also a strong association between effectiveness and adherence analyzed as a continuous variable (P < .001) (eFigure 2 in the Supplement), which accounted for all of the between-study heterogeneity. Findings were similar when analyses were restricted to trials that evaluated adherence based on plasma levels.

PrEP was effective across HIV risk categories (persons at risk because of heterosexual contact, men who have sex with men, or PWID; P = .43 for interaction) (Table 2). Four trials[12,14,17,43] found similar PrEP effectiveness in subgroups defined by age, and 3 trials[12,14,42] found similar effectiveness in male and female participants (eTable 7 in the Supplement). Few trials examined the interaction between presence of risk behaviors and effectiveness of PrEP, the risk behaviors examined in these trials varied (receptive anal intercourse, condomless sex, drug injection or needle sharing), and effectiveness of PrEP did not consistently vary according to presence of risk behaviors.[12,14,17]

Estimates were similar when trials were stratified according to duration of follow-up, when the analysis was restricted to good-quality trials, or when trials were stratified according to whether they reported some industry support (usually donated study drugs) (Table 2). The estimate from 1 trial (n = 400) of event-driven PrEP (RR, 0.14 [95% CI, 0.03-0.63]) was similar to the pooled estimate from daily-dosing trials that reported high adherence (5 trials [n = 6928]; RR, 0.28 [95% CI, 0.20-0.41]).[12,18,31,39,42] In this trial, men who have sex with men randomized to PrEP took a median of about 4 doses of PrEP per week (15 doses per month) based on pill counts. PrEP was more effective in trials conducted in the United States, Europe, or Canada (3 trials [n = 1323]; RR, 0.13 [95% CI, 0.05-0.32]; I^2 = 0%)[18,31,33] than in trials conducted in Africa, Asia,

Table 1. Study Characteristics of RCTs of PrEP

Source[a]	Country	Duration of Follow-up	Interventions[b]	HIV Risk Group; Risk-Based Inclusion Criteria	Patient Characteristics	Adherence, % (Method Used to Assess Adherence	Quality	Funding
Bangkok Tenofovir Study Choopanya et al,[14] 2013	Thailand	4 y (mean)	A. Tenofovir disoproxil fumarate (300 mg) (n = 1204) B. Placebo (n = 1209)	PWID: Injection drug use in the previous 12 mo	A vs B: Age 20-29 y: 43% vs 43% Age 30-39 y: 38% vs 37% Age 40-49 y: 15% vs 15% Age 50-60 y: 5% vs 5% Men: 80% vs 80% Race: NR	67 (plasma)	Good	CDC; Bangkok Metropolitan Administration
CDC Safety Study Grohskopf et al,[18] 2013	United States	2 y	A. Tenofovir disoproxil fumarate (300 mg) (n = 201) B. Placebo (n = 199)	MSM: Biological male engaging in anal sex with another man in the previous 12 mo	A vs B: Mean age: 38 vs 37 y 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)	Good	US Department of Health and Human Services; CDC
FEM PrEP Van Damme et al,[43] 2012	Kenya, South Africa, Tanzania	1 y	A. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 1062) B. Placebo (n = 1058)	High-risk women: >1 vaginal sex act in previous 2 wk or >1 sex partner in previous mo	A vs B: Mean age: 24 vs 24 y Race: NR	37 (plasma)	Good	USAID; Bill and Melinda Gates Foundation; Gilead Sciences (provided study drug)
IAVI Uganda Study Kibengo et al,[21] 2013	Uganda	4 mo	A. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 24) B. Intermittent tenofovir disoproxil fumarate/emtricitabine (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 mo	A vs B vs C vs D: Mean age: 33 vs 33 vs 33 vs 33 y Women: 50% vs 46% vs 67% vs 42% Race: NR	98 (MEMS)	Good	IAVI; Gilead Sciences (provided study drug)
IAVI Kenya Study Mutua et al,[39] 2012	Kenya	4 mo	A. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 24) B. Intermittent tenofovir disoproxil fumarate/emtricitabine (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 mo	A vs B vs C vs D: Mean age: 26 vs 26 vs 27 vs 28 y Women: 12% vs 0% vs 8% vs 8% Race: NR	82 (MEMS)	Good	IAVI; Gilead Sciences (provided study drug)
IPERGAY Molina et al,[33] 2015	France, Canada	9 mo (median)	A. On-demand tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 199) B. Placebo (n = 201)	MSM: Unprotected anal sex with ≥2 partners in previous 6 mo	A vs B: Median age: 35 vs 34 y (IQR, 29-43) White: 94% vs 89% Other races: NR	86 (plasma)	Good	ANRS; Canadian HIV Trials Network; Fonds de Dotation Pierre Berge pour la Prevention; Bill and Melinda Gates Foundation
iPrEx Grant et al,[17] 2010	Brazil, Ecuador, Peru, Thailand, South Africa, United States	1.2 y (median)	A. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 1251) B. Placebo (n = 1248)	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 previous 6 mo	A vs B: Age 18-24 y: 47% vs 53% Age 25-29 y: 22% vs 19% Age 30-39 y: 20% vs 18% Age ≥40 y: 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)	Good	NIH; Bill and Melinda Gates Foundation

(continued)

Table 1. Study Characteristics of RCTs of PrEP (continued)

