US Public Health Service

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2017 UPDATE

A CLINICAL PRACTICE GUIDELINE

What's New in the Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2017 Update – A Clinical Practice Guideline?

(Published online March 2018)

The Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 was published in an electronic format in July 2014 so that it could be updated as relevant changes in supporting evidence became available. The Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2016: Update – A Clinical Practice Guideline includes revisions to several sections. These revisions are highlighted throughout the document and are intended solely to update the developing evidence base or to clarify specific points in clinical care. No changes were made to the graded recommendations for the use of PrEP in the US.

Evidence of the Safety and Efficacy of Antiretroviral Prophylaxis

Based on an updated systematic review of publications through June 2017, data from trials and open-label studies were added to the text summary and evidence tables.

Identifying Indications for PrEP

In Box B3 (recommended indications for PrEP use by injection drug users) we deleted whether they had been in drug treatment in the prior 6 months as this was causing confusion for many clinicians.

Laboratory Tests and other Diagnostic Procedures

We replaced the HIV test characteristic tables previously in appendices with a link to a CDC website that is more frequently updated.

The figure and text on testing by clinicians to determine HIV status for PrEP provision (including detection of acute HIV infection) was revised to include a preference for antigen/antibody testing whenever available (rather than antibody-only tests) and use of a 3,000 copies/ml cut-off for suspected false-positive viral load tests.

Additional information about hepatitis C screening associated with provision of PrEP is provided, consistent with the 2017 American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) guidance.

Providing PrEP

Ledipasvir/sofosbuvir was added to the table (10) of drug interactions

Tenofovir alafenamide (TAF) was added to the section "What not to use"

We revised the clinical follow up schedule to include STI testing for asymptomatic MSM at high risk for recurrent STIs (e.g., those with recent STIs or multiple sex partners) at the 3 month visit in addition to testing for all symptomatic sexually-active persons. This is consistent with 2015 STD guidelines recommendation for STD screening every 3-6 months with multiple sex partners (https://www.cdc.gov/std/tg2015/tg-2015-print.pdf).

Minor revisions were also made to correct typos, add references, and update content from cited guidelines and source materials.

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For more clinical advice about PrEP guidelines:

- call the National Clinicians Consultation Center PrEPline at **855-448-7737** or
- go to their website at http://nccc.ucsf.edu/clinician-consultation/prep-pre-exposure-prophylaxis/

Table of Contents

List of Tables, Figures, and Boxes

Abbreviations (In Guideline and Clinical Providers' 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
IQR	interquartile range
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 name Viread®)
TAF	tenofovir alafenamide
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 – 2017 Update: 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 persons who inject drugs (PWID) (also called 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 PWID 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)**

[1] See Appendix 1, Grading of Strength of Recommendations and Quality of Evidence (Tables 12-13)

- 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 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

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

STI: sexually transmitted infection

† Gonorrhea, chlamydia, syphilis for MSM including those who inject drugs
‡ Gonorrhea, syphilis for heterosexual women and men including those who inject drugs

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 persons who injection drugs (PWID) (also called 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 the 2014 recommendations were 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. For the 2017 update, the systematic review of published literature was updated through June 2017 and expanded to include the terms *chemoprophylaxis* and *chemoprevention* and searches of the MEDLINE, Embase, CINAHL, and Cochrane Library database in addition to those used in 2014. The results of this systematic review were crosschecked for completeness with the review conducted by the World Health

[§] 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.

Organization[9]. For additional information about the systematic review process, see the Clinical Providers' Supplement, Section 14 at https://www.cdc.gov/hiv/pdf/risk/prep-cdc-hiv-prep-provider-supplement-2017.pdf

Potential conflicts of interest: CDC and individual employees involved in the guideline development process are named in US government patents and patent applications related to methods for HIV prophylaxis.

