US Public Health Service

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014

A CLINICAL PRACTICE GUIDELINE

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Abbreviations (In Guideline and Provider Supplement)

ACTG	AIDS Clinical Trials Group
AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immunodeficiency syndrome
BMD	bone mineral density
CDC	Centers for Disease Control and Prevention
CPT	common procedural terminology
DEXA	dual-emission X-ray absorptiometry
DHAP	Division of HIV/AIDS Prevention, CDC
DHHS	Department of Health and Human Services
eCrCl	estimated creatinine clearance rate (ml/min)
EIA	enzyme-linked immunoassay
FDA	Food and Drug Administration
FHI	Family Health International
FTC	emtricitabine (trade name Emtriva)
GEM	Guidelines Elements Model
GLIA	GuideLine Implementability Appraisal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRSA	Health Resources and Services Administration
ICD	International Classification of Diseases
IDU	injection drug users (also called PWID)
IFA	indirect immunofluorescence assay
IHS	Indian Health Service
MSM	men who have sex with men
MTN	Microbicide Trials Network
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NGC	National Guidelines Clearinghouse
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
nPEP	nonoccupational postexposure prophylaxis
NSAID	non-steroidal anti-inflammatory drug
NQMC	National Quality Measures Clearinghouse
OHAP	Office of HIV/AIDS Policy, DHHS
ONAP	Office of National AIDS Policy
ONDCP	Office of National Drug Control Policy
OPA	Office of Population Affairs, DHHS
PCR	polymerase chain reaction

PEP	postexposure prophylaxis
PHS	(U.S.) Public Health Service
PWID	persons who inject drugs (also called IDU)
PrEP	preexposure prophylaxis
SAMHSA	Substance Abuse and Mental Health Services Administration
STD	sexually transmitted disease
STI	sexually transmitted infection
TB	tuberculosis
TDF	tenofovir disoproxil fumarate (trade nanme Viread®)
TDM	therapeutic drug monitoring
UNAIDS	Joint United National Programme on HIV/AIDS
VA	Veterans Administration
WHO	World Health Organization

Summary

Preexposure Prophylaxis for HIV Prevention in the United States - 2013: A Clinical Practice Guideline provides comprehensive information for the use of daily oral antiretroviral preexposure prophylaxis (PrEP) to reduce the risk of acquiring HIV infection in adults. The key messages of the guideline are as follows:

- Daily oral PrEP with the fixed-dose combination of tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg has been shown to be safe and effective in reducing the risk of sexual HIV acquisition in adults; therefore,
    - PrEP is recommended as one prevention option for sexually-active adult MSM (men who have sex with men) at substantial risk of HIV acquisition **(IA)**[1]
    - PrEP is recommended as one prevention option for adult heterosexually active men and women who are at substantial risk of HIV acquisition. **(IA)**
    - PrEP is recommended as one prevention option for adult injection drug users (IDU) at substantial risk of HIV acquisition. **(IA)**
    - PrEP should be discussed with heterosexually-active women and men whose partners are known to have HIV infection (i.e., HIV-discordant couples) as one of several options to protect the uninfected partner during conception and pregnancy so that an informed decision can be made in awareness of what is known and unknown about benefits and risks of PrEP for mother and fetus **(IIB)**
- Currently the data on the efficacy and safety of PrEP for adolescents are insufficient. Therefore, the risks and benefits of PrEP for adolescents should be weighed carefully in the context of local laws and regulations about autonomy in health care decision-making by minors. **(IIIB)**
- Acute and chronic HIV infection must be excluded by symptom history and HIV testing immediately before PrEP is prescribed. **(IA)**
- The only medication regimen approved by the Food and Drug Administration and recommended for PrEP with all the populations specified in this guideline is daily TDF 300 mg co-formulated with FTC 200 mg (Truvada) **(IA)**
    - TDF alone has shown substantial efficacy and safety in trials with IDUs and heterosexually active adults and can be considered as an alternative regimen for these populations, but not for MSM, among whom its efficacy has not been studied. **(IC)**
    - The use of other antiretroviral medications for PrEP, either in place of or in addition to TDF/FTC (or TDF) is not recommended. **(IIIA)**
    - The prescription of oral PrEP for coitally-timed or other noncontinuous daily use is not recommended. **(IIIA)**
- HIV infection should be assessed at least every 3 months while patients are taking PrEP so that those with incident infection do not continue taking it. The 2-drug regimen of TDF/FTC

[1] See Appendix 2, Grading of Strength of Recommendations and Quality of Evidence (Tables 13-14)

is inadequate therapy for established HIV infection, and its use may engender resistance to either or both drugs. **(IA)**

- Renal function should be assessed at baseline and monitored at least every 6 months while patients are taking PrEP so that those in whom renal failure is developing do not continue to take it. **(IIIA)**
- When PrEP is prescribed, clinicians should provide access, directly or by facilitated referral, to proven effective risk-reduction services. Because high medication adherence is critical to PrEP efficacy but was not uniformly achieved by trial participants, patients should be encouraged and enabled to use PrEP in combination with other effective prevention methods. (**IIIA**)

Table 1: Summary of Guidance for PrEP Use

<table>
<tr><th></th><th>Men Who Have Sex with Men</th><th>Heterosexual Women and Men</th><th>Injection Drug Users</th></tr>
<tr><td>Detecting substantial risk of acquiring HIV infection</td><td>HIV-positive sexual partner
Recent bacterial STI
High number of sex partners
History of inconsistent or no condom use
Commercial sex work</td><td>HIV-positive sexual partner
Recent bacterial STI
High number of sex partners
History of inconsistent or no condom use
Commercial sex work

In high-prevalence area or network</td><td>HIV-positive injecting partner
Sharing injection equipment
Recent drug treatment (but currently injecting)</td></tr>
<tr><td>Clinically eligible</td><td colspan="3">Documented negative HIV test result before prescribing PrEP
No signs/symptoms of acute HIV infection
Normal renal function; no contraindicated medications
Documented hepatitis B virus infection and vaccination status</td></tr>
<tr><td>Prescription</td><td colspan="3">Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90-day supply</td></tr>
<tr><td rowspan="2">Other services</td><td colspan="3">Follow-up visits at least every 3 months to provide the following:
HIV test, medication adherence counseling, behavioral risk reduction support,
side effect assessment, STI symptom assessment
At 3 months and every 6 months thereafter, assess renal function
Every 6 months, test for bacterial STIs</td></tr>
<tr><td>Do oral/rectal STI testing</td><td>Assess pregnancy intent
Pregnancy test every 3 months</td><td>Access to clean needles/syringes and drug treatment services</td></tr>
</table>

STI: sexually transmitted infection

Introduction

Recent findings from several clinical trials have demonstrated safety[1] and a substantial reduction in the rate of HIV acquisition for men who have sex with men (MSM)[2], men and women in heterosexual HIV-discordant couples[3], and heterosexual men and women recruited as individuals[4] who were prescribed daily oral antiretroviral preexposure prophylaxis (PrEP) with a fixed-dose combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). In addition, one clinical trial among injection drug users (IDU)[5] and one among men and women in heterosexual HIV-discordant couples[3] have demonstrated substantial efficacy and safety of daily oral PrEP with TDF alone. The demonstrated efficacy of PrEP was in addition to the effects of repeated condom provision, sexual risk-reduction counseling, and the diagnosis and treatment of sexually transmitted infection (STI), all of which were provided to trial participants, including those in the drug treatment group and those in the placebo group. In July 2012, after reviewing the available trial results, the U.S. Food and Drug Administration (FDA) approved an indication for the use of Truvada[†] (TDF/FC) "in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk"[6,7].

On the basis of these trial results and the FDA approval, the U.S. Public Health Service recommends that clinicians evaluate their male and female patients who are sexually active or who are injecting illicit drugs and consider offering PrEP as one prevention option to those whose sexual or injection behaviors and epidemiologic context place them at substantial risk of acquiring HIV infection.

The evidence base for these recommendations is derived from a systematic search and review of published literature. To identify all PrEP safety and efficacy trials pertaining to the prevention of sexual and injection acquisition of HIV, a search of the clinical trials registry (http://www.clinicaltrials.gov) was performed by using combinations search terms (preexposure prophylaxis, pre-exposure prophylaxis, PrEP, HIV, Truvada, tenofovir, and antiretroviral). In addition, the same search terms were used to search conference abstracts for major HIV conferences (e.g., International AIDS Conference, Conference on Retroviruses and Opportunistic Infections) for the years 2009-2013. These same search terms were used to search PubMed and Web of Science databases for the years 2006-2013. Finally, a review of references from published PrEP trial data and the data summary prepared by FDA for its approval decision[8] confirmed that no additional trial results were available.

This publication provides a comprehensive clinical practice guideline for the use of PrEP for the prevention of HIV infection in the United States. It incorporates and extends information provided in interim guidance for PrEP use with MSM[9], with heterosexually active adults[10], and with IDU (also called persons who injection drugs [PWID])[11]. Currently, prescribing daily oral

[†] Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

PrEP with TDF/FTC is recommended as one prevention option for MSM, heterosexual men, heterosexual women, and IDU at substantial risk of HIV acquisition. As the results of additional PrEP clinical trials and studies in these and other populations at risk of HIV acquisition become known, this guideline will be updated.

The intended users of this guideline include

- primary care clinicians who provide care to persons at risk of acquiring HIV infection
- clinicians who provide substance abuse treatment
- infectious disease and HIV treatment specialists who may provide PrEP or serve as consultants to primary care physicians about the use of antiretroviral medications
- health program policymakers.

Evidence of Need for Additional HIV Prevention Methods

Approximately 50,000 people in the United States are infected with HIV each year[12]. From 2008 through 2010, HIV incidence remained stable or declined among IDU and heterosexuals of all races and Hispanic/Latino ethnicity, but incidence increased among MSM (12% increase), especially among adolescent and young adult MSM (aged 13-24 years) (22% increase)[12]. The greatest number of new HIV infections among MSM occurred in young African American MSM (4,800). In 2010, 63% of the estimated 47,500 new infections were attributed to male-male sexual activity without injection drug use, 4% to male-male sexual activity with injection drug use, 25% to male-female sexual contact without injection drug use, and 8% to injection drug use. Among the 25% of persons newly infected through heterosexual activity, 66% were African-American women and men. These data indicate a need for additional methods of HIV prevention to further reduce new HIV infections, especially (but not exclusively) among young adult and adolescent MSM of all races and Hispanic/Latino ethnicity and for African American heterosexuals (populations with higher HIV prevalence and at higher risk of HIV infection among those without HIV infection).

Evidence of the Safety and Efficacy of Antiretroviral Prophylaxis

The biological plausibility and the short-term safety of antiretroviral use to prevent HIV acquisition in other exposure situations have been demonstrated in 2 studies conducted prior to the PrEP trials. In a randomized placebo-controlled trial, perinatal transmission was reduced 68% among the HIV-infected women who received zidovudine during pregnancy and labor and whose infants received zidovudine for 6 weeks after birth[13]. That is, these infants received both preexposure and postexposure prophylaxis. In 1995, investigators used case-control surveillance data from health- care workers to demonstrate that zidovudine provided within 72 hours after percutaneous exposure to HIV-infected blood and continued for 28 days (PEP, or postexposure prophylaxis) was associated with an 81% reduction in the risk of acquiring HIV infection[14-16].