Source[a]	Country	Duration of Follow-up	Interventions[b]	HIV Risk Group; Risk-Based Inclusion Criteria	Patient Characteristics	Adherence, % (Method Used to Assess Adherence	Quality	Funding
Partners PrEP Baeten et al,[12] 2012	Kenya, Uganda	2 y (median)	A. Tenofovir disoproxil fumarate (300 mg) + placebo tenofovir disoproxil fumarate/emtricitabine (n = 1571) B. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) + placebo tenofovir disoproxil fumarate (n = 1565) C. Placebo tenofovir disoproxil fumarate + placebo tenofovir disoproxil fumarate/emtricitabine (n = 1570)	High-risk heterosexual men and women: ART-naive HIV-infected partner	A vs B vs C: Age 18-24 y: 12% vs 11% vs 11% Age 25-34 y: 46% vs 44% vs 43% Age 35-44 y: 30% vs 32% vs 32% Age ≥45 y: 13% vs 14% vs 13% Men: 62% vs 64% vs 61% Race: NR	82 (plasma)	Good	Bill and Melinda Gates Foundation
PROUD McCormack et al,[31] 2016	England	1 y	A. Immediate tenofovir disoproxil fumarate/emtricitabine (245/200 mg) (n = 275) B. Tenofovir disoproxil fumarate/emtricitabine deferred for 1 y (n = 269)	MSM: Anal intercourse without a condom in the previous 90 d and likely to have anal intercourse without a condom in the next 90 d	A vs B Mean age: 35 vs 35 y White: 81% vs 83% Asian: 5% vs 6% Black: 4% vs 4% Other race: 10% vs 8%	100 (plasma)[c]	Fair	Medical Research Counsel Clinical Trials Unit; Public Health England; Gilead Sciences
Study of TDF Peterson et al,[40] 2007	Cameroon, Ghana, Nigeria	6 mo (mean)	A. Tenofovir disoproxil fumarate (300 mg) (n = 469) B. Placebo (n = 467)	High-risk women: Mean of ≥3 coital acts per wk and ≥4 sexual partners per mo	A vs B: Mean age: 24 vs 24 y Race: NR	69 (pill count)	Good	Bill and Melinda Gates Foundation
TDF2 Thigpen et al,[42] 2012	Botswana	1 y (median)	A. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 611) B. Placebo (n = 608)	High-risk heterosexual men and women: Sexually active in high-prevalence area	A vs B: Age 18-20 y: 2% vs 3% Age 21-29 y: 90% vs 87% Age 30-39 y: 8% vs 10% Women: 46% vs 46% Race: NR	80 (plasma)	Good	Division of HIV/AIDS Prevention, CDC, and Division of AIDS, NIH; 1 investigator reported royalties from Roche and 1 reported funding from Gilead
VOICE Marrazzo et al,[27] 2015	South Africa, Uganda, Zimbabwe	3 y (maximum)	A. Tenofovir disoproxil fumarate (300 mg) + placebo (n = 1007) B. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) + placebo (n = 1003) C. Placebo only (n = 1009)	High-risk women: Sexually active in a high-prevalence area	A vs B vs C: Mean age: 26 vs 25 vs 25 y Race: NR	30 (plasma)	Good	NIH

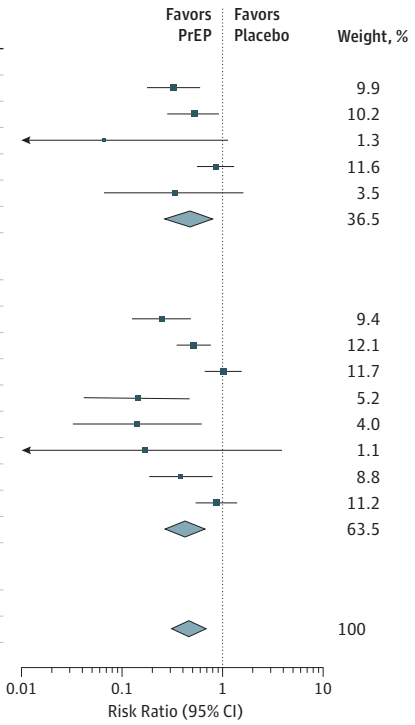
Abbreviations: ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; FEM-PrEP, PRe-Exposure Prophylaxis trial for HIV Prevention Among African Women; IAVI, International AIDS Vaccine Initiative; IPERGAY, Intervention Préventive de l'Exposition aux Risques avec et pour les GAYs; iPrEx, Pre-Exposure Prophylaxis Initiative; MEMS, medication event monitoring system; MSM, men who have sex with men; NIH, National Institutes of Health; NR, not reported; PrEP, preexposure prophylaxis; PROUD, PRe-exposure Option for Reducing HIV in the UK: immediate or Deferred; PWID, people who inject drugs; STI, sexually transmitted infection; TDF2, Tenofovir Disoproxil Fumarate 2 study; USAID, United States Agency for International Development; VOICE, Vaginal and Oral Interventions to Control the Epidemic.

[a] Primary publication; details on all included publications appear in full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/prevention-of-human-immunodeficiency-virus-hiv-infection-pre-exposure-prophylaxis.

[b] Daily, oral dose unless specified.

[c] Sample of patient who reported that they were taking PrEP.