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[10], with heterosexually active adults[11], and with PWID (also called IDU)[12]. Currently, prescribing daily oral PrEP with TDF/FTC is recommended as one prevention option for MSM, heterosexual men, heterosexual women, and PWID 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 40,000 people in the United States are infected with HIV each year[13]. From 2008 through 2014, estimated annual HIV incidence declined 18% overall but progress was uneven. Although declines occurred among heterosexuals, PWID, and white MSM, no decline was observed in the estimated number of annual HIV infections among black MSM and an increase was documented among Latino MSM[13]. In 2015, 67% of the 39,513 newly diagnosed HIV infections were attributed to male-male sexual activity without injection drug use, 3% to male-male sexual activity with injection drug use, 24% to male-female sexual contact without injection drug use, and 6% to injection drug use. Among the 24% of persons with newly diagnosed HIV infection attributed to heterosexual activity, 64% were African-American women and men[14]. 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[15]. 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[16-18].

Evidence from these human studies of blood-borne and perinatal transmission as well as studies of vaginal and rectal exposure among animals 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 and open label or observational studies published as of June 2017 are summarized below. See also Tables 2-7. The quality of evidence in each study was assessed using GRADE criteria (http://www.gradeworkinggroup.org/FAQ/evidence_qual.htm) and the strength of evidence for all studies relevant to a specific recommendation was assessed by the method used in the DHHS antiretroviral treatment guidelines (See Appendix 1)

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.

In the original iPrEx publication[2], of 2,499 MSM, 29 identified as female (i.e., transgender women). In a subsequent subgroup analysis[19], men were categorized as transgender women (n=339) if they were born male and either identified as women (n=29), identified as transgender (n=296), or identified as male and used feminizing hormones (n=14). Using this expanded definition, among transgender women, no efficacy of PrEP was demonstrated. There were 11 infections among the PrEP group and 10 in the placebo group (HR 1.1, 95% CI: 0.5-2.7). By drug level testing (*always* versus *less than always*), compared with MSM, transgender women had less consistent PrEP use OR 0.39 (95% CI: 0.16-0.96). In the subsequent open-label extension study (see below), one transgender woman seroconverted while receiving PrEP and one seroconversion occurred in a woman who elected not to use PrEP.

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.

ADOLESCENT TRIALS NETWORK (ATN) 082

ATN 082[21] was a randomized, blinded, pilot feasibility study comparing daily PrEP with TDF/FTC with and without a behavioral intervention (Many Men, Many Voices) to a third group with no pill and no behavioral intervention. Participants had study visits every 4 weeks with audio-computer assisted interviews (ACASI), blood draws, and risk-reduction counseling. The outcomes of interest were acceptability of study procedures, adherence to pill-taking, safety of TDF/FTC, and levels of sexual risk behaviors among a population of young (ages 18-22 years) MSM in Chicago. One hundred participants were to be followed for 24 weeks, but enrollment was stopped and the study was unblinded early when the iPrEx study published its efficacy result. Sixty-eight participants were enrolled. By drug level detection, adherence was modest at week 4 (62%), and declined to 20% by week 24. No HIV seroconversions were observed.

IPERGAY (INTERVENTION PRÉVENTIVE DE L'EXPOSITION AUX RISQUES AVEC ET POUR LES GAYS)

The results of a randomized, blinded, trial of non-daily dosing of TDF/FTC or placebo for HIV preexposure prophylaxis has also been published[22] and is included here for completeness, although non-daily dosing is not currently recommended by the FDA or CDC.