Evidence from these human studies of blood-borne and perinatal transmission as well as studies of vaginal and rectal exposure among animals[17-19] suggested that PrEP (using antiretroviral drugs) could reduce the risk of acquiring HIV infection from sexual and drug-use exposures. Clinical trials were launched to evaluate the safety and efficacy of PrEP in populations at risk of HIV infection through several routes of exposure. The results of completed trials published as of August 2013 are summarized below. See also Tables 2-6.

Published Trials of Antiretroviral Preexposure Prophylaxis Among Men Who Have Sex with Men

iPrEx (Preexposure Prophylaxis Initiative) Trial

The iPrEx study[2] was a phase 3, randomized, double-blind, placebo-controlled trial conducted in Peru, Ecuador, Brazil, Thailand, South Africa, and the United States among men and male-to-female transgender adults who reported sex with a man during the 6 months preceding enrollment. Participants were randomly assigned to receive a daily oral dose of either the fixed-dose combination of TDF and FTC or a placebo. All participants (drug and placebo groups) were seen every 4 weeks for an interview, HIV testing, counseling about risk- reduction and adherence to PrEP medication doses, pill count, and dispensing of pills and condoms. Analysis of data through May 1, 2010, revealed that after the exclusion of 58 participants (10 later determined to be HIV- infected at enrollment and 48 who did not have an HIV test after enrollment), 36 of 1,224 participants in the TDF/FTC group and 64 of 1,217 in the placebo group had acquired HIV infection. Enrollment in the TDF/FTC group was associated with a 44% reduction in the risk of HIV acquisition (95% CI, 15-63). The reduction was greater in the as-treated analysis: at the visits at which adherence was ≥50% (by self-report and pill count/dispensing), the reduction in HIV acquisition was 50% (95% CI, 18-70). The reduction in the risk of HIV acquisition was 73% at visits at which self-reported adherence was ≥90% (95% CI, 41-88) during the preceding 30 days. Among participants randomly assigned to the TDF/FTC group, plasma and intracellular drug-level testing was performed for all those who acquired HIV infection during the trial and for a matched subset who remained HIV- uninfected: a 92% reduction in the risk of HIV

acquisition (95% CI, 40-99) was found in participants with detectable levels of TDF/FTC versus those with no drug detected.

Generally, TDF/FTC was well tolerated, although nausea in the first month was more common among participants taking medication than among those taking placebo (9% versus 5%). No differences in severe (grade 3) or life-threatening (grade 4) adverse laboratory events were observed between the active and placebo group, and no drug-resistant virus was found in the 100 participants infected after enrollment. Among 10 participants who were HIV-negative at enrollment but later found to have been infected before enrollment, FTC-resistant virus was detected in 2 of 2 men in the active group and 1 of 8 men in the placebo group. Compared to participant reports at baseline, over the course of the study participants in both the TDF/FTC and placebo groups reported fewer total numbers of sex partners with whom the participants had receptive anal intercourse and higher percentages of partners who used condoms.

US MSM Safety Trial

The US MSM Safety Trial[1] was a phase 2 randomized, double-blind, placebo-controlled study of the clinical safety and behavioral effects of TDF for HIV prevention among 400 MSM in San Francisco, Boston, and Atlanta. Participants were randomly assigned 1:1:1:1 to receive daily oral TDF or placebo immediately or after a 9- month delay. Participants were seen for follow-up visits 1 month after enrollment and quarterly thereafter. Among those without directed drug interruptions, medication adherence was high: 92% by pill count and 77% by pill bottle openings recorded by Medication Event Monitoring System (MEMS) caps. Temporary drug interruptions and the overall frequency of adverse events did not differ significantly between TDF and placebo groups. In multivariable analyses, back pain was the only adverse event associated with receipt of TDF. In a subset of men at the San Francisco site (n=184) for whom bone mineral density (BMD) was assessed, receipt of TDF was associated with small decrease in BMD (1% decrease at the femoral neck, 0.8% decrease for total hip)[20]. TDF was not associated with reported bone fractures at any anatomical site. Among 7 seroconversions, no HIV with mutations associated with TDF resistance was detected. No HIV infections occurred while participants were being given TDF; 3 occurred in men while taking placebo, 3 occurred among men in the delayed TDF group who had not started receiving drug; 1 occurred in a man who had been randomly assigned to receive placebo and who was later determined to have had acute HIV infection at the enrollment visit.

Daily oral PrEP with TDF/FTC is recommended as one HIV prevention option for sexually-active MSM at substantial risk of HIV acquisition because the iPrEx trial presents evidence of its safety and efficacy in this population, especially when medication adherence is high. **(IA)**

Published Trials of Antiretroviral Preexposure Prophylaxis Among Heterosexual Men and Women

Partners PrEP Trial

The Partners PrEP trial[3,21] was a phase 3 randomized, double-blind, placebo-controlled study of daily oral TDF/FTC or TDF for the prevention of acquisition of HIV by the uninfected partner in 4,758 HIV-discordant heterosexual couples in Uganda and Kenya. The trial was stopped after an interim analysis in mid-2011 showed statistically significant efficacy in the medication groups (TDF/FTC or TDF) compared with the placebo group. In 48% of couples, the infected partner was male. HIV-positive partners had a median CD4 count of 495 cells/μL and were not being prescribed antiretroviral therapy because they were not eligible by local treatment guidelines. Participants had monthly follow-up visits and the study drug was discontinued among women who became pregnant during the trial.

Adherence to medication was very high: 98% by pills dispensed, 92% by pill count, and 82% by plasma drug-level testing among randomly selected participants in the TDF and TDF/FTC study groups. Rates of serious adverse events and serum creatinine or phosphorus abnormalities did not differ by study group. Modest increases in gastrointestinal symptoms and fatigue were reported in the antiretroviral medication groups compared with the placebo group, primarily in the first month of use. Among participants of both sexes combined, efficacy estimates for each of the 2 antiretroviral regimens compared with placebo were 67% (95% CI, 44-81) for TDF and 75% (95% CI, 55-87) for TDF/FTC. Among women, the estimated efficacy was 71% for TDF and 66% for TDF/FTC. Among men, the estimated efficacy was 63% for TDF and 84% for TDF/FTC. Efficacy estimates by drug regimen were not statistically different among men, women, men and women combined, or between men and women. In a Partners PrEP substudy that measured plasma TDF levels among participants randomly assigned to receive TDF/FTC, detectable drug was associated with a 90% reduction in the risk of HIV acquisition. TDF- or FTC- resistant virus was detected in 3 of 14 persons determined to have been infected when enrolled (2 of 5 in the TDF group; 1 of 3 in the TDF/FTC group)[8]. No TDF or FTC resistant virus was detected among those infected after enrollment. Among women, the pregnancy rate was high (10.3 per 100 person –years) and rates did not differ significantly between the study groups.

TDF2 Trial

The Botswana TDF2 Trial[22], a phase 2 randomized, double-blind, placebo-controlled study of the safety and efficacy of daily oral TDF/FTC, enrolled 1,219 heterosexual men and women in Botswana, and follow-up has been completed. Participants were seen for monthly follow-up visits, and study drug was discontinued in women who became pregnant during the trial.

Among participants of both sexes combined, the efficacy of TDF/FTC was 62% (22%-83%). Efficacy estimates by sex did not statistically differ from each other or from the overall estimate, although the small number of endpoints in the subsets of men and women limited the statistical power to detect a difference. Compliance with study visits was low: 33.1% of participants did not complete the study per protocol. However, many were re-engaged for an exit visit, and 89.3% of enrolled participants had a final HIV test.

Among 3 participants later found to have been infected at enrollment, TDF/FTC-resistant virus was detected in 1 participant in the TDF/FTC group and a low level of TDF/FTC-resistant virus was transiently detected in 1 participant in the placebo group. No resistant virus was detected in the 33 participants who seroconverted after enrollment.

Medication adherence by pill count was 84% in both groups. Nausea, vomiting, and dizziness occurred more commonly, primarily during the first month of use, among those randomly assigned to TDF/FTC than among those assigned to placebo. The groups did not differ in rates of serious clinical or laboratory adverse events. Pregnancy rates and rates of fetal loss did not differ by study group.

FEM-PrEP Trial

The FEM-PrEP trial[23] was a phase 3 randomized, double-blind, placebo-controlled study of the HIV prevention efficacy and clinical safety of daily TDF/FTC among heterosexual women in South Africa, Kenya, and Tanzania. Participants were seen at monthly follow-up visits, and study drug was discontinued among women who became pregnant during the trial. The trial was stopped in 2011, when an interim analysis determined that the trial would be unlikely to detect a statistically significant difference in efficacy between the two study groups.

Adherence was low in this trial: study drug was detected in plasma samples of <50% of women randomly assigned to TDF/FTC. Among adverse events, only nausea and vomiting (in the first month) and transient, modest elevations in liver function test values were more common among those assigned to TDF/FTC than those assigned to placebo. No changes in renal function were seen in either group. Initial analyses of efficacy results showed 4.7 infections per 100/ person-years in the TDF/FTC group and 5.0 infections per 100 person-years in the placebo group. The hazard ratio 0.94 (95% CI, 0.59-1.52) indicated no reduction in HIV incidence associated with TDF/FTC use. Of the 68 women who acquired HIV infection during the trial, TDF or FTC resistant virus was detected in 5 women: 1 in the placebo group and 4 in the TDF/FTC group. In multivariate analyses, there was no association between pregnancy rate and study group.

Phase 2 Trial of Preexposure Prophylaxis with Tenofovir Among Women in Ghana, Cameroon, and Nigeria

A randomized, double-blind, placebo-controlled trial of oral tenofovir TDF was conducted among heterosexual women in West Africa - Ghana (n = 200), Cameroon (n = 200), and Nigeria

(n = 136)[24]. The study was designed to assess the safety of TDF use and the efficacy of daily TDF in reducing the rate of HIV infection. The Cameroon and Nigeria study sites were closed prematurely because operational obstacles developed, so participant follow-up data were insufficient for the planned efficacy analysis. Analysis of trial safety data from Ghana and Cameroon found no statistically significant differences in grade 3 or 4 hepatic or renal events or in reports of clinical adverse events. Eight HIV seroconversions occurred among women in the trial: 2 among women in the TDF group (rate=0.86 per 100 person-years) and 6 among women receiving placebo (rate, 2.48 per 100 person-years), yielding a rate ratio of 0.35 (95% CI, 0.03-1.93; *P*=0.24). Blood specimens were available from 1 of the 2 participants who seroconverted while taking TDF; standard genotypic analysis revealed no evidence of drug-resistance mutations.

VOICE (VAGINAL AND ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC) TRIAL

VOICE (MTN-003)[25] was a phase 2B randomized, double-blind study comparing oral (TDF or TDF/FTC) and topical vaginal (tenofovir) antiretroviral regimens against corresponding oral and topical placebos among 5,029 heterosexual women enrolled in eastern and southern Africa. Of these women, 3,019 were randomly assigned to daily oral medication (TDF/FTC, 1,003; TDF, 1,007; oral placebo, 1,009). In 2011, the trial group receiving oral TDF and the group receiving topical tenofovir were stopped after interim analyses determined futility[26]. The group receiving oral TDF/FTC continued to the planned trial conclusion.

After the exclusion of 15 women later determined to have had acute HIV infection when enrolled in an oral medication group and 27 with no follow-up visit after baseline, 52 incident HIV infections occurred in the oral TDF group, 61 in the TDF/FTC group, and 60 in the oral placebo group. Effectiveness was not significant for either oral PrEP medication group; −49%% for TDF (hazard ratio [HR] 1.49; 95% CI, 0.97-2.29) and −4.4% for TDF/FTC (HR, 1.04; 95% CI, 0.73-1.49) in the modified-intent-to-treat analysis.