Figure 3. Meta-analysis: HIV Infection Stratified by Study Drug



Source	No. of Events/Total PrEP	Placebo	Risk Ratio (95% CI)	Weight, %
Tenofovir disoproxil fumarate				
Baeten et al,[12] 2012[a]	17/1572	26/793	0.33 (0.18-0.60)	9.9
Choopanya et al,[14] 2013	17/1204	33/1207	0.52 (0.29-0.92)	10.2
Grohskopf et al,[18] 2013[b]	0/201	7/199	0.07 (0.00-1.15)	1.3
Marrazzo et al,[27] 2015[a]	52/1007	30/504	0.87 (0.56-1.34)	11.6
Peterson et al,[40] 2007	2/427	6/432	0.34 (0.07-1.66)	3.5
Subtotal	88/4411	12/3135	0.49 (0.28-0.84)	36.5
I^2 = 58%; χ^2_4 = 9.50 for heterogeneity, P = .05; τ^2 = 0.19 Overall effect: z = 2.60, P = .009				
Tenofovir disoproxil fumarate/emtricitabine				
Baeten et al,[12] 2012[c]	13/1568	26/793	0.25 (0.13-0.49)	9.4
Grant et al,[17] 2010	38/1251	72/1248	0.53 (0.36-0.77)	12.1
Marrazzo et al,[27] 2015[c]	61/1003	30/505	1.02 (0.67-1.56)	11.7
McCormack et al,[31] 2016[b]	3/268	20/255	0.14 (0.04-0.47)	5.2
Molina et al,[33] 2015[b]	2/199	14/201	0.14 (0.03-0.63)	4.0
Mutua et al,[39] 2012	0/48	1/24	0.17 (0.01-4.03)	1.1
Thigpen et al,[42] 2012	10/601	26/606	0.39 (0.19-0.80)	8.8
Van Damme et al,[43] 2012	31/1024	35/1032	0.89 (0.55-1.44)	11.2
Subtotal	158/5962	224/4664	0.44 (0.27-0.72)	63.5
I^2 = 74%; χ^2_7 = 27.08 for heterogeneity, P <.001; τ^2 = 0.30 Overall effect: z = 3.31, P <.001				
Overall				
Subtotal	246/10373	326/7799	0.46 (0.33-0.66)	100
I^2 = 67%; χ^2_{12} = 36.59 for heterogeneity, P <.001; τ^2 = 0.22 Overall effect: z = 4.34, P < .001 Subgroup differences: I^2 = 0%; χ^2_1 = 0.07 for heterogeneity, P = .79				

The area of each square represents the weight given to the study in the meta-analysis. The area of each diamond represents the sample size for each pooled estimate (subgroup or overall analysis), and the width of each diamond represents the confidence interval for the pooled estimate. The Mantel-Haenszel method was used the calculate the heterogeneity (I^2) test statistic. PrEP indicates preexposure prophylaxis; PWID, people who inject drugs.

[a] Tenofovir disoproxil fumarate group.

[b] Study conducted in the United States, Canada, or Europe.

[c] Tenofovir disoproxil fumarate/emtricitabine group.

or internationally (8 trials [n = 16 849]; RR, 0.54 [95% CI, 0.37-0.79]; I^2 = 72%; P = .004 for interaction).[12,14,17,21,27,39,40,42,43] All trials conducted in the United States, Europe, or Canada reported high adherence and enrolled men who have sex with men.

Associations of PrEP vs placebo or no PrEP with mortality did not meet the threshold for statistical significance (9 trials [n = 17 744]; RR, 0.81 [95% CI, 0.59-1.11]; I^2 = 0%).[12,14,17,18,27,31,40,42,43] Individual trials reported few mortality events and risk estimates were imprecise (eFigure 3 in the Supplement). No trial reported effects of PrEP on quality of life.

Diagnostic Accuracy of Risk Assessment Tools

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?

Seven studies evaluated instruments developed and validated in US cohorts for predicting incident HIV infection[56-62] (eTables 8-9 in the Supplement). Six studies evaluated men who have sex with men[56-59,61,62] and 1 study evaluated PWID.[60] Sample sizes (including development and validation cohorts) ranged from 300 to 9481 patients (total n = 32 311). Methodological shortcomings included application of risk instruments to previously collected data, evaluation of older (before 2000) cohorts,[58-60] failure to validate accuracy in a separate (nondevelopment) cohort,[56,60] and failure to predefine positive test thresholds.[56-60]

For men who have sex with men, studies evaluated the predictive utility of 4 different instruments (number of criteria ranged from 4 to 10). For 3 instruments (n = 20 064), discrimination was similar, with area under the receiver operating characteristic (AUROC) curves in the original validation cohorts ranging from 0.66 to 0.72.[57-59] A fourth study (n = 9481)[56] found a 10-item instrument associated with better goodness of fit than 2 of these instruments[58,59] but did not report AUROC values and did not validate findings in a separate (nondevelopment) sample. The initial development and validation cohorts used to develop these instruments primarily consisted of white men who have sex with men. Two subsequent studies (n = 862) reported poorer discrimination in black men who have sex with men, with AUROC values ranging from 0.49 to 0.63.[61,62]

A 7-item instrument for predicting risk in PWID reported an AUROC value of 0.72 (CI not reported) in a cohort of 1904 primarily (93%) black participants.[60] This instrument was not evaluated in a separate validation cohort.

No study evaluated a US-applicable instrument for predicting risk of HIV infection in persons at risk of HIV infection due to heterosexual contact. Instruments for predicting risk in women were developed using African cohorts.[63-65]

Table 2. Risk of HIV Infection in Randomized Clinical Trials of PrEP vs Placebo or No PrEP

	No. of Trials	RR (95% CI)	I^2, %
All trials	11[12,14,17,18,27,31,33,39,40,42,43]	0.46 (0.33-0.66)	67
Restricted to good-quality trials	10[12,14,17,18,27,33,39,40,42,43]	0.48 (0.33-0.71)	71
PrEP drug regimen (*P* = .79 for interaction)			
Tenofovir disoproxil fumarate	5[12,14,18,27,40]	0.49 (0.28-0.84)	58
Tenofovir disoproxil fumarate/emtricitabine	8[12,17,27,31,33,39,40,43]	0.44 (0.27-0.72)	67
Adherence, % (*P* < .001 for interaction)			
≥70	6[12,18,31,33,39,42]	0.27 (0.19-0.39)	0
>40 to <70	3[14,17,40]	0.51 (0.38-0.70)	0
≤40	2[27,43]	0.93 (0.72-1.20)	0
HIV risk category (*P* = .43 for interaction)			
Heterosexual men and women	5[12,27,40,42,43]	0.54 (0.31-0.97)	82
Men who have sex with men	4[17,18,31,33]	0.23 (0.08-0.62)	64
People who inject drugs	1[14]	0.52 (0.29-0.92)	NA
Dosing schedule (*P* = .13 for interaction)			
Daily	9[12,14,17,18,27,31,39,40,42,43]	0.47 (0.32-0.71)	75
On-demand	1[33]	0.14 (0.03-0.63)	NA
Duration of follow-up, y (*P* = .35 for interaction)			
<1	3[33,39,40]	0.21 (0.07-0.58)	0
≥1-2	4[17,31,42,43]	0.48 (0.28-0.84)	70
≥2	4[12,14,18,27]	0.47 (0.22-1.00)	86
Study-reported support (*P* = .38 for interaction)			
Industry	3[39,42,43]	0.58 (0.27-1.22)	5
Government or not-for-profit funding only	8[12,14,17,18,27,31,33,40]	0.39 (0.23-0.64)	77
Country setting (*P* = .004 for interaction)			
United States or other high-income countries	3[18,31,33]	0.13 (0.05-0.32)	0
Africa, Asia, or international trial	8[12,14,17,27,39,40,42,43]	0.54 (0.37-0.79)	72

Abbreviations: NA, not applicable; PrEP, preexposure prophylaxis; RR, relative risk.