Four-hundred MSM in France and Canada were randomized to a complex peri-coital dosing regimen that involved taking 1) 2 pills (TDF/FTC or placebo) between 2 and 24 hours before sex, 2) 1 pill 24 hours after the first dose, 3) 1 pill 48 hours after the first dose, 4) continuing daily pills if sexual activity continues until 48 hours after the last sex. If more than a 1 week break occurred since the last pill, retreatment initiation was with 2 pills before sex or if less than a 1 week break occurred since the last pill, retreatment initiation was with 1 pill before sex. Each pre-sex dose was then followed by the 2 post-sex doses. Study visits were scheduled at 4 and 8 weeks after enrollment, and then every 8 weeks. At study visits, participants completed a computer-assisted interview, had blood drawn, received adherence and risk reduction counseling, received diagnosis and treatment of STIs as indicated, and had a pill count and a medication refill. Following an interim analysis by the data and safety monitoring board at which efficacy was determined, the placebo group was discontinued and all study participants were offered TDF/FTC. In the blinded phase of the trial, efficacy was 86% (95% CI: 40-98). By self-report,

patients took a median of 15 pills per month. By measured plasma drug levels in a subset of those randomized to TDF/FTC, 86% had TDF levels consistent with having taken the drug during the previous week.

Because of the high frequency of sex and therefore of pill-taking among those in this study population, it is not yet known whether the regimen will work if taken only a few hours or days before sex, without any buildup of the drug in rectal tissue from prior use. Studies suggest that it may take days, depending on the site of sexual exposure, for the active drug in PrEP to build up to an optimal level for preventing HIV infection. No data yet exist on how effective this regimen would be for heterosexual men and women, and persons who inject drugs, or on adherence to this relatively complex PrEP regimen outside a trial setting. IPERGAY findings, combined with other recent research, suggest that even with less than perfect daily adherence, PrEP may still offer substantial protection for MSM if taken consistently.

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 Observational and Open-Label Studies of Antiretroviral Preexposure Prophylaxis Among Men Who Have Sex with Men

iPrEx Open-Label Extension (OLE) Study

Persons previously enrolled in the iPrEx, ATN 082, and CDC safety PrEP clinical trials were enrolled in a 72 week open-label study and were offered PrEP free of charge[23]. Seventy-six percent of 1,603 persons (1,428 MSM and 175 transgender women) enrolled received PrEP. HIV incidence among those receiving PrEP was 1.8 per 100 person-years (py) versus 2.6 per 100 py in those concurrently not choosing PrEP (HR 0.51, 95% CI: 0.26-1.01), adjusted for baseline sexual behaviors. Among those receiving PrEP, by dried blood spot drug levels, there were no infections in persons with drug levels associated with having taken 4 or more doses per week ($p<0.0001$) compared with those taking < 2 doses per week.

PROUD Open-Label Extension (OLE) Study

PROUD was an open-label, randomized, wait-list controlled trial designed for MSM attending sexual health clinics in England[24]. A pilot was initiated to enroll 500 MSM, in which 275 men were randomized to receive daily oral TDF/FTC immediately, and 269 were deferred to start after 1 year. At an interim analysis, the data monitoring committee stopped the trial early for efficacy at an interim analysis and recommended that all deferred participants be offered PrEP. Follow-up was completed for 94% of those in the immediate PrEP arm and 90% of those in the deferred arm. PrEP efficacy was 86% (90% CI: 64-96).

KAISER PERMANENTE OBSERVATIONAL STUDY

An evaluation of a specialized PrEP program provided at the Kaiser Permanente San Francisco Medical Center[25] reported on a cohort of 653 MSM, 3 heterosexual women, and 1 transgender man (with male sexual partners) who initiated PrEP between July 2012 and February 2015. Of these, 20 restarted PrEP after discontinuing it during the study period. The mean duration of use was 7.2 months. No HIV diagnoses were made during 388 py of follow-up on PrEP. No medication adherence measures were reported. After 12 months of use, 50% of PrEP users had received a diagnosis of one or more STI (95% CI: 26-35). In a recent report on PrEP patients seen at this center, as of February 2017, there were no HIV infections during 5104 py of PrEP use while they were being prescribed medication[26].