Face-to-face interview, audio computer-assisted self-interview, and pill-count medication adherence were high in all 3 groups (84%-91%). However, among 315 participants in the random cohort of the case-cohort subset for whom quarterly plasma samples were available, tenofovir was detected, on average, in 30% of samples from women randomly assigned to TDF and in 29% of samples from women randomly assigned to TDF/FTC. No drug was detected at any quarterly visit during study participation for 58% of women in the TDF group and 50% of women in the TDF/FTC group. The percentage of samples with detectable drug was less than 40% in all study drug groups and declined throughout the study. In a multivariate analysis that adjusted for baseline confounding variables (including age, marital status), the detection of study drug was not associated with reduced risk of HIV acquisition.

The number of confirmed creatinine elevations (grade not specified) observed was higher in the oral TDF/FTC group than in the oral placebo group. However, there were no significant

differences between active product and placebo groups for other safety outcomes. Of women determined after enrollment to have had acute HIV infection at baseline, two women from the TDF/FTC group had virus with the M184I/V mutation associated with FTC resistance. One woman in the TDF/FTC group who acquired HIV infection after enrollment had virus with the M184I/V mutation; No participants with HIV infection had virus with a mutation associated with tenofovir resistance.

In summary, although low adherence and operational issues precluded reliable conclusions regarding efficacy in 3 trials (VOICE, FEM-PrEP and the West African trial) [27], 2 trials (Partners PrEP and TDF2) with high medication adherence have provided substantial evidence of efficacy among heterosexual men and women. All 5 trials have found PrEP to be safe for these populations.

Daily oral PrEP with TDF/FTC is recommended as one HIV prevention option for heterosexually-active men and women at substantial risk of HIV acquisition because these trials present evidence of its safety and 2 present evidence of efficacy in these populations, especially when medication adherence is high. **(IA).**

PUBLISHED TRIAL OF ANTIRETROVIRAL PREEXPOSURE PROPHYLAXIS AMONG INJECTION DRUG USERS

BANGKOK TENOFOVIR STUDY (BTS)

BTS[5] was a phase 3 randomized, double-blind, placebo-controlled study of the safety and efficacy of daily oral TDF for HIV prevention among 2,413 IDUs in Bangkok, Thailand. The study was conducted at drug treatment clinics; 22% of participants were receiving methadone treatment at baseline. At each monthly visit, participants could choose to receive either a 28-day supply of pills or to receive medication daily by directly- observed therapy. Study clinics (n=17) provided condoms, bleach (for cleaning injection equipment), methadone, primary medical care, and social services free of charge. Participants were followed for 4.6 years (mean) and received directly- observed therapy 87% of the time.

In the modified intent- to-treat analysis (excluding 2 participants with evidence of HIV infection at enrollment), efficacy of TDF was 48.9% (95% CI, 9.6-72.2; P = .01). A post-hoc modified intent-to-treat analysis was done, removing 2 additional participants in whom HIV infection was identified within 28 days of enrollment, including only participants on directly observed therapy who met pre-established criteria for high adherence (taking a pill at least 71% of days and missing no more than two consecutive doses), and had detectable levels of tenofovir in their blood. Among this set of participants, the efficacy of TDF in plasma was associated with a 73.5% reduction in the risk for HIV acquisition (95% CI, 16.6-94.0; P = .03). Among participants in an unmatched case-control study that included the 50 persons with incident HIV infection and 282 participants at 4 clinics who remained HIV uninfected, detection of TDF in

plasma was associated with a 70.0% reduction in the risk for acquiring HIV infection (95% CI, 2.3-90.6; *P* = .04).

Rates of nausea and vomiting were higher among TDF than among placebo recipients in the first 2 months of medication but not thereafter. The rates of adverse events, deaths, or elevated creatinine did not differ significantly between the TDF and the placebo groups. Among the 49 HIV infections for which viral RNA could be amplified (of 50 incident infections and 2 infections later determined to have been present at enrollment), no virus with mutations associated with TDF resistance were identified.

Among participants with HIV infection followed up for a maximum of 24 months, HIV plasma viral load was lower in the TDF than in the placebo group at the visit when HIV infection was detected (*P* = .01), but not thereafter (*P* = .10).

Daily oral PrEP with TDF/FTC (or TDF alone) is recommended as one HIV prevention option for IDUs at substantial risk of HIV acquisition because this trial presents evidence of the safety and efficacy of TDF as PrEP in this population, especially when medication adherence is high. **(IA)**

Table 2: Evidence Summary—Overall Evidence Quality (per GRADE Criteria[28])

Study	Design[a]	Participants		Limitations	Quality of Evidence (See Table 14, Appendix 2)
		Agent	Control		
Among Men Who have Sex with Men					
iPrEx Trial	Phase 3	TDF/FTC (n = 1251)	Placebo (n = 1248)	Adherence	High
US MSM Safety Trial	Phase 2	TDF (n = 201)	Placebo (n = 199)	Minimal	High
Among Heterosexual Men and Women					
Partners PrEP	Phase 3	TDF (n = 1589) TDF/FTC (n = 1583)	Placebo (n = 1586)	Minimal	High
TDF2	Phase 2	TDF/FTC (n = 611)	Placebo (n = 608)	High loss to follow-up; modest sample size	Moderate
Among Heterosexual Women					
FEM-PrEP	Phase 3	TDF/FTC (n = 1062)	Placebo (n = 1058)	Stopped at interim analysis, limited follow-up time; very low adherence to drug regimen	Low
West African Trial	Phase 2	TDF (n = 469)	Placebo (n = 467)	Stopped early for operational concerns; small sample size; limited follow-up time on assigned drug	Low
VOICE	Phase 2B	TDF (n = 1007) TDF/FTC (n = 1003)	Placebo (n = 1009)	TDF arm stopped at interim analysis (futility); very low adherence to drug regimen in both TDF and TDF/FTC arms	Low
Among Injection Drug Users					
BTS	Phase 3	TDF (n = 1204)	Placebo (n = 1207)	Minimal	High

Note: GRADE quality ratings:
high = further research is very unlikely to change our confidence in the estimate of effect;
moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
very low = any estimate of effect is very uncertain.

[a] All trials in this table were randomized, double-blind, prospective clinical trials

Table 3: Evidence Summary—HIV Incidence Findings

Study	Outcome Analyses— HIV incidence (mITT)		Effect — HR [Efficacy Estimate] (95% CI)		
	Agent	Control			
iPrEx (MSM)	36 infections among 1224 persons	64 infections among 1217 persons	0.56 [44%] (0.37–0.85)		
US MSM Safety Trial	3 infections among 201 persons (all 3 in delayed arm, not on TDF)	4 infections among 199 persons (1 acute infection at enrollment)	Not Reported		
Partners PrEP (heterosexual men and women)	TDF 17 infections among 1572 persons TDF/FTC 13 infections among 1568 persons	52 infections among 1568 persons		TDF	TDF/FTC
			All	0. 33 [67%] (0.19–0.56)	0.25 [75%] (0.13–0.45)
			Women	0.29 [71%] (0.13–0.63)	0.34 [66%] (0.16–0.72)
			Men	0.37 [63%] (0.17–0.80)	0.16 [84%] (0.06–0.46)
TDF2 (heterosexual men and women)	9 infections among 601 persons 1.2 infections/100 person-years	24 infections among 599 persons 3.1 infections per 100 person-years	0.38 [62%] (0.17–0.79)		
FEM-PrEP (heterosexual women)	33 infections among 1024 persons 4.7 infections per 100 person-years	35 infections among 1032 persons 5.0 infections per 100 person-years	0.94 [6%] [a] (0.59–1.52)		
West African Trial (heterosexual women)	2 infections among 427 persons 0.86 infections per 100 person-years	6 infections among 432 persons 2.48 infections per 100 person-years	0.35 [65%] [a] (0.03–1.93)		
VOICE (heterosexual women)	TDF 52 infections among 993 persons 6.3 infections per 100 person-years TDF/FTC 61 infections among 985 persons 4.7 infections per 100 person-years	35 infections among 999 persons 4.2 infections per 100 person-years	TDF	TDF/FTC	
			1.49 [-50 %] [a] (0.97–2.3)	1.04 [-4%] [a] (0.73, 1.5)	
BTS (injection drug users)	17 infections among 1204 persons 0.35 infections per 100 person-years	33 infections among 1207 persons 0.68 infections per 100 person-years	0.51 [49%] (9.6, 72.2)		

mITT: modified intent to treat analysis; HR: hazard ratio.

[a] Not statistically significant.

Table 4: Measures of Efficacy, by Medication Adherence, Percentage Reduction in HIV Incidence (95% Confidence Interval)

Study	Modified Intent-to-Treat Efficacy			Efficacy by Self-report Adherence Measures	Efficacy by Pill-count Adherence Measures	Efficacy by Blood Detection of Drug Measures [a]
iPrEx (TDF/FTC)	44% (15–63%)			>50% 50% (18–70%) >90% 73% (41–88%)		92% (40–99%)
Partners PrEP	All TDF: 67% TDF/FTC: 75%	Men TDF: 63% TDF/FTC: 84%	Women TDF: 71% TDF/FTC: 66%	NR	100% (87–100%)	TDF: 86% (67–94%) TDF/FTC: 90% (58–98%)
TDF2 (TDF/FTC)	All 63%	Men 80%	Women 49% [b]	NR	NR	TDF detected: 85% [b]
FEM-PrEP (TDF/FTC)	NR			NR	NR	NR
VOICE (TDF,TDF/FTC)	NR			NR	NR	NR
BTS (TDF)	49%			NR	56% (-19 to 86%) [c]	74% (17–94%)

NR, not reported.

[a] Tenofovir detection assays were done in subsets of persons randomly assigned to receive TDF or TDF/FTC

[b] Finding not statistically significant

[c] Among participants on directly observed therapy

Table 5: Evidence Summary— Safety and Toxicity

Study	Outcome Analyses	
	Agent	**Control**
Grade 3/4 Adverse Clinical Events[a]		
iPrEx	52 events	59 events
TDF2	9 events	10 events
West African Trial	NR	NR
Grade 3/4 Adverse Laboratory Events [a]		
iPrEx	59 events	48 events
TDF2	32 events	32 events
West African Trial	1 event	5 events
Grade 3/4 Adverse Events (Clinical and Laboratory)[a]		
Partners PrEP	TDF: 323 events TDF/FTC: 337 events	307 events
FEM-PrEP	NR	NR
US MSM Safety Trial	36 events	26 events
VOICE	NR	NR
BTS	175 events	173 events

NR, not reported.