PrEP Adherence

Key Question 3. What are rates of adherence to PrEP in US primary care–applicable settings?

Ten studies evaluated rates of adherence to PrEP in US primary care and primary care–applicable settings (eTable 10 in the Supplement).[18,46-50,52-55] The studies enrolled between 20 and 1086 study participants (total n = 3177), and duration of PrEP use ranged from 6 months to 2 years. One study was rated good quality[18] and the others were rated fair quality.

Three observational studies of US men who have sex with men (mean age, 34-36 years; n = 908) found adherence to PrEP of 66% to 90%, based on a tenofovir diphosphate level of 700 fmol/punch or greater on dried blood sampling (consistent with ≥4 doses/wk).[52-54] Using the same measure, 2 observational studies of younger US men who have sex with men (mean age, 16-20 years; n = 272) found adherence to PrEP of approximately 50% at 12 weeks and 22% to 34% at 48 weeks.[49,50] An RCT (n = 179) of primarily (97%) US men who have sex with men found adherence was higher with daily (48%) than with intermittent (31%) or event-driven (17%) PrEP during weeks in which sex was reported.[46] No study evaluated PrEP adherence rates in US PWID or persons at increased risk of HIV infection due to heterosexual contact.

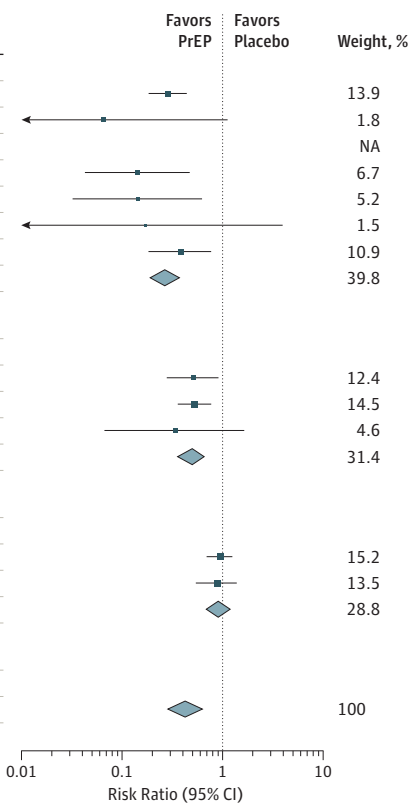
Key Question 4. What is the association between adherence to PrEP and effectiveness for preventing HIV acquisition?

Three RCTs (n = 5591) found PrEP associated with greater effectiveness compared with placebo for reducing risk of HIV infection among participants having higher adherence to daily PrEP based on daily pill counts or daily diaries, compared with particpants having lower adherence (eTable 11 in the Supplement).[12,14,16,17,29] Four of 5 RCTs (n = 6013) 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.[12,14,16,27,29,42,43] Five studies (n = 1138)[33,49,50,52,54] found that all participants with seroconversion receiving PrEP had undetectable plasma levels of tenofovir or levels consistent with low adherence. The number of participants with seroconversion in each study was small (1 to 4 patients per study).

Harms of PrEP

Key Question 5. What are the harms of PrEP vs placebo or no PrEP when used for the prevention of HIV infection?

Figure 4. Meta-analysis: HIV Infection Stratified by Adherence



Source	No. of Events/Total PrEP	Placebo	Risk Ratio (95% CI)	Weight, %
Adherence ≥70%				
Baeten et al,[12] 2012	30/3140	52/1586	0.29 (0.19-0.45)	13.9
Grohskopf et al,[18] 2013[a,b]	0/201	7/199	0.07 (0.00-1.15)	1.8
Kibengo et al,[21] 2013[b]	0/48	0/24	NA[c]	NA
McCormack et al,[31] 2016[a,d]	3/268	20/255	0.14 (0.04-0.47)	6.7
Molina et al,[33] 2015[a]	2/199	14/201	0.14 (0.03-0.63)	5.2
Mutua et al,[39] 2012[a,b]	0/48	1/24	0.17 (0.01-4.03)	1.5
Thigpen et al,[42] 2012[e]	10/601	26/606	0.39 (0.19-0.80)	10.9
Subtotal	45/4505	120/2895	0.27 (0.19-0.39)	39.8
I^2 = 0%; χ^2_5 = 3.98 for heterogeneity, P = .55; τ^2 = 0.00 Overall effect: z = 7.33, P < .001				
Adherence >40% to <70%				
Choopanya et al,[14] 2013	17/1204	33/1207	0.52 (0.29-0.92)	12.4
Grant et al,[17] 2010	38/1251	72/1248	0.53 (0.36-0.77)	14.5
Peterson et al,[40] 2007	2/427	6/432	0.34 (0.07-1.66)	4.6
Subtotal	57/2882	111/2887	0.51 (0.38-0.70)	31.4
I^2 = 0%; χ^2_2 = 0.28 for heterogeneity, P = .87; τ^2 = 0.00 Overall effect: z = 4.14, P < .001				
Adherence ≤40%				
Marrazzo et al,[27] 2015	113/2010	60/1009	0.95 (0.70-1.28)	15.2
Van Damme et al,[43] 2012	31/1024	35/1032	0.89 (0.55-1.44)	13.5
Subtotal	144/3034	95/2041	0.93 (0.72-1.20)	28.8
I^2 = 0%; χ^2_1 = 0.04 for heterogeneity, P = .84; τ^2 = 0.00 Overall effect: z = 0.56, P = .58				
Overall				
Subtotal	246/10421	326/7823	0.44 (0.29-0.65)	100
I^2 = 72%; χ^2_{10} = 36.11 for heterogeneity, P < .001; τ^2 = 0.25 Overall effect: z = 4.04, P < .001 Subgroup differences: I^2 = 93.7%; χ^2_2 = 31.59 for heterogeneity, P < .001				