DEMO PROJECT OPEN-LABEL STUDY

In this demonstration project, conducted at 3 community-based clinics in the United States[27], MSM (n = 430) and transgender women (n=5) were offered daily oral TDF/FTC free of charge for 48 weeks. All patients received HIV testing, brief counseling, clinical monitoring, and STI diagnosis and treatment at quarterly follow-up visits. A subset of men underwent drug level monitoring with dried-blood spot testing and protective levels (associated with ≥4 doses per week) were high (80.0%-85.6%) at follow-up visits across the sites. STI incidence remained high but did not increase over time. Two men became infected (HIV incidence 0.43 infections per 100 py, 95% CI: 0.05-1.54), both of whom had drug levels consistent with having taken fewer than 2 doses per week at the visit when seroconversion was detected.

IPERGAY OPEN-LABEL EXTENSION (OLE) STUDY

Findings have been reported from the open-label phase of the Ipergay trial that enrolled 361 of the original trial participants[28]. All of the open-label study participants were provided peri-coital PrEP as in the original trial. After a mean follow-up time of 18.4 months (IQR: 17.7-19.1), the HIV incidence observed was 0.19 per 100 py which, compared to the incidence in the placebo group of the original trial (6.60 per 100 py), represented a 97% (95% CI: 81-100) relative reduction in HIV incidence. The one participant who acquired HIV had not taken any PrEP in the 30 days before his reactive HIV test and was in an ongoing relationship with an HIV positive partner. Of 336 participants with plasma drug levels obtained at the 6-month visit, 71% had tenofovir detected. By self-report, PrEP was used at the prescribed dosing for the most recent sexual intercourse by 50% of participants, with suboptimal dosing by 24%, and not used by 26%. Reported condomless receptive anal sex at most recent sexual intercourse increased from 77% at baseline to 86% at the 18-month follow-up visit (p=0.0004). The incidence of a first bacterial STI in the observational study (59.0 per 100 py) was not higher than that seen in the randomized trial (49.1 per 100 py) (p=0.11).

The frequency of pill-taking in the open label study population was higher (median 18 pills per month) than that in the original trial (median 15 pills per month), Therefore it remains unclear

whether the regimen will be highly protective if taken only a few hours or days before sex, without any buildup of the drug from prior use.

Published Trials of Antiretroviral Preexposure Prophylaxis Among Heterosexual Men and Women

Partners PrEP Trial

The Partners PrEP trial[3,29] 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 py) and rates did not differ significantly between the study groups.

TDF2 Trial

The Botswana TDF2 Trial[4], 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[30] 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.