[a] RDBPCT = randomized, double-blind, prospective clinical trial

Table 6: Evidence Summary— HIV Resistance Findings (TDF or FTC Drug Resistant Virus Detected)

Study	Outcome Analyses	
	Agent	Control
iPrEx	2 resistant viruses among 2 persons infected at baseline 0 resistant viruses among 36 persons infected after baseline	1 resistant virus among 8 persons infected at baseline 0 resistant viruses among 64 persons infected after baseline
US MSM Safety Trial	0 resistant viruses among 3 persons infected after baseline (in delayed arm before starting drug)	1 resistant virus among 1 person infected at baseline 0 resistant viruses among 3 persons infected after baseline
Partners PrEP	2 resistant viruses among 5 persons infected at baseline and randomly assigned to TDF 1 resistant virus among 3 persons infected at baseline and randomly assigned to TDF/FTC 0 resistant viruses among 27 persons infected after baseline	0 resistant viruses among 6 persons infected at baseline 0 resistant viruses among 51 persons infected after baseline
TDF2	1 resistant virus in 1 person infected at baseline 0 resistant viruses among 9 persons infected after baseline	1 resistant virus in 1 person infected at baseline (very low frequency and transient detection) 0 resistant viruses among 24 persons infected after baseline
FEM-PrEP	4 resistant viruses among 33 persons infected after baseline	1 resistant virus in 35 persons infected after baseline
West African Trial	0 resistant viruses among 2 persons infected while on TDF	NR
VOICE	NR	—
BTS	0 resistant viruses among 49 persons infected after baseline	

NR, not reported.

Identifying Indications for PrEP

Taking a sexual history is recommended for all adult and adolescent patients as part of ongoing primary care, but the sexual history is often deferred because of urgent care issues, provider discomfort, or anticipated patient discomfort. This deferral is common among providers of primary care[29], STI care,[30] and HIV care[31-33].

Routinely taking a sexual history is a necessary first step to identify which patients in a clinical practice are having sex with same-sex partners, which are having sex with opposite-sex partners, and what specific sexual behaviors may place them at risk for, or protect them from, HIV acquisition. The clinician can introduce this topic by stating that taking a brief sexual history is routine practice, go on to explain that the information is necessary to the provision of individually appropriate sexual health care, and close by reaffirming the confidentiality of patient information.

Assessing Risk of Sexual HIV Acquisition

Because offering PrEP is currently indicated for MSM at substantial risk of HIV acquisition, it is important to consider that although 76% of MSM surveyed in 2008 in 21 US cities reported a health care visit during the past year[34], other studies reported that health care providers do not ask about, and patients often do not disclose, same-sex behaviors[35].

Box A1 contains a set of brief questions designed to identify men who are currently having sex with men and to assess a key set of sexual practices that are associated with the risk of HIV acquisition. In studies to develop scored risk indexes predictive of incident HIV infection among MSM[36,37] (see Providers' Supplement, Section 5), several critical factors were identified.

Box A1: Risk Behavior Assessment for MSM[36]

In the past 6 months:

- Have you had sex with men, women, or both?
- *(if men or both sexes)* How many men have you had sex with?
- How many times did you have receptive anal sex (you were the bottom) with a man who was not wearing a condom?
- How many of your male sex partners were HIV-positive?
- *(if any positive)* With these HIV-positive male partners, how many times did you have insertive anal sex (you were the top) without you wearing a condom?
- Have you used methamphetamines (such as crystal or speed)?

Box A2 contains a set of brief questions designed to identify women and men who are currently having sex with opposite-sex partners (heterosexually active) and to assess a key set of sexual practices that are associated with the risk of HIV acquisition as identified both in PrEP trials and epidemiologic studies[38-40].

BOX A2: RISK BEHAVIOR ASSESSMENT FOR HETEROSEXUAL MEN AND WOMEN

In the past 6 months:

- Have you had sex with men, women, or both?
- *(if opposite sex or both sexes)* How many men/women have you had sex with?
- How many times did you have vaginal or anal sex when neither you nor your partner wore a condom?
- How many of your sex partners were HIV-positive?
- *(if any positive)* With these HIV-positive partners, how many times did you have vaginal or anal sex without a condom?

In addition, for all sexually active patients, clinicians may want to consider reports of diagnoses of bacterial STIs (chlamydia, syphilis, gonorrhea) during the past 6 months as evidence of sexual activity that could result in HIV exposure. For heterosexual women and men, sex without a condom (or its correct use) may also be indicated by recent pregnancy of a female patient or sexual partner of a male patient.

Clinicians should also briefly screen all patients for alcohol abuse[41] (especially before sexual activity) and the use of illicit non-injection drugs (e.g., amyl nitrite, stimulants).[42,43] The use of these substances may affect sexual risk behavior[44], hepatic or renal health, or medication adherence, any of which may affect decisions about the appropriateness of prescribing PrEP medication. In addition, if substance abuse is reported, the clinician should provide referral for appropriate treatment or harm-reduction services acceptable to the patient.

Lastly, clinicians should consider the epidemiologic context of the sexual practices reported by the patient. The risk of HIV acquisition is determined by both the frequency of specific sexual practices (e.g., unprotected anal intercourse) and the likelihood that a sex partner has HIV infection. The same behaviors when reported as occurring in communities and demographic populations with high HIV prevalence or occurring with partners known to have HIV infection, are more likely to result in exposure to HIV and so will indicate greater need for intensive risk-reduction methods (PrEP, multisession behavioral counseling) than when they occur in a community or population with low HIV prevalence (see http://www.AIDSvu.org or http://www.cdc.gov/nchhstp/atlas/).

After assessing the risk of HIV acquisition, clinicians should discuss with the patient which of several effective prevention methods (e.g., PrEP, behavioral interventions)[45] will be pursued. When supporting consistent and correct condom use is feasible and the patient is motivated to achieve it, high levels of protection against both HIV and several STIs[46,47] are afforded without the side effects or cost of medication. A clinician can support consistent condom use by providing brief clinical counseling (see Providers' Supplement, Section 7), by referring the patient to behavioral medicine or health education staff in the clinical setting, or by referring the patient to community-based or local health department counseling and support services.

Reported consistent ("always") condom use is associated with an 80% reduction in HIV acquisition among heterosexual couples[48]. However, inconsistent condom use is less effective,[37,49] and studies have reported low rates of recent consistent condom use among MSM[50] and other sexually active adults[51]. Especially low rates have been reported when condom use was measured over several months rather than during most recent sex or the past 30 days[52]. Therefore, unless the patient reports confidence that consistent condom use can be achieved, additional HIV prevention methods, including the consideration of PrEP should be provided while continuing to support condom.

A patient who reports that 1 or more regular sex partners is of unknown HIV status should be offered HIV testing for those partners, either in the clinician's practice or at a confidential testing site (see zip code lookup at http://www.hivtest.org/).

Lastly, for any regular sex partner reported to be HIV-positive, clinicians should determine whether the partner is receiving antiretroviral therapy and whether a recent evaluation indicates an undetectable viral load. In addition to the known health benefits of viral load suppression, a recent clinical trial (HPTN 052[53]) demonstrated that viral load suppression is highly, but not completely, protective against HIV transmission to a heterosexual partner (96% reduction). No similar trial has been done with MSM in HIV-discordant couples, so it is unknown how much viral load suppression reduces HIV transmission among partners who are MSM. Persons who know they have HIV infection may not be in care, may not be receiving antiretroviral therapy, may not be receiving highly effective regimens, may not be adherent to their medications, or for other reasons may not have viral loads that are associated with the least risk of transmission to an uninfected sex partner[54].

BOX B1: RECOMMENDED INDICATIONS FOR PREP USE BY MSM[2]

- Adult man
- Without acute or established HIV infection
- Any male sex partners in past 6 months (if also has sex with women, see Box B2)
- Not in a monogamous partnership with a recently tested, HIV-negative man

AND at least one of the following

- Any anal sex without condoms (receptive or insertive) in past 6 months
- Any STI diagnosed or reported in past 6 months
- Is in an ongoing sexual relationship with an HIV-positive male partner

BOX B2: RECOMMENDED INDICATIONS FOR PREP USE BY HETEROSEXUALLY ACTIVE MEN AND WOMEN

- Adult person
- Without acute or established HIV infection
- Any sex with opposite sex partners in past 6 months
- Not in a monogamous partnership with a recently tested HIV-negative partner

AND at least one of the following

- Is a man who has sex with both women and men (behaviorally bisexual) [also evaluate indications for PrEP use by Box B1 criteria]
- Infrequently uses condoms during sex with 1 or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (IDU or bisexual male partner)
- Is in an ongoing sexual relationship with an HIV-positive partner

ASSESSING RISK OF HIV ACQUISITION THROUGH INJECTION PRACTICES

Although the annual number of new HIV infections among IDU in the United States has declined, a sizable number occur each year. In 2010, IDUs accounted for 8% of estimated incident HIV infections[55]. According to the National HIV Behavioral Surveillance System (NHBS)[56] substantial proportions of IDU report sharing syringes (34%) and sharing injection equipment (58%). In addition, in NHBS and epidemiologic studies conducted with IDU, most IDU report sexual behaviors that also confer risk of HIV acquisition[57]. Because of the efficacy and safety demonstrated in the PrEP trial with IDU, providing PrEP to those who report injection behaviors that place them at substantial risk of acquiring HIV infection could contribute to HIV prevention for IDU at both the individual and the population level.

Although current evidence is insufficient for a recommendation that all patients be screened for injection or other illicit drug use, the US Preventive Services Task Force recommends that clinicians be alert to the signs and symptoms of illicit drug use in patients.[26] Clinicians should determine whether patients who are currently using illicit drugs are in (or want to enter) behavioral, medication-assisted, or in-patient drug treatment. For persons with a history of injecting illicit drugs but who are currently not injecting, clinicians should assess the risk of relapse along with the patients' use of relapse prevention services (e.g., a drug-related behavioral support program, use of mental health services, 12-step program).

Box A3 contains a set of brief questions that may help identify persons who are injecting illicit drugs, and to assess a key set of injection practices that are associated with the risk of HIV acquisition as identified in the PrEP trial with IDU[5] and in epidemiologic studies[56,58].

BOX A3: RISK BEHAVIOR ASSESSMENT FOR INJECTION DRUG USERS

- Have you ever injected drugs that were not prescribed to you by a clinician?
- *(if yes),* When did you last inject unprescribed drugs?
- In the past 6 months, have you injected by using needles, syringes, or other drug preparation equipment that had already been used by another person?
- In the past 6 months, have you been in a methadone or other medication-based drug treatment program?

BOX B3: RECOMMENDED INDICATIONS FOR PREP USE BY INJECTION DRUG USERS

- Adult person
- Without acute or established HIV infection
- Any injection of drugs not prescribed by a clinician in past 6 months

AND at least one of the following

- Any sharing of injection or drug preparation equipment in past 6 months
- Been in a methadone, buprenorphine, or suboxone treatment program in past 6 months
- Risk of sexual acquisition (also evaluate by criteria in Box B1 or B2)

PrEP or other HIV prevention should be integrated with prevention and clinical care services for the many health threats IDU may face (e.g., hepatitis B and C infection, abscesses, septicemia, endocarditis, overdose)[59]. In addition, referrals for drug treatment, mental health services, and social services may be indicated[59].

LABORATORY TESTS AND OTHER DIAGNOSTIC PROCEDURES

All patients whose sexual or drug injection history indicates consideration of PrEP and who are interested in taking PrEP must undergo laboratory testing to identify those for whom this intervention would be harmful or for whom it would present specific health risks that would require close monitoring.

HIV TESTING

HIV testing and the documentation of results are required to confirm that patients do not have HIV infection when they start taking PrEP medications. For patient safety, HIV testing and should be repeated at least every 3 months (before prescriptions are refilled or reissued). This requirement should be explained to patients during the discussion about whether PrEP is appropriate for them.

The Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force recommends that MSM, IDUs, patients with a sex partner who has HIV infection, and others at substantial risk of HIV acquisition undergo an HIV test at least annually or for those

with additional risk factors, every 3-6.[60] However, outside the context of PrEP delivery, testing is often not done as frequently as recommended.[61]

At a minimum, clinicians should document a negative antibody test result within the week before initiating (or reinitiating) PrEP medications. The required HIV testing can be accomplished by (1) drawing blood (serum) and sending the specimen to a laboratory for a routine HIV EIA (enzyme-linked immunoassay) or (2) performing a rapid, point-of-care, FDA-approved, fingerstick blood test. Oral rapid tests should not be used to screen for HIV infection when considering PrEP use because they can be less sensitive than blood tests [1,21,62]. Clinicians should not accept patient-reported test results or documented anonymous test results. A preliminary positive HIV antibody test must be confirmed by Western blot or IFA (immunofluorescence assay) according to the local laboratory standard practice[63] and viral load and CD4 lymphocyte tests should be ordered to assist in future treatment decisions.

See Appendix 1 for Tables 11 - 12 for FDA-approved HIV tests, specimen requirements, and time to detection of HIV infection[64].

ACUTE HIV INFECTION

In the iPrEx trial, drug-resistant virus developed in 2 persons with unrecognized acute HIV infection at enrollment and for whom TDF/FTC had been dispensed. These participants had negative antibody test results before they started taking PrEP, tested positive at a later study visit, and PCR (polymerase chain reaction) on stored specimens from the initial visit detected the presence of virus. When questioned, most of the 10 acutely infected participants (8 of whom had been randomly assigned the placebo group) reported signs and symptoms consistent with a viral syndrome[2]. Both acutely infected patients to whom TDF/FTC had been dispensed had the M184V/I mutation associated with emtricitabine resistance, but not the K65R mutation associated with tenofovir resistance[2]. Among participants who were dispensed PrEP medication in the US MSM Safety Trial and in the Partners PrEP, TDF2, and VOICE trials (see Table 6), the M184V mutation, developed in several persons who were enrolled and had started taking medication with unrecognized acute HIV infection but K65R developed in only one (in the TDF2 study). However, no mutations emerged in persons who acquired infection after baseline. In the one trial with very low medication adherence that has published its resistance testing results, the emtricitabine resistance mutation, but not the K65R mutation was found in a few persons with incident infection after baseline (4 persons in the FEM-PrEP trial).

PrEP is indicated for MSM, heterosexual men and women, and IDUs who report injection or sexual behaviors that place them at substantial risk of HIV acquisition. Therefore clinicians should suspect acute HIV infection in persons known to have been exposed recently (e.g., a condom broke during sex with an HIV-infected partner, relapse to injection drug use with shared injection equipment). In addition, clinicians should solicit a history of nonspecific signs or

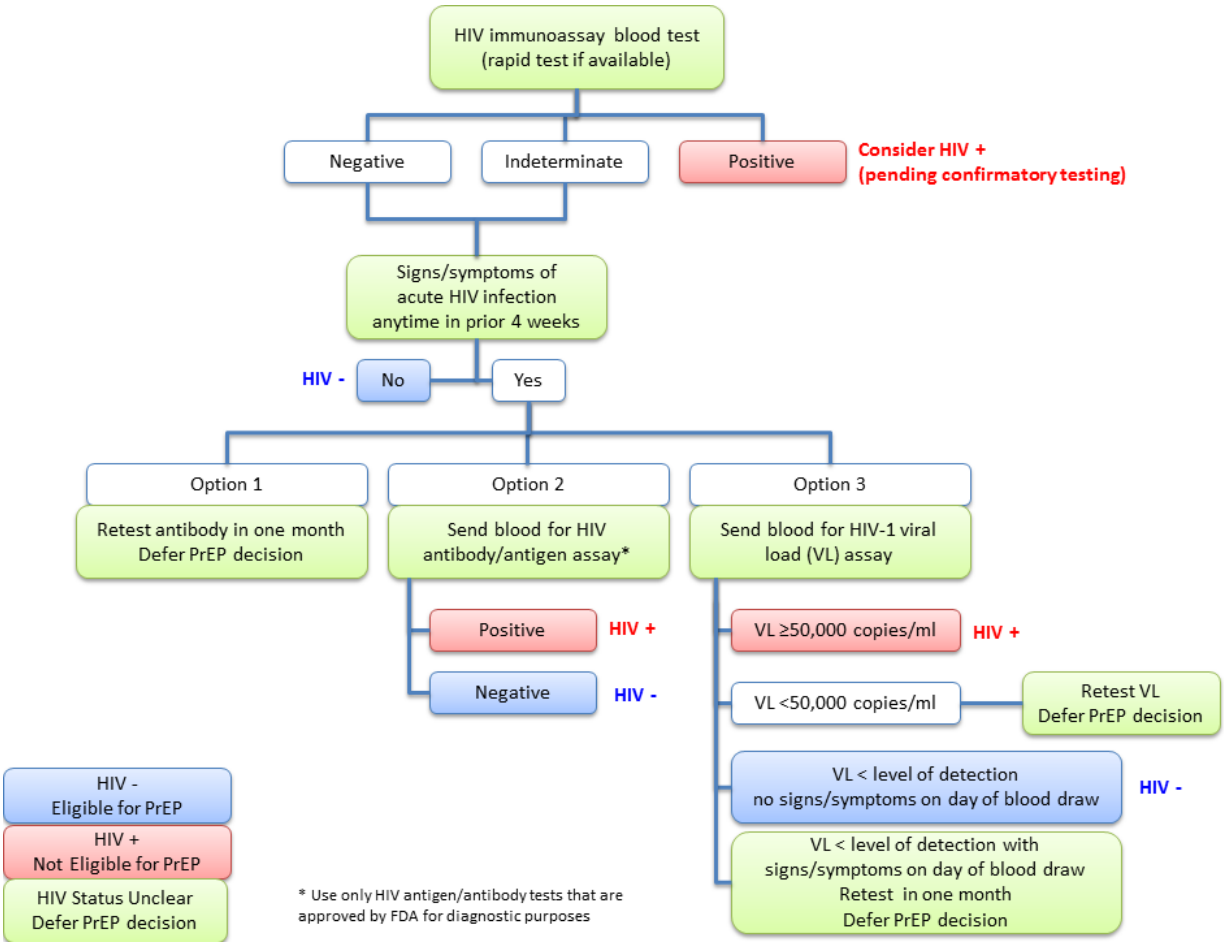
symptoms of viral infection during the preceding month or on the day of evaluation (Table 7) in all PrEP candidates with a negative or an indeterminate result on an HIV antibody test.

Table 7: Clinical Signs and Symptoms of Acute (Primary) HIV Infection[65]

Features (%)	Overall (n = 375)	Sex		Route of transmission	
		Male (n = 355)	Female (n = 23)	Sexual (n = 324)	Injection Drug Use (n = 34)
Fever	75	74	83	77	50
Fatigue	68	67	78	71	50
Myalgia	49	50	26	52	29
Skin rash	48	48	48	51	21
Headache	45	45	44	47	30
Pharyngitis	40	40	48	43	18
Cervical adenopathy	39	39	39	41	27
Arthralgia	30	30	26	28	26
Night sweats	28	28	22	30	27
Diarrhea	27	27	21	28	23

An additional blood specimen should be tested for any patient who has a negative or indeterminate result from a rapid HIV test or laboratory HIV antibody test, and who reports recent signs and symptoms suggestive of acute HIV. See the Figure below for the testing algorithm recommended for the documentation of HIV infection status before the initiation of PrEP or its re-initiation after more than a week off PrEP medication.

Figure Documenting HIV Status



RENAL FUNCTION

In addition to confirming that any person starting PrEP medication is not infected with HIV, a clinician should determine renal function and test for infection with hepatitis B virus (HBV) because both decreased renal function and active HBV infection are potential safety issues for the use of TDF/FTC as PrEP.

TDF is widely used in combination antiretroviral regimens for the treatment of HIV infection[66]. Among HIV-infected persons prescribed TDF-containing regimens, decreases in renal function (as measured by estimated creatinine clearance [eCrCl]) have been documented, and occasional cases of acute renal failure, including Fanconi's syndrome, have occurred[67,-69].

In the PrEP trials among otherwise healthy, HIV-uninfected adults, an eCrCl of ≥60 ml/min was an eligibility criterion. Safety data for TDF/FTC prescribed to persons with reduced renal function are not available. Therefore, for all persons considered for PrEP, a serum creatinine test

should be done, and an eCrCL should be calculated by using the Cockcroft-Gault formula (see Box C). Any person with an eCrCl of <60 ml/min should not be prescribed PrEP with TDF/FTC.

BOX C COCKCROFT-GAULT FORMULAS

Basic Formula[70]

$eCrCl_{CG}$ = [[(140 - age) × IBW × 0.85 for females] ÷ (serum creatinine × 72)]

IBW = ideal body weight Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet

Age in years, weight in kg, and serum creatinine in mg/100mL

Optional adjustment for low actual body weight[71]
If the actual body weight is less than the IBW (ideal body weight) use the actual body weight for calculating the eCrCl.

Optional adjustment of high actual body weight[71]
Used only if the actual body weight is 30% greater than the IBW. Otherwise, the IBW is used.

eCrCl = [[(140 - age) × AjBW] ÷ (serum creatinine × 72)] (× 0.85 for females)

AjBW = IBW + 0.3(ABW - IBW)
AjBW = adjusted body weight ABW = actual body weight

Optional adjustment for body surface area (BSA)[72]
Can be used if actual body weight is greater or less than IBW

$eCrCl_{BSAadj}$ =1.73m^2 × $eCrCl_{CG}$ (ml/min) ÷ BSA of the patient (m^2)

BSA (DuBois and DuBois formula[74]) = (height (m)$^{0.725}$ × weight (kg)$^{0.425}$) ÷ 139.2

HEPATITIS SEROLOGY

Sexually active adults (especially MSM), and persons who inject illicit drugs, are at risk of acquiring HBV infection[74] and hepatitis C virus (HCV) infection[75]. Vaccination against HBV is recommended for all adolescents and adults, especially for MSM[76]. Therefore, HBV and HCV infection status should be documented by screening serology before TDF/FTC is prescribed as PrEP (see Table 8). Those patients determined to be susceptible to HBV infection should be vaccinated.

In addition, both TDF and FTC are active against HBV. This has 2 implications for PrEP use. First, if patients with active HBV infection stop taking these medications, liver function must be closely monitored because reactivated HBV infection can result in hepatic damage[77]. In addition, a recent study demonstrated a lower rate of incident HBV infections among HIV-infected MSM whose treatment regimens included TDF or lamivudine (closely related to FTC) than among men whose regimens did not contain these drugs (0.7 vs 6.7 infections per 100 person-years).[78]

Table 8: Hepatitis B Screening Serology

HBsAg	Total Anti-HBc	IgM Anti-HBc	Anti-HBs	Interpretation	Action
Negative	Negative	—	Negative	Susceptible	Vaccinate
Negative	Positive	—	Positive	Immune (natural infection)	Document
Negative	Negative	—	Positive	Immune (prior vaccination)	Document
Positive	Positive	Negative	Negative	Chronic HBV infection	Evaluate for treatment
Positive	Positive	Positive	Negative	Acute HBV infection	Follow and evaluate for treatment
Negative	Positive	—	Negative	Unclear—could be: • Resolved infection (most common) • False-positive anti-HBc; susceptible • "low level" chronic infection • Resolving acute infection	Case-by-case evaluation

For additional guidance about the management of PrEP in persons with chronic active HBV infection see the section Special Clinical Considerations.