Adherence was based on plasma testing, unless otherwise noted. The area of each square represents the weight given to the study in the meta-analysis. The area of each diamond represents the sample size for each pooled estimate (subgroup or overall analysis), and the width of each diamond represents the confidence interval for the pooled estimate. The Mantel-Haenszel method was used the calculate the heterogeneity (I^2) test statistic. NA indicates not available; PrEP, preexposure prophylaxis.

[a] Study conducted in the United States, Canada, or Europe.

[b] Assessed using medication event monitoring system.

[c] Not estimable.

[d] Assessed by self-report, confirmed by plasma sample.

[e] Assessed by self-report.

There was no significant difference between PrEP vs placebo in risk of serious adverse events (12 trials [n = 18 282]; RR, 0.93 [95% CI, 0.77-1.12]; I^2 = 56%) (**Table 3**; eFigure 4 in the Supplement)[12,14,17,18,21,27,31,33,39,40,42,43] or withdrawal because of adverse events (4 trials [n = 9704]; RR, 1.25 [95% CI, 0.99-1.59]; I^2 = 0%) (eFigure 5 in the Supplement).[12,17,33,40]

PrEP was associated with increased risk vs placebo of renal adverse events (12 trials [n = 18 170]; RR, 1.43 [95% CI, 1.18-1.75]; I^2 = 0%; ARD, 0.56% [95% CI, 0.09%-1.04%]) (eFigure 6 in the Supplement)[12,14,17,18,21,27,31,33,39,40,42,43] 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 7 in the Supplement).[12,14,17,18,21,27,31,33,39,40,42,43] Renal abnormalities were primarily 1 or more grade-1 elevation of serum creatinine level and generally resolved following PrEP cessation[12,25,28,41] or with ongoing PrEP.[21,39] Three trials reported that the risk of gastrointestinal events diminished over time.[14,17,42] Serious renal and gastrointestinal events were rare. There was no significant difference between PrEP vs placebo in risk of fracture (7 trials [n = 15 241]; RR, 1.23 [95% CI, 0.97-1.56]; I^2 = 0%) (eFigure 8 in the Supplement).[12,14,17,18,27,33,42]

There were no significant differences between PrEP vs placebo or no PrEP in risk of gonorrhea, chlamydia, or syphilis (Table 3).[12,17,31,42,43] All of the trials except 1 were blinded, which could attenuate sexual risk behaviors associated with use of PrEP. One open-label trial (n = 544), which enrolled men who have sex with men, found no statistically significant associations between PrEP vs no PrEP and risk of bacterial sexually transmitted infections (STIs), although estimates for syphilis (RR, 1.28 [95% CI, 0.76-2.16]) and chlamydia (RR, 1.32 [95% CI, 0.98-1.79]) may have been underpowered.[31] There was no significant difference between PrEP vs placebo in risk of herpes simplex virus infection (3 trials [n = 4088]; RR, 0.85 [95% CI, 0.67-1.07]; I^2 = 19%)[26,42,66] or hepatitis C virus infection (2 trials [n = 896]; RR, 0.73 [95% CI, 0.25-2.10]; I^2 = 0%).[31,33]

No trial of PrEP enrolled pregnant women. In women withdrawn from PrEP trials because of pregnancy, PrEP was not associated with increased risk of spontaneous abortion (RR, 1.09 [95% CI, 0.79-1.50]; I^2 = 0%) (eFigure 9 in the Supplement).[21,34,43] The Partners PrEP trial (n = 4706) found no significant differences between PrEP vs placebo in pregnancy rate, risk of preterm birth, birth anomalies, or postpartum infant mortality, and the FEM-PrEP trial

Table 3. Adverse Events and Sexually Transmitted Infections in Randomized Clinical Trials of PrEP vs Placebo/No PrEP