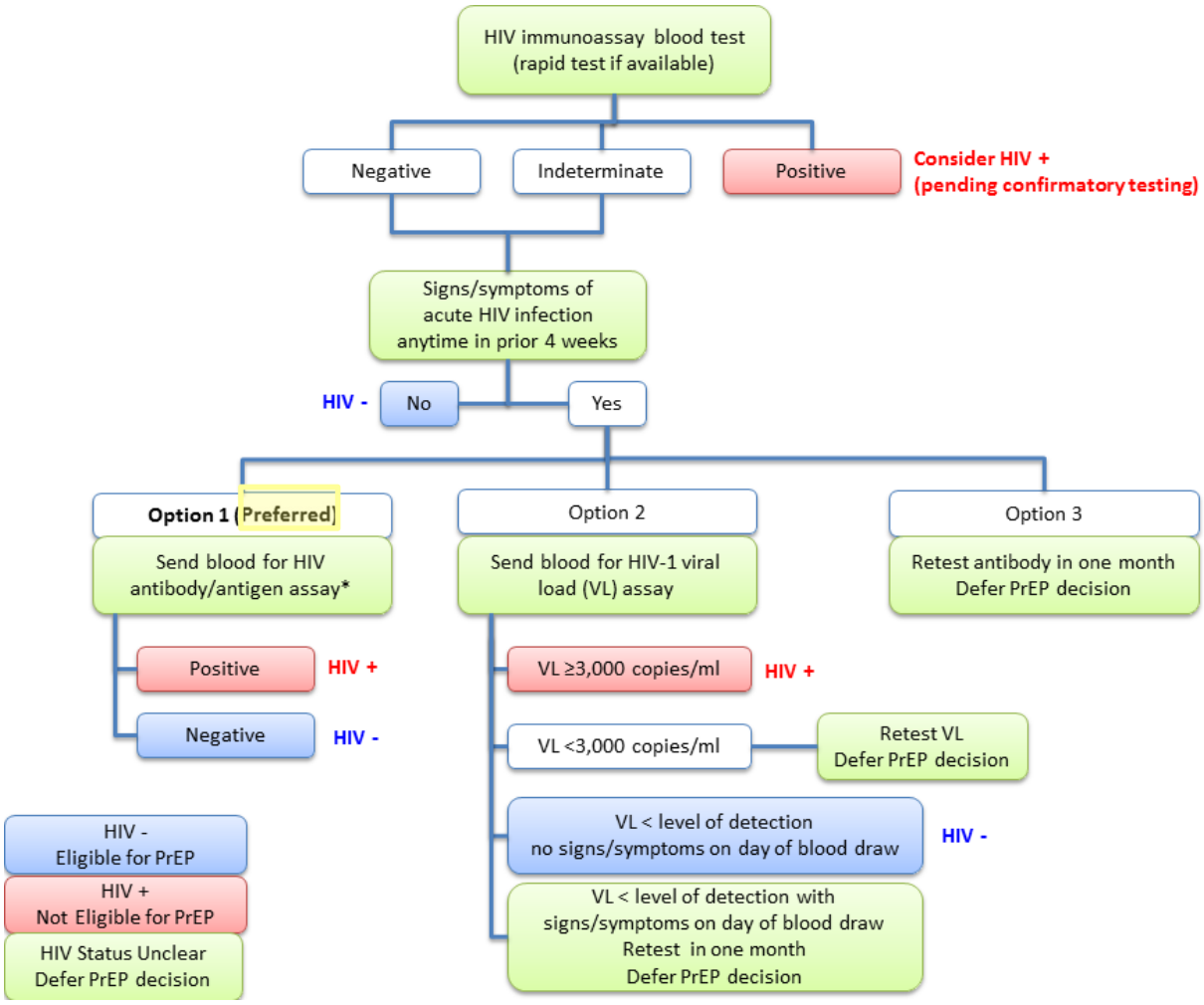
Adherence was low in this trial: study drug was detected in plasma samples of <50% of women randomly assigned to TDF/FTC. Among adverse events, only nausea and vomiting (in the first month) and transient, modest elevations in liver function test values were more common among those assigned to TDF/FTC 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.

Table 8: Clinical Signs and Symptoms of Acute (Primary) HIV Infection[75]

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

The figure below illustrates the recommended clinical testing algorithm to establish HIV infection status before the initiation of PrEP or its re-initiation after more than a week off PrEP medication. . Laboratory antigen/antibody tests (option 1) are preferred because they have the highest sensitivity for detecting acute HIV infection which is associated with high viral loads. While viral load testing is sensitive (option 2), healthcare providers should be aware that available assays might yield false-positive low viral load results (e.g., <3,000 copies/mL) among persons without HIV infection. Without confirmatory tests, such false-positive results can lead to misdiagnosis of HIV infection.[76,.77] Repeat antibody testing (option 3) is least preferred because it delays determination of true HIV status and uninfected patients may have additional exposures and become infected without PrEP while waiting to retest. When clinicians prescribe PrEP based solely on the results of antibody-only or rapid tests, ordering a laboratory antigen/antibody test at the time baseline labs are drawn is recommended. This will increase the likelihood of detecting unrecognized acute infection so that PrEP can be stopped and the patient started on antiretroviral treatment in a timely manner.