Providing PrEP

Goals of PrEP Therapy

The ultimate goal of PrEP is to reduce the acquisition of HIV infection with its resulting morbidity, mortality, and cost to individuals and society. Therefore clinicians initiating the provision of PrEP should

- Prescribe medication regimens that are proven safe and effective for uninfected persons who meet recommended criteria to reduce their risk of HIV acquisition

- Educate patients about the medications and the regimen to maximize their safe use
- Provide support for medication-adherence to help patients achieve and maintain protective levels of medication in their bodies
- Provide HIV risk-reduction support and prevention services or service referrals to help patients minimize their exposure to HIV
- Provide effective contraception to women who are taking PrEP and who do not wish to become pregnant
- Monitor patients to detect HIV infection, medication toxicities, and levels of risk behavior in order to make indicated changes in strategies to support patients' long-term health

INDICATED MEDICATION

The medication proven safe and effective, and currently approved by FDA for PrEP in healthy adults at risk of acquiring HIV infection, is the fixed-dose combination of TDF and FTC in a single daily dose (see Table 9). Therefore, TDF/FTC is the recommended medication that should be prescribed for PrEP for MSM, heterosexually active men and women, and IDU who meet recommended criteria. Because TDF alone has been proven effective in trials with IDU and heterosexually active men and women, it can be considered as an alternative regimen for these specific populations. As PrEP for MSM, TDF alone is not recommended because no trials have been done, so the efficacy of TDF alone for MSM is unknown.

Table 9: Recommended Oral PrEP Medications

Generic Name	Trade Name	Dose	Frequency	Common Side Effects[66]
Tenofovir disoproxil fumarate (TDF)	Viread	300 mg	Once a day	Nausea, flatulence
Emtricitabine (FTC)[a]	Emtriva	200 mg	Once a day	Rash, headache
TDF + FTC	Truvada	300mg/200 mg	Once a day	—

[a] Not recommended alone; only for use in combination with TDF.

In addition to the safety data obtained in PrEP clinical trials, data on drug interactions and longer-term toxicities have been obtained by studying the component drugs individually for their use in treatment of HIV-infected persons. Studies have also been done in small numbers of HIV-uninfected, healthy adults (see Table 10).

Table 10: PrEP Medication Drug Interactions[6,66,79]

	TDF	FTC
Buprenorphine	No significant effect. No dosage adjustment necessary.	No data
Methadone	No significant effect. No dosage adjustment necessary.	No data
Oral contraceptives	No significant effect. No dosage adjustment necessary.	No data
Acyclovir, valacyclovir, cidofovir, ganciclovir, valganciclovir, aminoglycosides, high-dose or multiple NSAIDS or other drugs that reduce renal function or compete for active renal tubular secretion	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related renal toxicities.	No data

WHAT NOT TO USE

No antiretroviral regimens should be used for PrEP other than a daily oral dose of TDF/FTC, or a daily dose of TDF alone as an alternative only for IDU and heterosexually active adults.

Other medications and other dosing schedules have not yet been shown to be safe or effective in preventing HIV acquisition among otherwise healthy adults and are not approved by FDA for PrEP.

- Do not use other antiretroviral medications (e.g., 3TC), either in place of, or in addition to, TDF/FTC or TDF.
- Do not use other than daily dosing (e.g., intermittent, episodic [pre/post sex only], or other discontinuous dosing)
- Do not provide PrEP as expedited partner therapy (i.e., do not prescribe for an uninfected person not in your care).

TIME TO ACHIEVING PROTECTION

The time from initiation of daily oral doses of TDF/FTC to maximal protection against HIV infection is unknown. There is not scientific consensus on what intracellular concentrations are protective for either drug or the protective contribution of each drug in specific body tissues. It has been shown that the pharmacokinetics of TDF and FTC vary by tissue[80].

Data from exploratory pharmacokinetic studies conducted with HIV-uninfected men and women does provide preliminary data on the lead-time required to achieve steady state levels of tenofovir diphosphate (TFV-DP, the activated form of the medication) in blood (PBMCs [peripheral blood mononuclear cells]), rectal, and vaginal tissues[81,82]. These data suggest that maximum intracellular concentrations of TFV-DP are reached in blood after approximately 20 days of daily oral dosing, in rectal tissue at approximately 7 days, and in cervicovaginal tissues at

approximately 20 days. No data are yet available about intracellular drug concentrations in penile tissues susceptible to HIV infection to inform considerations of protection for male insertive sex partners.

MANAGING SIDE EFFECTS

Patients taking PrEP should be informed of side effects among HIV-uninfected participants in clinical trials (see Table 5). In these trials, side effects were uncommon and usually resolved within the first month of taking PrEP ("start-up syndrome"). Clinicians should discuss the use of over-the-counter medications for headache, nausea, and flatulence should they occur. Patients should also be counseled about signs or symptoms that indicate a need for urgent evaluation (e.g., those suggesting possible acute renal injury or acute HIV infection).

CLINICAL FOLLOW-UP AND MONITORING

Once PrEP is initiated, patients should return for follow-up approximately every 3 months. Clinicians may wish to see patients more frequently at the beginning of PrEP (e.g., 1 month after initiation, to assess and confirm HIV-negative test status, assess for early side effects, discuss any difficulties with medication adherence, and answer questions.

All patients receiving PrEP should be seen as follows:

- **At least every 3 months to**
  - Repeat HIV testing and assess for signs or symptoms of acute infection to document that patients are still HIV negative (see Figure)
  - Repeat pregnancy testing for women who may become pregnant
  - Provide a prescription or refill authorization of daily TDF/FTC for no more than 90 days (until the next HIV test)
  - Assess side effects, adherence, and HIV acquisition risk behaviors
  - Provide support for medication adherence and risk-reduction behaviors
  - Respond to new questions and provide any new information about PrEP use
- **At least every 6 months to**
  - Monitor eCrCl
    - If other threats to renal safety are present (e.g., hypertension, diabetes), renal function may require more frequent monitoring or may need to include additional tests (e.g., urinalysis for proteinuria)
    - A rise in serum creatinine is not a reason to withhold treatment if eCrCl remains ≥60 ml/min.
    - If eCrCl is declining steadily (but still ≥60 ml/min), consultation with a nephrologist or other evaluation of possible threats to renal health may be indicated.
  - Conduct STI testing recommended for sexually active adolescents and adults (i.e., syphilis, gonorrhea, chlamydia)[83]

- **At least every 12 months to**
  - Evaluate the need to continue PrEP as a component of HIV prevention

Optional Assessments

Bone Health

Decreases in bone mineral density (BMD) have been observed in HIV-infected persons treated with combination antiretroviral therapy (including TDF-containing regimes)[84,85]. However, it is unclear whether this 3%-4% decline would be seen in HIV-uninfected persons taking fewer antiretroviral medications for PrEP. The iPrEx trial (TDF/FTC) and the CDC PrEP safety trial in MSM (TDF) conducted serial dual-emission x-ray absorptiometry (DEXA) scans on a subset of MSM in the trials and determined that a small (~1%) decline in BMD that occurred during the first few months of PrEP either stabilized or returned to normal[20,86] . There was no increase in fragility (atraumatic) fractures over the 1-2 years of observation in these studies comparing those persons randomized to receive PrEP medication and those randomized to receive placebo.

Therefore, DEXA scans or other assessments of bone health are not recommended before the initiation of PrEP or for the monitoring of persons while taking PrEP. However, any person being considered for PrEP who has a history of pathologic or fragility bone fractures or who has significant risk factors for osteoporosis should be referred for appropriate consultation and management.

Therapeutic drug monitoring

Similar to the limited use of therapeutic drug monitoring (TDM) in the treatment of HIV infection[66], several factors mitigate against the routine use of TDM during PrEP. These factors include (1) a lack of established concentrations in blood associated with robust efficacy of TDF or FTC for the prevention of HIV acquisition in adults after exposure during penile-rectal or penile-vaginal intercourse[87] and (2) the limited but growing availability of clinical laboratories that perform quantitation of antiretroviral medicine concentrations under rigorous quality assurance and quality control standards.

However, some clinicians may want to use TDM periodically to assess adherence to PrEP medication. If so, a key limitation should be recognized. The levels of medication in serum or plasma reflect only very recent doses, so they are not valid estimates of consistent adherence[88]. However, if medication is not detected or is detected at a very low level, support to reinforce medication adherence would be indicated.

Persons with Documented HIV Infection

All persons with HIV-positive test results whether at screening or while taking TDF/FTC or TDF alone as PrEP should be provided the following services[66].

- Laboratory confirmation of HIV status (see Figure)

- Determination of CD4 lymphocyte count and viral load to guide therapeutic decisions
- Documentation of results of genotypic HIV viral resistance testing to guide future treatment decisions
- Provision of, or referral to, an experienced provider for the ongoing medical management of HIV infection
- Counseling about their HIV status and steps they should take to prevent HIV transmission to others and to improve their own health
- Assistance with, or referral to, the local health department for the identification of sex partners who may have been recently exposed to HIV so that they can be tested for HIV infection, considered for nonoccupational postexposure prophylaxis (nPEP), and counseled about their risk-reduction practices[89]

In addition, a confidential report of new HIV infection should be provided to the local health department.

Discontinuing PrEP

Patients may discontinue PrEP medication for several reasons, including personal choice, changed life situations resulting in lowered risk of HIV acquisition, intolerable toxicities, chronic nonadherence to the prescribed dosing regimen despite efforts to improve daily pill-taking, or acquisition of HIV infection.

Upon discontinuation for any reason, the following should be documented in the health record:

- HIV status at the time of discontinuation
- Reason for PrEP discontinuation
- Recent medication adherence and reported sexual risk behavior

For persons with incident HIV infection, see Persons with Documented HIV Infection.

For persons with active hepatitis B infection, see Special Clinical Considerations.

Any person who wishes to resume taking PrEP medications after having stopped should undergo all the same pre-prescription evaluation as a person being newly prescribed PrEP. In addition, a frank discussion should clarify the changed circumstances since discontinuing medication that indicate the need to resume medication, and the commitment to, take it,

Special Clinical Considerations

The patient with certain clinical conditions requires special attention and follow-up by the clinician.

Women who become pregnant or breastfeed while taking PrEP medication

Women without HIV infection who have sex partners with documented HIV infection are at substantial risk of HIV acquisition during attempts to conceive (i.e., without a condom). In

addition, pregnancy is associated with an increased risk of HIV acquisition[90]. PrEP use periconception and during pregnancy by the uninfected partner may offer an additional tool to reduce the risk of sexual HIV acquisition. Both the FDA labeling information[6] and the perinatal antiretroviral treatment guidelines[91] permit this use. However, data directly related to the safety of PrEP use for a developing fetus are limited. Providers should discuss available information about potential risks and benefits of beginning or continuing PrEP during pregnancy so that an informed decision can be made. (See Clinical Providers' Supplement, Section 5 at http://www.cdc.gov/hiv/pdf/guidelines/PrEPProviderSupplement2014.pdf).

In the PrEP trials with heterosexual women, medication was promptly discontinued for those who became pregnant, so the safety for exposed fetuses could not be adequately assessed. A single small study of periconception use of TDF in 46 uninfected women in HIV-discordant couples found no ill effects on the pregnancy and no HIV infections.[92] Additionally, because TDF and FTC are widely used for the treatment of HIV infection and continued during pregnancies that occur,[76,77,93] The data on pregnancy outcomes in the Antiretroviral Pregnancy Registry provide no evidence of adverse effects among fetuses exposed to these medications[94].