Outcome	No. of Trials[a]	RR (95% CI)	I^2, %
Serious adverse events	12[12,14,17,18,21,27,31,33,39,40,42,43]	0.93 (0.77-1.12)	56
PrEP drug regimen (*P* = .23 for interaction)			
Tenofovir disoproxil fumarate	5[12,14,18,27,40]	0.79 (0.56-1.12)	72
Tenofovir disoproxil fumarate/emtricitabine	9[12,17,21,27,31,33,39,42,43]	1.02 (0.81-1.30)	46
Withdrawal due to adverse events	4[12,17,33,43]	1.25 (0.99-1.59)	0
PrEP drug regimen (*P* = .67 for interaction)			
Tenofovir disoproxil fumarate	1[12]	1.00 (0.34-2.92)	NA
Tenofovir disoproxil fumarate/emtricitabine	4[12,17,33,43]	1.27 (1.00-1.59)	0
Fracture	8[12,14,17,18,27,31,33,42]	1.23 (0.97-1.56)	0
PrEP drug regimen (*P* = .50 for interaction)			
Tenofovir disoproxil fumarate	4[12,14,18,27]	1.29 (0.98-1.70)	0
Tenofovir disoproxil fumarate/emtricitabine	6[12,17,27,31,33,42]	1.06 (0.66-1.72)	0
Renal adverse events	12[12,14,17,18,21,27,31,33,39,40,42,43]	1.43 (1.18-1.75)	0
PrEP drug regimen (*P* = .31 for interaction)			
Tenofovir disoproxil fumarate	5[12,14,18,27,40]	1.24 (0.87-1.76)	0
Tenofovir disoproxil fumarate/emtricitabine	9[12,17,21,27,31,33,39,42,43]	1.54 (1.21-1.96)	0
Gastrointestinal adverse events	12[12,14,17,18,21,27,31,33,39,40,42,43]	1.63 (1.26-2.11)	43
PrEP drug regimen (*P* = .30 for interaction)			
Tenofovir disoproxil fumarate	5[12,14,18,27,40]	1.45 (1.13-1.85)	0
Tenofovir disoproxil fumarate/emtricitabine	9[12,17,21,27,31,33,39,42,43]	1.84 (1.26-2.70)	49
Any bacterial sexually transmitted infection	2[12,31]	1.14 (0.97-1.34)	16
PrEP drug regimen (*P* = .60 for interaction)			
Tenofovir disoproxil fumarate	1[12]	1.21 (0.86-1.72)	NA
Tenofovir disoproxil fumarate/emtricitabine	2[12,31]	1.07 (0.80-1.44)	58
HIV risk category (*P* = .38 for interaction)			
Heterosexual men and women	1[12]	1.05 (0.82-1.35)	NA
MSM	1[31]	1.20 (1.01-1.42)	NA
Syphilis	4[12,17,27,31]	1.08 (0.98-1.18)	0
PrEP drug regimen (*P* = .86 for interaction)			
Tenofovir disoproxil fumarate	2[12,27]	1.13 (0.66-1.93)	0
Tenofovir disoproxil fumarate/emtricitabine	4[12,17,27,31]	1.07 (0.98-1.18)	0
HIV risk category (*P* = .90 for interaction)			
Heterosexual men and women	2[12,27]	1.05 (0.71-1.54)	0
MSM	2[17,31]	1.08 (0.98-1.18)	0
Gonorrhea	5[17,27,31,42,43]	1.07 (0.82-1.39)	49
PrEP drug regimen (*P* = .02)			
Tenofovir disoproxil fumarate	1[27]	0.57 (0.33-0.98)	NA
Tenofovir disoproxil fumarate/emtricitabine	5[17,27,31,42,43]	1.15 (0.97-1.37)	2
HIV risk category (*P* = .59 for interaction)			
Heterosexual men and women	3[27,42,43]	1.20 (0.76-1.92)	69
MSM	2[17,31]	1.05 (0.85-1.30)	0
Chlamydia	5[17,27,31,42,43]	0.97 (0.80-1.18)	59
PrEP drug regimen (*P* = .004 for interaction)			
Tenofovir disoproxil fumarate	1[27]	0.68 (0.52-0.90)	NA
Tenofovir disoproxil fumarate/emtricitabine	5[17,27,31,42,43]	1.07 (0.94-1.22)	0
HIV risk category (*P* = .46 for interaction)			
Heterosexual men and women	3[27,42,43]	0.81 (0.47-1.41)	93
MSM	2[17,31]	1.09 (0.62-1.92)	50

(continued)

Table 3. Adverse Events and Sexually Transmitted Infections in Randomized Clinical Trials of PrEP vs Placebo/No PrEP (continued)

Outcome	No. of Trials[a]	RR (95% CI)	I^2, %
Herpes simplex virus infection	3[26,42,66]	0.85 (0.67-1.07)	19
PrEP drug regimen (P = .67 for interaction)			
Tenofovir disoproxil fumarate	1[66]	0.76 (0.48-1.21)	NA
Tenofovir disoproxil fumarate/emtricitabine	3[26,42,66]	0.86 (0.62-1.18)	40
HIV risk category (P = .06 for interaction)			
Heterosexual men and women	2[42,66]	0.73 (0.56-0.96)	0
MSM	1[26]	1.12 (0.80-1.56)	NA
Hepatitis C virus infection[b]	2[31,33]	0.73 (0.25-2.10)	0

Abbreviations: MSM, men who have sex with men; PrEP, preexposure prophylaxis; RR, relative risk.

[a] Two trials included both tenofovir disoproxil fumarate and tenofovir disoproxil fumarate/emtricitabine groups.

[b] Both trials evaluated tenofovir disoproxil fumarate/emtricitabine in MSM.

(n = 2120) found no significant difference in risk of any adverse pregnancy outcome.[34]

For all adverse events, there was no statistically significant interaction between PrEP regimen and any adverse event except for gonorrhea and chlamydia infection (Table 3). However, for both of these adverse events there was only 1 trial of tenofovir disoproxil fumarate. There was no statistically significant interaction between HIV risk category and risk of STIs.

Discussion

The findings in this evidence report are summarized in **Table 4**. In populations at increased HIV infection risk, PrEP was associated with decreased risk of acquiring HIV infection that varies according to the level of adherence. In trials for which adherence was 70% or greater, the reduction in risk was approximately 75%, with a number needed to treat of approximately 33.[12,18,31,33,39,42] In studies of US men who have sex with men, adherence varied widely and was generally lower in younger (16-20 years) men who have sex with men.[49,50,52-54] Trials were not designed to assess effects of PrEP on mortality, and no trial reported effects on quality of life.