Figure Clinician Determination of HIV Status for PrEP Provision



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[78]. 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 [79-81].

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[82]

$eCrCl_{CG}$ = [[(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[83]
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[83]
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)[84]
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[85] and hepatitis C virus (HCV) infection[86].

Vaccination against HBV is recommended for all adolescents and adults at substantial risk for HIV infection, especially for MSM. Therefore, HBV infection status should be documented by screening serology before TDF/FTC is prescribed as PrEP (see Table 9). Those patients determined to be susceptible to HBV infection should be vaccinated. Those patients found to be HBsAg positive should

be evaluated for possible treatment either by the clinician providing PrEP care or by linkage to an experienced HBV care provider.

HBV infection is not a contraindication to PrEP use. Both TDF and FTC are active against HBV[87]. HBV-monoinfected patients taking TDF or FTC, whether as PrEP or to treat HBV infection, who then stop these medications must have their liver function closely monitored for reactivation of HBV replication that can result in hepatic damage[6].

Table 9: 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

*= seroprotective levels of >10 mIU/mL

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

Serologic testing for HCV is recommended for persons who have ever injected drugs[88]. MSM at substantial risk for HIV infection being started on PrEP have been shown to have a high prevalence of HCV infection [89,9091]. Therefore, MSM starting PrEP should be tested for HCV infection as a part of baseline laboratory assessment. HCV testing for all sexually active persons starting PrEP is a recommended consideration by guidance from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA)[92]. In addition, persons born during 1945 through 1965 should be tested for HCV at least once in a lifetime (without prior ascertainment of HCV risk factors). Guidance from AASLD-IDSA recommends annual HCV retesting

for PWID, and clinicians can consider annual retesting for other persons with ongoing risk of HCV exposure[92].

Patients with active HCV infection (HCV RNA+ with or without anti-HCV seropositivity) should be evaluated for possible treatment because TDF/FTC does not treat HCV infection. When the clinician providing PrEP care is not able to provide HCV care, the patient should be linked to an experienced HCV care provider

TESTING FOR SEXUALLY TRANSMITTED INFECTIONS

Tests to screen for syphilis are recommended for all adults prescribed PrEP, both at screening and at semi-annual visits. See the 2015 STD guidelines for recommended assays[93].

Tests to screen for gonorrhea are recommended for all sexually active adults prescribed PrEP, both at screening and at semi-annual visits. Tests to screen for chlamydia are recommended for all sexually active MSM prescribed PrEP, both at screening prior to initiation and at semi-annual visits.

Because chlamydia is very common, especially in young women[94] and does not strongly correlate with risk of HIV acquisition[61], regular screening for chlamydia is not recommended for all sexually active women as a component of PrEP care. However, clinicians should refer to the 2015 STD guidelines for recommendations about chlamydia testing frequency for women regardless of PrEP use[93].

For gonorrhea and chlamydia testing in MSM, NAAT tests are preferred because of their sensitivity. Pharyngeal, rectal, and urine specimens should be collected ("3-site testing") to maximize the identification of infection, which may occur at any of these sites of exposure during sex. Self-collected samples have equivalent performance as clinician-obtained samples [95-97] and can help streamline patient visit flow.

For gonorrhea testing in women, vaginal specimens for NAAT tests are preferred. They may also be self-collected. For women who report engaging in anal sex, rectal specimens for gonorrhea and chlamydia testing should be collected in addition to vaginal specimens[98-100]. Studies have estimated that 29% of HIV infections in women are linked to sex with MSM (i.e., bisexual men)[101,102], and that more than 1/3 of women report having had anal sex[103]. In the HPTN 064 trial that recruited women at high risk of HIV acquisition, 38% reported condomless anal sex in the 6 months prior to enrollment[104]. Identifying asymptomatic rectal gonorrhea in women at substantial risk for HIV infection and providing treatment can provide benefits to the woman's health and help reduce the burden of infection in her sexual networks as well[105,106], especially when accompanied by partner services[107] or expedited partner therapy[108-110].