Providers should educate HIV-discordant couples who wish to become pregnant about the potential risks and benefits of all available alternatives for safer conception[95] and if indicated make referrals for assisted reproduction therapies. Whether or not PrEP is elected, the HIV-infected partner should be prescribed effective antiretroviral therapy before conception attempts[96]: if the infected partner is male, to reduce the risk of transmission-related viral load in semen; and in both sexes, for the benefit of their own health[53].

In addition, health care providers are strongly encouraged to prospectively and anonymously submit information about any pregnancies in which PrEP is used to the Antiretroviral Pregnancy Registry at http://www.apregistry.com/.

The safety of PrEP with TDF/FTC or TDF alone for infants exposed during lactation has not been adequately studied. However, data from studies of infants born to HIV-infected mothers and exposed to TDF or FTC through breast milk suggest limited drug exposure.[93,97] Additionally, the World Health Organization has recommended the use of TDF/FTC or 3TC/efavirenz for all pregnant and breastfeeding women for the prevention of perinatal and postpartum mother-to-child transmission of HIV[98]. Therefore, providers should discuss current evidence about the potential risks and benefits of beginning or continuing PrEP during breastfeeding so that an informed decision can be made.

Patients with Chronic Active Hepatitis B Virus Infection

TDF and FTC are each active against both HIV infection and HBV infection and thus may prevent the development of significant liver disease by suppressing the replication of HBV. Only TDF, however, is currently FDA-approved for this use. Therefore, in persons with substantial

risk of both HIV acquisition and active HBV infection, daily doses of TDF/FTC may be especially indicated.

All persons screened for PrEP who test positive for hepatitis B surface antigen (HBsAg) should be evaluated by a clinician experienced in the treatment of HBV infection. For clinicians without this experience, co-management with an infectious disease or a hepatic disease specialist should be considered. Patients should be tested for HBV DNA by the use of a quantitative assay to determine the level of HBV replication[99] before PrEP is prescribed and every 6-12 months while taking PrEP.

TDF presents a very high barrier to the development of HBV resistance. However, it is important to reinforce the need for consistent adherence to the daily doses of TDF/FTC to prevent reactivation of HBV infection with the attendant risk of hepatic injury, and to minimize the possible risk of developing TDF-resistant HBV infection[100].

If PrEP is no longer needed to prevent HIV infection, a separate determination should be made to about whether to continue TDF/FTC as a means of providing TDF to treat HBV infection. Acute flares resulting from the reactivation of HBV infection have been seen in HIV-infected persons after the cessation of TDF and other medications used to treat HBV infection. Such flares have not yet been seen in HIV-uninfected persons with chronic active HBV infection who have stopped taking TDF-containing PrEP regimens. Nonetheless, when such patients discontinue PrEP, they should continue to receive care from a clinician experienced in the management of HBV infection so that if flares occur, they can be detected promptly and treated appropriately.

Patients with Chronic Renal Failure

HIV-uninfected patients with chronic renal failure, as evidenced by an eCrCl of <60 ml/min, should not take PrEP because the safety of TDF/FTC for such persons was not evaluated in the clinical trials. TDF is associated with modestly reduced renal function when used as part of an antiretroviral treatment regimen in persons with HIV infection (which itself can affect renal function). Because other HIV prevention options are available, the only PrEP regimen proven effective to date (TDF/FTC) and approved by FDA for PrEP is not indicated for persons with chronic renal failure.[6]

Adolescent Minors[101]

As a part of primary health care, HIV screening should be discussed with all adolescents who are sexually active or have a history of injection drug use. Parental/guardian involvement in an adolescent's health care is often desirable but is sometimes contraindicated for the safety of the adolescent. However, laws and regulations that may be relevant for PrEP-related services (including HIV testing), such as those concerning consent, confidentiality, parental disclosure, and circumstances requiring reporting to local agencies, differ by jurisdiction[5]. Clinicians considering providing PrEP to a person under the age of legal adulthood (a minor) should be aware of local laws, regulations, and policies that may apply[102].

Although the FDA labeling information specifies PrEP indications for "adults," an age above which an adolescent is considered an adult is not provided.[6] None of the completed PrEP trials have included persons under the age of 18. Therefore, clinicians should consider carefully the lack of data on safety and effectiveness of PrEP taken by persons under 18 years of age, the possibility of bone or other toxicities among youth who are still growing, and the safety evidence available when TDF/FTC is used in treatment regimens for HIV-infected youth[103]. These factors should be weighed against the potential benefit of providing PrEP for an individual adolescent at substantial risk of HIV acquisition.

Nonoccupational Postexposure Prophylaxis

Persons not receiving PrEP who seek care within 72 hours after an isolated sexual or injection-related HIV exposure should be evaluated for the potential need for nPEP[104]. If such exposures are not isolated, and the person is determined not to have HIV infection, clinicians should consider beginning PrEP immediately because PrEP during the first 28 days is consistent with a recommended nPEP regimen[104]. If the exposure is isolated (e.g., sexual assault, infrequent condom failure), nPEP should be prescribed, but continued antiretroviral medication is not indicated after completion of the 28-day PEP course.

Persons who repeatedly seek nPEP should be evaluated for possible PrEP use after confirming they have not acquired HIV infection[105]. Because HIV infection has been reported in association with exposures soon after an nPEP course[98], daily PrEP may be more protective than repeated episodes of nPEP.

Improving Medication Adherence

Data from the published studies of daily oral PrEP indicate that medication adherence is critical to achieving the maximum prevention benefit (see Table 4) and reducing the risk of selecting for a drug-resistant virus if non-adherence leads to HIV acquisition[106,107]. Three additional studies reinforce the need to prescribe, and support adherence to uninterrupted daily doses of TDF/FTC.

A study of the pharmacokinetics of directly observed TDF dosing in MSM in the STRAND trial found that the intracellular levels of the active form of TDF (tenofovir diphosphate), when applied to the drug detection-efficacy statistical model with iPrEx participants, corresponded to an HIV risk reduction efficacy of 99% for 7 doses per week, 96% for 4 doses per week, and 76% for 2 doses per week[87]. This finding adds to the evidence that despite some "forgiveness" for occasional missed doses, a high level of prevention efficacy requires a high level of adherence to daily medication.

A pilot study of daily TDF/FTC as PrEP with young MSM was stopped when the iPrEx trial results were reported.[108] Among the 68 men enrolled (mean age, 20 years; 53% African American; 40% Hispanic/Latino) plasma specimens were tested to objectively measure

medication adherence. At week 4, 63% had detectable levels of tenofovir, but at week 24, only 20% had detectable levels of tenofovir.

In addition, a study with MSM and commercial sex workers in Kenya evaluated adherence to daily, fixed-interval (Mondays and Fridays), and coitally-timed (single post-coital) TDF/FTC dosing schedules by the use of pill bottles with caps monitored by an electronic medication event monitoring system (MEMS) and monthly interviews about sexual behavior[12]. Among the 67 men and 5 women in this study, 83% adhered to daily dosing, 55% to fixed-interval dosing, and 26% to post-coital dosing regimens. These findings suggest that adherence is better with daily dosing, as currently recommended, than with non-daily regimens (not yet proven effective as PrEP). These data confirm that medication education and adherence counseling (also called medication self-management) will need to be provided to support daily PrEP use.

A recent review of the antiretroviral treatment adherence studies over the past 15 years and adherence data from the completed PrEP trials suggests various approaches to effectively support medication adherence[109]. These approaches include educating patients about their medications; helping them anticipate and manage side effects; helping them establish dosing routines that mesh with their work and social schedules; providing reminder systems and tools; addressing financial, substance abuse, or mental health needs that may impede adherence; and facilitating social support.

Although many published articles address antiretroviral medication adherence among persons being treated for HIV infection, these findings may be only partially applicable to PrEP users. HIV treatment regimens include more than 2 drugs (commonly including more than 1 pill per day), resulting in an increased pill burden, and the possibility of side effects and toxicities with 3 or more drugs may occur that would not occur with TDF/FTC alone. The motivations of persons being treated for HIV infection and persons trying to prevent HIV infection may differ. Because PrEP will be used in otherwise healthy adults, studies of the use of medications in asymptomatic adults for the prevention of potential serious future health outcomes may also be informative for enhancing adherence to PrEP medications. The most cost-effective interventions for improving adherence to antihypertensive and lipid-lowering medications were initiated soon after the patients started taking medication and involved personalized, regularly scheduled education and symptom management (patients were aware that adherence was being monitored)[110]. Patients with chronic diseases reported that the most important factors in adherence to medications were incorporating medication into their daily routines, knowing that the medications work, believing that the benefits outweigh the risks, knowing how to manage side effects, and low out-of pocket costs.[111,112]

When initiating a PrEP regimen, clinicians must educate patients so that they understand clearly how to take their medications (i.e., when to take them, how many pills to take at each dose) and what to do if they experience problems (e.g., what constitutes a missed dose [number of hours after the failure to take a scheduled dose], what to do if they miss a dose). Patients should be

told to take a single missed dose as soon as they remember it, unless it is almost time for the next dose. If it is almost time for the next dose, patients should skip the missed dose and continue with the regular dosing schedule.

Side effects can lead to non-adherence, so clinicians need a plan for addressing them. Clinicians should tell patients about the most common side effects and should work with patients to develop a specific plan for handling them, including the use of specific over-the-counter medications that can mitigate symptoms[113]. The importance of using condoms during sex, especially for patients who decide to stop taking their medications, should be reinforced.

Box D: Key Components of Medication Adherence Counseling

Establish trust and bidirectional communication

Provide simple explanations and education

- Medication dosage and schedule
- Management of common side effects
- Relationship of adherence to the efficacy of PrEP
- Signs and symptoms of acute HIV infection and recommended actions

Support adherence

- Tailor daily dose to patient's daily routine
- Identify reminders and devices to minimize forgetting doses
- Identify and address barriers to adherence

Monitor medication adherence in a non-judgmental manner

- Normalize occasional missed doses, while ensuring patient understands importance of daily dosing for optimal protection
- Reinforce success
- Identify factors interfering with adherence and plan with patient to address them
- Assess side effects and plan how to manage them

Using a broad array of a health care professionals (e.g., physicians, nurses, case-managers, physician assistants, clinic-based and community pharmacists) that work together on a health care team to influence and reinforce adherence instructions[114] significantly improves medication adherence and may alleviate the time constraints of individual providers.[115,116] This broad-team approach may also provide a larger number of providers to counsel patients about self-management of behavioral risks.

For additional information on adherence counseling, see the Clinical Providers' Supplement, Section 6 at http://www.cdc.gov/hiv/pdf/guidelines/PrEPProviderSupplement2014.pdf.

Reducing HIV Risk Behaviors

The adoption and the maintenance of safer behaviors (sexual, injection, and other substance abuse) are critical for the lifelong prevention of HIV infection and are important for the clinical management of persons prescribed PrEP.

Video-based interventions such as Safe in the City, which make use of waiting-room time rather than clinician time,[117] have reduced STI incidence in a general clinic population. However, they take a general approach, so they do not allow tailoring to the sexual risk-reduction needs of individual patients (e.g., as partners change, PrEP is initiated or discontinued).