Event-driven or intermittent (nondaily) dosing strategies might improve adherence while maintaining effectiveness.[67] One trial found event-driven PrEP in men who have sex with men associated with substantially reduced risk of HIV infection vs no PrEP.[33] No study evaluated the effectiveness of intermittent or event-driven dosing in women or PWID, which may depend on the antiretroviral drugs used, how quickly and at what concentrations they accumulate at exposure sites (eg, genital vs rectal mucosa), and the correlation between tissue concentration and effectiveness.[68,69]

Findings were robust in subgroup and stratified analyses based on the PrEP drugs used (tenofovir disoproxil fumarate/emtricitabine [the only FDA-approved PrEP regimen] or tenofovir disoproxil fumarate monotherapy), HIV risk category, study duration, study quality, age, and sex. Evidence in PWID was limited to 1 Thai trial,[14] and all trials of persons at risk due to heterosexual contact were conducted in Africa. No randomized trial enrolled adolescents. In 2018, the FDA approved tenofovir disoproxil fumarate/emtricitabine for PrEP in adolescents who weigh 35 kg or more, based on safety data.[49]

Although PrEP was associated with increased risk of gastrointestinal and renal adverse events, most events appeared mild and reversible. There was no statistically significant association between PrEP and increased risk of fracture,[12,14,17,18,27,33,42] based on trials with relatively brief follow-up. Although there was no association between PrEP and increased risk of bacterial STIs,[12,17,31,42,43] most trials blinded patients to PrEP allocation, and sexual risk behaviors might differ in persons who know they are taking PrEP. A systematic review of an open-label RCT and nonrandomized studies found PrEP associated with an increased risk of rectal chlamydia (4 studies; odds ratio, 1.59 [95% CI, 1.19-2.13]) but found no association between PrEP and risk of chlamydia at any site, STIs overall, syphilis, or gonorrhea.[70] Individuals who engage in riskier behaviors may be more adherent to PrEP,[14,50,54] which could offset any adverse behavioral effects.

The findings of this review are generally consistent with those from other recent meta-analyses that found PrEP to be effective at reducing risk of HIV infection and found greater effectiveness in trials reporting higher adherence.[8,71,72] The findings are strengthened by the inclusion of recent large new trials, including the only trial of event-driven PrEP[33] and an open-label pragmatic trial.[31]

Data on effects on PrEP in pregnancy were very limited. Trials excluded pregnant women and discontinued PrEP at the time pregnancy was confirmed. FDA labeling information and perinatal antiretroviral treatment guidelines permit use of tenofovir disoproxil fumarate/emtricitabine during pregnancy, although guidelines note that data on safety of PrEP during pregnancy and lactation are limited.[73]

For predicting incident HIV infection, several instruments in men who have sex with men[56-59] and 1 instrument in PWID[60] were associated with moderate discrimination, but studies had methodological shortcomings. Discrimination was poorer in some studies of black men who have sex with men,[61,62] and all instruments require further validation. Instruments for predicting risk of HIV infection in women were developed using African cohorts.

Research is needed to directly compare effects of daily vs alternative PrEP dosing strategies in studies adequately powered to assess effects on HIV infection[45,46]; to verify the effectiveness of PrEP in high-income settings in persons at higher risk because of heterosexual contact and PWID; to determine the safety and effectiveness of PrEP during pregnancy or lactation and in transgender women and men; to understand effectiveness and long-term safety in adolescents; to understand effects of PrEP on quality of life; to understand effects of PrEP on behavioral risk compensation using open-label studies; to develop accurate instruments for identifying persons at higher risk for acquiring HIV infection; and to determine methods for increasing uptake and adherence to PrEP, to optimize effectiveness. Research on a number of alternative PrEP drugs and regimens is ongoing.[74-79]

Table 4. Summary of Evidence

No. of Studies; No. of Participants; Study Design[a]	Summary of Findings by Outcome	Consistency/Precision; Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ1: Benefits of PrEP vs Placebo or No PrEP						
HIV infection 12 RCTs (n = 18 244)	11 Trials: RR, 0.46 (95% CI, 0.33-0.66); I^2 = 67%; ARR, −2.0% (95% CI, −2.8% to −1.2%) after 4 mo to 4 y Stratified by adherence (P < .001 for interaction) ≥70% adherence: 6 trials; RR, 0.27 (95% CI, 0.19-0.39); I^2 = 0% >40% to <70% adherence: 3 trials; RR, 0.51 (95% CI, 0.38-0.70); I^2 = 0% ≤40% adherence: 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, but results consistent when trials stratified according to follow-up duration Three trials reported some industry support, but no significant difference between studies that only reported industry support and those that only reported governmental or not-for-profit funding	High	Studies of women and men at increased risk of heterosexual contact conducted in Africa; the only study of PWID was conducted in Asia; several studies of MSM were conducted in the United States, Europe, and Canada PrEP was more effective in trials conducted in the United States, Europe, and Canada (all of these trials reported high adherence and enrolled MSM)
Mortality 9 RCTs (n = 17 756)	RR, 0.81 (95% CI, 0.59-1.11); I^2 = 0%	Consistent; imprecise No reporting bias detected	Good	See Body of Evidence Limitations column for KQ1, HIV infection	Moderate	See Applicability column for KQ1, HIV infection
Quality of life 0	NA	NA	NA	NA	NA	NA
KQ1a: Benefits of PrEP by Population Subgroups						
HIV infection 12 RCTs (n = 18 244)	Stratified by risk category (P = .43 for interaction) MSM: 4 trials; RR, 0.23 (95% CI, 0.08-0.62); I^2 = 64% PWID: 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 significant differences in within-study subgroup analyses by age (4 trials) or sex (3 trials)	Some inconsistency within risk category subgroups; precise No reporting bias detected	Good	See Body of Evidence Limitations column for KQ1, HIV infection	Moderate	Studies of women and men at increased risk of heterosexual contact conducted in Africa; the only study of PWID conducted in Asia; several studies of MSM conducted in the United States, Europe, and Canada
KQ1b: Benefits of 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 on-demand PrEP (n = 535)	PrEP vs placebo or no PrEP: Stratified by tenofovir disoproxil fumarate or tenofovir disoproxil fumarate/emtricitabine (P = .65 for interaction) Tenofovir disoproxil fumarate: 5 trials; RR, 0.49 (95% CI, 0.28-0.84); I^2 = 58% Tenofovir disoproxil fumarate/emtricitabine: 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 significant 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 column for KQ1, HIV infection.	High for tenofovir disoproxil fumarate vs tenofovir disoproxil fumarate/emtricitabine, moderate for daily dosing vs on-demand dosing	Five trials evaluated tenofovir disoproxil fumarate monotherapy, which is not approved for PrEP in the United States One trial evaluated on-demand dosing of PrEP vs placebo in MSM; no studies on intermittent or on-demand dosing in women or PWID