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 10). Therefore, TDF/FTC is the recommended medication that should be prescribed for PrEP for MSM, heterosexually active men and women, and PWID who meet recommended criteria. Because TDF alone has been proven effective in trials with PWID 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 10: Recommended Oral PrEP Medications

Generic Name	Trade Name	Dose	Frequency	Common Side Effects[73]
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 11).

Table 11: PrEP Medication Drug Interactions [6,80]

	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
Ledipasvir/sofosbuvir	Serum concentrations of TDF may be increased. Monitor for toxicities.	No significant effect

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 PWID 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, TAF [tenofovir alafenamide]), 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[111].

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[112,113]. 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
  - Conduct STI testing for sexually active persons with signs or symptoms of infection and screening for asymptomatic MSM at high risk for recurrent bacterial STIs (e.g., those with syphilis, gonorrhea, or chlamydia at prior visits or multiple sex partners)
- **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 screening for sexually active adolescents and adults (i.e., syphilis and gonorrhea for both men and women, chlamydia for MSM) even if asymptomatic
- **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)[114,115]. 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[23,116]. 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[117].

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[80], 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[118] 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[118]. 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[80].

- 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
- If on PrEP, conversion of the PrEP regimen to an HIV treatment regimen recommended by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents[80] without waiting for additional laboratory test results. See Clinical Providers' Supplement Section 8.
- 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)[119], and counseled about their risk-reduction practices

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. How to safely discontinue and restart PrEP use should be discussed with patients both when starting PrEP and when discontinuing PrEP. Protection from HIV infection will wane over 7-10 days after ceasing daily PrEP use[120-122]. Because some patients have acquired HIV infection soon after stopping PrEP use[29], alternative methods to reduce risk for HIV acquisition should be discussed, including indications for PEP and how to access it quickly if needed.

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. See also Clinical Providers' Supplement Section 8 for a suggested management protocol.

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, including an HIV test to establish that they are still without HIV infection. 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 may be at risk of HIV acquisition during attempts to conceive (i.e., sex without a condom). Pregnancy is associated with an increased risk of HIV acquisition[123]. Risk is substantial for women whose partners are not taking antiretroviral treatment medication or women whose partners are treated but not virally suppressed. Women whose partners have documented sustained viral load suppression are at effectively no risk of sexual acquisition of HIV infection (see page 32 above). The extent to which PrEP use further decreases risk of HIV acquisition when the male partner has a documented recent undetectable viral load is unknown.

However, clinicians providing pre-conception and pregnancy care to women who report their partners have HIV infection, may not be providing care to the male partner and so may not have access to their medical records documenting the recent viral load status of the partner with HIV infection[65]. When the HIV status of the male partner is unknown, the clinician should offer HIV testing for the partner. When the male partner is reported to have HIV infection but his recent viral load status is not known, is reported detectable, or cannot be documented as undetectable, PrEP use during the preconception period and pregnancy by the uninfected woman offers an additional tool to reduce the risk of sexual HIV acquisition. Both the FDA labeling information[6] and the perinatal antiretroviral treatment guidelines[124] permit off-label use in pregnancy. 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 https://www.cdc.gov/hiv/pdf/risk/prep-cdc-hiv-prep-provider-supplement-2017.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[125]. Additionally, TDF and FTC are widely used for the treatment of HIV infection and continued during pregnancies that occur[126-128]. The data on pregnancy outcomes in the Antiretroviral Pregnancy Registry provide no evidence of adverse effects among fetuses exposed to these medications[129].

Providers should educate HIV-discordant couples who wish to become pregnant about the potential risks and benefits of all available alternatives for safer conception[130,131] 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[124,132]: 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[133].