Interactive, client-centered counseling (in which content is tailored to a patient's sexual risk behaviors and the situations in which risks occur), in conjunction with goal-setting strategies is effective in HIV prevention[105,118-120]. An example of this method is Project Respect: although this counseling protocol alone did not reduce HIV incidence significantly 20-minute clinical counseling sessions to develop and review patient-specific, incremental risk-reduction plans led to reduced incidence of STIs in a heterosexual population,[121] . Project Aware included MSM and heterosexuals attending STD clinics and provided a single brief counseling session (using the Respect-2 protocol) while conducting rapid HIV testing. There was no reduction in the incidence of STIs attributed to counseling[122] . However, in the context of PrEP delivery, brief, repeated counseling sessions can take advantage of multiple visits for follow-up care[123] while addressing the limited time available for individual visits[124] and the multiple prevention[115,116] and treatment topics that busy practitioners need to address.

Reducing or eliminating injection risk practices can be achieved by providing access to drug treatment and relapse prevention services (e.g., methadone, buprenorphine for opiate users) for persons who are willing to participate[125]. For persons not able (e.g., on a waiting list or lacking insurance) or not motivated to engage in drug treatment, providing access to unused injection equipment through syringe service programs (where available), prescriptions for syringes or purchase from pharmacies without a prescription (where legal) can reduce HIV exposure. In addition, providing or referring for cognitive or behavioral counseling and any indicated mental health or social services may help reduce risky injection practices. See the Substance Abuse Treatment and Mental Health Treatment Locators at http://findtreatment.samhsa.gov/.

For additional information on risk reduction interventions, see Clinical Providers' Supplement, Section 7 at http://www.cdc.gov/hiv/pdf/guidelines/PrEPProviderSupplement2014.pdf.

Box E: Key Components of Behavioral Risk-Reduction Counseling

Establish trust and 2-way communication

Provide feedback on HIV risk factors identified during sexual and substance use history taking

- Elicit barriers to, and facilitators of, consistent condom use
- Elicit barriers to, and facilitators of, reducing substance abuse

Support risk-reduction efforts

- Assist patient to identify 1 or 2 feasible, acceptable, incremental steps toward risk reduction
- Identify and address anticipated barriers to accomplishing planned actions to reduce risk

Monitor behavioral adherence in a non-judgmental manner

- Acknowledge the effort required for behavior change
- Reinforce success
- If not fully successful, assess factors interfering with completion of planned actions and assist patient to identify next steps

Financial Case-Management Issues for PrEP

One critical component in providing PrEP medications and related clinical and counseling services is identifying insurance and other reimbursement sources. Although some commercial insurance and employee benefits programs have defined policies for the coverage of PrEP, others have not yet done so. Similarly, public insurance sources vary in their coverage policy.

For patients who do not have health insurance, whose insurance does not cover PrEP medication, and whose personal resources are inadequate to pay out-of-pocket, Gilead Sciences has established a PrEP medication assistance program. In addition to providing Truvada to providers for eligible patients and access to free HIV testing, the program provides co-pay assistance for medical care visits and free condoms to patients on request[126]. Providers may obtain applications for their patients at https://start.truvada.com/.

Decision Support, Training and Technical Assistance

Decision support systems (electronic and paper), flow sheets, checklists (see Clinical Providers' Supplement, Section 1 for a PrEP provider/patient checklist at http://www.cdc.gov/hiv/pdf/guidelines/PrEPProviderSupplement2014.pdf), feedback reminders, and involvement of nurse clinicians and pharmacists will be helpful in managing the many steps indicated for the safe use of PrEP and to increase the likelihood that patients will follow them. Often these systems are locally developed but may become available from various sources including training centers and Web sites funded by government agencies; professional associations, or interested private companies. Examples include downloadable applications (widgets) to support the delivery of nPEP or locate nearby sites for confidential HIV tests (http://www.hivtest.org); and confidential commercial services to electronically monitor

medication-taking, send text message reminders, or provide telephone assistance to help patients with problems concerning medication adherence.

Training and technical assistance in providing components of PrEP-related services, medications, and counseling are available at the following Web sites:

- AIDS Info (http://www.aidsinfo.nih.gov, http://www.aids.gov);
- The National Network of STD/HIV Prevention Training Centers (http://nnptc.org/),
- The AIDS Education Training Centers National Resource Center (http://www.aids-ed.org)
- The Addiction Technology Transfer Center Network (http://www.attcnetwork.org);
- The National HIV/AIDS Clinicians' Consultation Service (http://www.nccc.ucsf.edu).

Related DHHS Guidelines

This document is consistent with several other guidelines from several DHHS agencies related to sexual health, HIV prevention, and the use of antiretroviral medications. Clinicians should refer to these other documents for detailed guidance in their respective areas of care.

- Sexually Transmitted Diseases Treatment Guidelines, 2010[83]
- Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents[66]
- Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, and Chlamydial Infection[89]
- Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States[104]
- Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings[60]
- Expedited Partner Therapy in the Management of Sexually Transmitted Diseases[127]
- Behavioral counseling to prevent sexually transmitted infections: U.S. Preventive Services Task Force recommendation statement[119]
- Recommendations on Screening For HIV[128]
- Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection[76]
- Integrated prevention services for HIV infection, viral hepatitis, sexually transmitted diseases, and tuberculosis for persons who use drugs illicitly: summary guidance from CDC and the U.S. Department of Health and Human Services[59]

Appendices

APPENDIX 1 HIV TEST TABLES

Table 11: FDA-Approved HIV Rapid Tests Typically Used for Point-of-Care testing or in Clinicians Offices[64,129] (as of February 2014)

Test Name	CLIA-Waived Testing[a]	CLIA-Moderately Complex Testing[a]	Approximate window period to HIV detection
OraQuick Advance Rapid HIV-1/2 Antibody Test	Oral fluid; fingerstick whole blood; EDTA, ACD, or heparin venipuncture whole blood	Plasma	4–5 weeks (blood) >4 weeks (oral fluid)
Alere Determine HIV-1/2 Ag/Ab Combo Test	Not approved for CLIA-Waived testing	Fingerstick whole blood; EDTA, ACD, or heparin venipuncture whole blood	2–4 weeks
Uni-Gold Recombigen HIV-1	Fingerstick whole blood; EDTA, ACD, or heparin venipuncture whole blood	Plasma/ Serum	4–5 weeks
Clearview HIV-1/2 STAT-PAK	Fingerstick whole blood; EDTA, ACD, or heparin venipuncture whole blood	Plasma/ Serum	4–5 weeks
Clearview Complete HIV-1/2	Fingerstick whole blood; EDTA, ACD, or heparin venipuncture whole blood	Plasma/ Serum	4–5 weeks
INSTI HIV-1 Antibody Test Kit	Fingerstick whole blood; EDTA, ACD, or heparin venipuncture whole blood	Plasma	4–5 weeks
Chembio DPP HIV-1/2 Assay	Not approved for CLIA-Waived testing	Fingerstick whole blood; EDTA, ACD, or heparin venipuncture whole blood; oral fluid; Plasma/Serum	3–4 weeks
Multispot HIV-1/HIV-2 Rapid Test (differentiates HIV-1 and HIV-2)	Not approved for CLIA-Waived testing	Plasma/Serum	3–4 weeks
Reveal Rapid HIV-1 Antibody Test	Not approved for CLIA-Waived testing	Plasma/Serum	3–4 weeks

CLIA, Clinical Laboratory Improvement Amendments

[a] Only unprocessed (not centrifuged) specimens can be used by sites with a CLIA Certificate of Waiver. However labs with certificates for moderate or high complexity testing can use centrifuged blood for testing. Many laboratories use rapid tests as part of their testing strategy.

Table 12: FDA-Approved Diagnostic Laboratory Based HIV Tests (CLIA-High Complexity Tests)[64,129] (as of February 2014)

Trade Name	Testing Format	Samples Used	Approximate Window Period to HIV Detection
GS HIV Combo Ag/Ab EIA Assay	Manual and semi-automated EIA	Serum/Plasma	2–3 weeks
Abbott ARCHITECT HIV Ag/Ab Combo	Fully automated chemiluminescent microparticle immunoassay	Serum/Plasma	2–3 weeks
ADVIA Centaur HIV 1/O/2 Enhanced (EHIV)	Fully automated chemiluminescent microparticle immunoassay	Serum/Plasma	2–3 weeks
Vitros Anti-HIV 1+2 Assay	Fully automated chemiluminescent microparticle immunoassay	Serum/Plasma	2–3 weeks
GS HIV-1/HIV-2 Plus O EIA	Manual and semi-automated EIA	Serum/Plasma	2–3 weeks
APTIMA HIV-1 RNA Qualitative Assay	Manual TMA	Serum/Plasma	1–2 weeks
GS HIV-1 Western Blot[a]	Manual Western blot	Serum/Plasma, Dried Blood Spot	4–5 weeks
Fluorognost HIV-1 IFA[a]	Manual immunofluorescent antibody	Serum/Plasma, Dried Blood Spot	4–5 weeks

[a] These are supplemental tests not intended for primary diagnostic screening; they are used to confirm the test result of a diagnostic screening test.

APPENDIX 2 GRADING OF STRENGTH OF RECOMMENDATIONS AND QUALITY OF EVIDENCE

Key recommendations in this guideline are based on the review of published scientific evidence and expert opinions. Using the same grading system as the DHHS antiretroviral treatment guidelines[66], these key recommendations are rated with a letter to indicate the strength of the recommendation and with a numeral to indicate the quality of the evidence supporting the recommendation.

Table 13: Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence Supporting a Recommendation
A. Strong recommendation for the statement	**I.** One or more well-executed randomized, controlled trials with clinical outcomes, validated laboratory endpoints, or both
B. Moderate recommendation for the statement	**II.** One or more well-executed, nonrandomized trials or observational cohort studies with clinical outcomes
C. Optional recommendation for the statement	**III.** Expert opinion

The quality of scientific evidence ratings in Table 2 are based on the GRADE rating system.[28]

Table 14: Criteria for rating quality of scientific evidence

Type of evidence	Randomized trial = high Observational study = low Any other evidence = very low
Decrease grade if[a]	▪ Serious or very serious limitation to study quality ▪ Important inconsistency ▪ Some or major uncertainty about directness ▪ Imprecise or sparse data ▪ High probability of reporting bias
Increase grade if[a]	▪ Strong evidence of association – significant relative risk >2 (<0.5) based on consistent evidence from 2 or more observational studies, with no plausible confounders (+1) ▪ Very strong evidence of association – significant relative risk of >5 (<0.2) based on direct evidence with no major threats to validity (+2) ▪ Evidence of a dose-response gradient (+1) ▪ All plausible confounders would have reduced the effect (+1)
Range	High-quality evidence Moderate-quality evidence Low-quality evidence Very-low quality evidence

[a] Each quality criterion can reduce or increase the quality by 1 or, if very significant, by 2 levels.
Source: http://www.gradeworkinggroup.org/FAQ/evidence_qual.htm

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The working groups and expert panels listed here were convened by teleconference before trial results were available (2009-2010) and some were reconvened after each trial results for each population group was published. As technical experts, prevention partners, and key stakeholders, they were asked to assist us to identify relevant scientific/medical literature and share thoughts on topics that would inform the development of possible future guidelines for PrEP use in the US. They did not participate in the writing of these guidelines. No financial disclosures were sought. See Providers' Supplement section 10 for a description of the criteria use for constitution of the working groups. Institutional associations listed for participants are those at the time of the group discussions and may have changed since.

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