(continued)

Table 4. Summary of Evidence (continued)

No. of Studies; No. of Participants; Study Design[a]	Summary of Findings by Outcome	Consistency/Precision; Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ2: Diagnostic Accuracy of Instruments for Identifying Individuals at Risk of Incident HIV Infection						
7 studies of risk prediction or diagnostic accuracy (n = 32 311)	MSM: AUROC 0.66-0.72 for different instruments in 3 studies; a fourth study reported better goodness of fit than with instruments evaluated in other studies (AUROC NR) AUROC 0.49-0.63 for different instruments in 2 studies of black MSM PWID: AUROC 0.72 in 1 study	Consistent; precise No reporting bias detected	Fair	Retrospective design; each instrument validated in 1 study or not validated in a cohort independent from the one used to develop the instrument; cutoffs not predefined in any study	Low	All studies conducted in the United States; 3 studies used cohorts that included individuals who underwent HIV testing before the year 2000; no study evaluated a US-applicable instrument for risk prediction in women
KQ3: Adherence to PrEP in US Primary Care–Applicable Settings						
3 RCTs and 7 observational studies (n = 3177)	In 5 studies of US MSM, adherence to PrEP (based on dried blood spot sampling levels consistent with ≥4 doses/wk) ranged from 22% to 90%; adherence rates were lower in studies of younger (mean age, 16-20 y) MSM One RCT of US MSM found higher adherence with daily than with 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 US MSM; no direct evidence on adherence in US PWID or women and men at increased risk of HIV infection because of 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						
7 RCTs and 5 observational studies (n = 11 479)	Three RCTs found higher adherence to PrEP associated with greater effectiveness for reducing risk of HIV infection than lower adherence Four of 5 RCTs found presence of tenofovir in plasma samples associated with decreased likelihood of HIV infection, compared with no detectable tenofovir (ORs ranged from 0.10-0.54)	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 with PrEP	High	Studies performed in diverse geographic settings; only 1 study evaluated PWID
KQ5: Harms of PrEP						
Serious adverse events 12 RCTs (n = 18 282)	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	See Applicability column for KQ1, HIV infection
Withdrawals resulting from adverse events 4 RCTs (n = 10 563)	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 resulting from adverse events	Good	Most trials did not report withdrawals resulting from 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 column for KQ1, HIV infection
Renal adverse events 12 RCTs (n = 18 170)	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 renal events (most trials defined as ≥1 grade 1 elevation of serum creatinine level)	High	See Applicability column for KQ1, HIV infection

(continued)

Table 4. Summary of Evidence (continued)

No. of Studies; No. of Participants; Study Design[a]	Summary of Findings by Outcome	Consistency/Precision; Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
Gastrointestinal adverse events 12 RCTs (n = 18 300)	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 significant difference for specific gastrointestinal adverse events	High	See Applicability column for KQ1, HIV infection
Fracture 7 RCTs (n = 15 241)	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 reported this information Results heavily weighted by 1 trial	Low	See Applicability column for KQ1, HIV infection
Syphilis 4 RCTs (n = 10 775)	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	See Applicability column for KQ1, HIV infection
Gonorrhea 5 RCTs (n = 9296)	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	See Applicability column for Q1, HIV infection
Chlamydia 5 RCTs (n = 9296)	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	See Applicability column for KQ1, HIV infection
Combined bacterial STIs 2 RCTs (n = 5291)	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	See Applicability column for KQ1, HIV infection
Herpes simplex virus infection 3 RCTs (n = 4103)	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	See Applicability column for KQ1, HIV infection
Hepatitis C virus infection 2 RCTs (n = 896)	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	See Applicability column for KQ1, HIV infection
Spontaneous abortion 3 RCTs (n = 485)[b]	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 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: ARD, adjusted risk difference; ARR, adjusted relative risk; AUROC, area under the receiver operating characteristics curve; EPC, Evidence-based Practice Center; KQ, key question, MSM, men who have sex with men; NA, not applicable; NR, not reported; OR, odds ratio; PrEP, preexposure prophylaxis; PWID, people who inject drugs; RCT, randomized clinical trial; RR, relative risk; STI, sexually transmitted infection.

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

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

Limitations

This review had some limitations. First, the DerSimonian and Laird random-effects model was used to pool studies, which may result in CIs that are too narrow, particularly when heterogeneity is present.[6] However, analyses were repeated using the profile likelihood method, which resulted in similar findings. Second, these findings are based on analyses of study-level data, limiting the ability to evaluate subgroup effects. Third, non–English-language articles were excluded, but large non–English-language trials of PrEP were not identified. Fourth, in the pooled analysis of HIV infection, graphical and statistical tests indicated small sample effects, a potential marker for publication bias. However, no unpublished PrEP trials were identified in searches on a clinical trials registry (ClinicalTrials.gov) or reviews of reference lists. Fifth, trials of PrEP in persons at risk because of heterosexual contact were conducted in Africa and 1 trial of PrEP in PWID was conducted in Asia, which could limit applicability to the United States and other high-income settings.

Conclusions

In adults at increased risk of HIV infection, PrEP with oral tenofovir disoproxil fumarate monotherapy or tenofovir disoproxil fumarate/emtricitabine was associated with decreased risk of HIV infection compared with placebo or no PrEP, although effectiveness decreased with suboptimal adherence.

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Concept and design: Chou, Korthuis.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Chou, Evans, Hoverman, Sun, Dana, Bougatsos, Grusing.
Critical revision of the manuscript for important intellectual content: Chou, Hoverman, Sun, Korthuis.
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Administrative, technical, or material support: Evans, Dana, Bougatsos, Grusing.
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