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.[134,135] 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[136]. 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[11]. (See Clinical Providers' Supplement, Section 5 at https://www.cdc.gov/hiv/pdf/risk/prep-cdc-hiv-prep-provider-supplement-2017.pdf

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[137] 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

[11]Although the DHHS Perinatal HIV Guidelines state that "pregnancy and breastfeeding are not contraindications for PrEP"[9], the FDA-approved package insert[6] says "If an uninfected individual becomes pregnant while taking TRUVADA for a PrEP indication, careful consideration should be given to whether use of TRUVADA should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy" and "mothers should be instructed not to breastfeed if they are receiving TRUVADA, whether they are taking TRUVADA for treatment or to reduce the risk of acquiring HIV-1.". Therefore both are currently off-label uses of Truvada.

HBV infection with the attendant risk of hepatic injury, and to minimize the possible risk of developing TDF-resistant HBV infection[138].

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

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. 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[1139].

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[140,141]. 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[119]. If the exposure is isolated (e.g., sexual assault, infrequent condom failure), nPEP should be prescribed, but PrEP or other continued antiretroviral medication is not indicated after completion of the 28-day PEP course.

Persons who repeatedly seek nPEP or who are at risk for ongoing HIV exposures should be evaluated for possible PrEP use after confirming they have not acquired HIV infection[142]. Because HIV infection has been reported in association with exposures soon after completing an nPEP course, daily PrEP may be more protective than repeated intermittent episodes of nPEP. Persons who engage in behaviors that result in frequent, recurrent exposures that would require sequential or near-continuous courses of nPEP should be offered PrEP at the conclusion of their 28-day nPEP medication course. Because no definitive evidence exists that prophylactic antiretroviral use delays seroconversion, and nPEP is highly effective when taken as prescribed, a gap is unnecessary between ending nPEP and beginning PrEP. Upon documenting HIV-negative status, preferably by using a laboratory-based Ag/Ab test, daily use of the fixed dose combination of TDF (300mg) and FTC (200 mg) can begin immediately for patients for whom PrEP is indicated. See Clinical Providers' Supplement Section 9 for a recommended transition management strategy.

In contrast, patients fully adhering to a daily PrEP regimen do not need nPEP if they experience a potential HIV exposure while on PrEP. PrEP is highly effective when taken daily or near daily. For patients who report taking their PrEP medication sporadically, and those who did not take it within the week before the recent exposure, initiating a 28-day course of nPEP might be indicated. In that instance, all nPEP baseline and follow-up laboratory evaluations should be conducted. After the 28-day nPEP regimen is completed, if confirmed to be HIV uninfected, the previously experienced barriers to PrEP adherence should be evaluated and if addressed, daily PrEP regimen can be reinitiated.

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[143-145]. 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 week143. This finding adds to the evidence that despite some "forgiveness" for occasional missed doses for MSM, a high level of prevention efficacy requires a high level of adherence to daily medication. However, a laboratory study comparing vaginal and colorectal tissue levels of active metabolites of TDF and FTC found that drug levels associated with significant protection against HIV infection

required 6-7 doses per week (~85% adherence) for lower vaginal tract tissues but only 2 doses per week (28% adherence) for colorectal tissures146. This strongly suggests that there is less "forgiveness" for missed doses among women than among MSM.

A pilot study of daily TDF/FTC as PrEP with young MSM was stopped when the iPrEx trial results were reported.[147] 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. Two open-label safety studies with 243 young MSM (median age 19, 46% African American, 32% Latino/Hispanic) similarly found lower adherence in young adult men than has been reported in older adult men taking PrEP, and lower adherence with quarterly visits than with monthly visits[148].

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[149]. 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[150]. 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)[151]. 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[152,153].

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. 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[154] significantly improves medication adherence and may alleviate the time constraints of individual providers[155,156]. 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 10 at https://www.cdc.gov/hiv/pdf/risk/prep-cdc-hiv-prep-provider-supplement-2017.pdf.

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