Pre-Exposure Prophylaxis of HIV with antiretroviral medications

Interim NSW guidelines

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I. Introduction

Management of HIV infection with antiretroviral therapy (ART) has proven to be extremely effective in reducing the amount of virus in different body compartments to undetectable levels and suggested a new application for its use – prevention of HIV acquisition in the first place i.e. preexposure prophylaxis (PrEP). Human studies of blood-borne [1] and perinatal transmission [2] as well as studies of vaginal and rectal exposure among animals [3-5] produced evidence to indicate that antiretroviral PrEP can reduce the risk of HIV infection through sexual and drug-use exposures.

The efficacy of antiretroviral drugs (ARVs) as PrEP has now been established by clinical trials conducted in men who have sex with men (iPrEx [6]), heterosexual adults (Partners PrEP [7] and TDF2 [8]), and injecting drug users (Bangkok Tenofovir study [9]). The daily oral pill containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) is considered safe [10, 11] and effective to reduce the risk of HIV infection in high-risk adults who are able to take the medication correctly and consistently.[12, 13] A summary of published trials [14] of antiretroviral PrEP among men who have sex with men (MSM), heterosexual men and women and injecting drug users which was performed by the US Public Health Service/CDC is included in Appendix 1. It includes a review of evidence on HIV incidence, PrEP efficacy, adherence, safety and side-effects and PrEP-associated viral resistance.

No significant increases in HIV risk behaviour have been reported in any of the clinical trials. All clinical trials of PrEP have promoted condom use and safe sex practices.

Based on this evidence, the TDF/FTC pill (marketed as TDF/FTC by Gilead Sciences Inc. [15]) was approved by the US Food and Drug Administration as PrEP. Clinical guidance for PrEP prescribers was issued by the US Centres for Disease Control and Prevention (CDC) for all three population groups: homosexual men, high-risk heterosexuals and injecting drug users. [16]

A wide gap between the average risk reduction provided by ARVs and their adherence-adjusted efficacy is a striking finding from the published clinical trials. [16] On average, TDF/FTC efficacy levels were moderate and ranged from 42% among homosexual men [6] to 72% among heterosexuals [7]). In the same studies, adherence-adjusted efficacy measured by TDF detection in blood rose significantly to 92% in homosexual men and 84% in heterosexuals. On the other hand, the FEM-PrEP[17] and VOICE[18] trials, where participating women did not adhere adequately to TDF/FTC, were stopped for futility. The observed gap between average and adherence-adjusted levels of protection appears to vary not only across studies, but also across countries and research sites. This is best illustrated by the iPrEx study, which found better adherence to PrEP among homosexual men in the US as opposed to the study sites in other countries.[6] Higher levels of adherence can be expected among self-selected, motivated PrEP users and among those who are better informed about PrEP and HIV prevention, as recorded by iPrEx study and its open-label extension.[19] The levels of adherence also vary depending on the adherence measures used. [20] For example, in the iPrEx study daily TDF/FTC use was self-reported by 95% of participants, pill counts adjusted adherence down to 86%, while TDF was detected in only 51% of blood samples from HIV-negative participants and 9% of seroconverters.[6]

Medication adherence is critical not only to achieving the maximum prevention benefit, but also for reducing the risk of selecting for a drug-resistant virus. [21, 22] In the clinical trials which investigated TDF/FTC safety, only FEM-PrEP found 4 resistant viruses among 33 participants in active and 1 among 35 in placebo group that were infected after baseline. [14] The same data source has reported a small number of drug-resistant HIV-1 variants identified with the use of TDF/FTC for a PrEP indication following undetected acute HIV-1 infection in the iPrEx, Partners PrEP and TDF2 trials (e.g. in the iPrEx study, among 10 participants who were HIV-negative at enrolment but later found to have been infected before baseline, FTC-resistant virus was detected in 2 of 2 men in the active group and 1 of 8 men in the placebo group).

The lead time to achieving protection (that is the time from initiating daily PrEP to maximum protection against HIV) remains unknown. There has only been limited evidence from pharmacokinetic studies, which provide some preliminary data on the lead time required to achieve steady levels of tenofovir diphosphate in blood, rectal and vaginal tissues. [20]

The protective effect of different levels of medication adherence among HIV-negative ARV users is also not clear. However, the study of pharmacokinetics of directly observed TDF dosing combined with detection-efficacy modelling on iPrEx data [23] reported that HIV risk reduction efficacy of 99% corresponded to 7 doses per week, 96% to 4 doses per week, and 76% to 2 doses per week. In one study, the levels of adherence declined with increasing duration of use of daily TDF/FTC (this was a US study among young MSM [11]). There is also an indication that high levels of adherence may be more difficult to achieve with fixed-interval or post-coital dosing regimens as compared to daily dosing. [24]

The safety profile of daily TDF/FTC use for HIV negative individuals is known from clinical trials with follow-up of participants from 1 to 4 years. Adverse reactions that were reported by more than 2% of TRUVADA subjects and that were more frequent in treatment than placebo groups were headache, abdominal pain, and weight loss. Appendix 2 lists side effects associated with the use of FTC and TDF among HIV-negative individuals. TRUVADA prescribing information [15] suggests that serious but rare side effects experienced by users of antiretroviral nucleoside analogues can include lactic acidosis and severe hepatomegaly with steatosis that may result in liver failure, other complications or death (observed more often in women) and worsening of hepatitis B virus (HBV) infection if TRUVADA is stopped. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported among HIV-infected individuals with the use of VIREAD; thus, the warning per the Prescribing Information may relate to longer periods of use. In previous studies [14], three to four percent decreases in bone mineral density (BMD) have been observed in people being treated for HIV with combination antiretroviral therapy including tenofovir. [25] Data published from PrEP studies that assessed BMD to date (iPrEx; CDC PrEP safety trial in MSM) found a 1% decline in BMD, but no increase in fragility (atraumatic) fractures over the one to two years of observation compared to placebo, although the studies were too small and too short to detect any impact of tenofovir on fracture incidence. In these studies, the decline in BMD was observed during the first few months on PrEP, and it either stabilized or returned to normal thereafter. [26]

Eligibility for PrEP implementation is one important issue for its implementation. Previous modelling analyses made it clear that daily oral PrEP could not be a prevention strategy for all, and it would only be cost-effective if specifically targeted to the highest risk groups. [27] Some approaches to identifying eligible individuals based on high-risk behaviour scoring

scales have been suggested recently for men who have sex with men and transgender women (MSM&TGW) [28, 29] and heterosexuals [30]. However, the ability of PrEP to achieve its maximum effects on the HIV epidemic would most likely depend on how well the eligibility criteria for PrEP implementation reflect the specific characteristics of a local HIV epidemic.

In the context of relationships where partners' HIV status is discordant, administration of PrEP for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission of HIV in periconception period. PrEP can be considered as one of several options to protect the uninfected partner during conception. [14]

The risk of HIV acquisition increases during pregnancy, as does the risk of HIV transmission to a child from a mother who becomes infected during pregnancy or breastfeeding.[31] Therefore, an HIV-negative woman at high risk of HIV infection may benefit from continuing PrEP use throughout her pregnancy and breastfeeding to protect herself and her infant. The US CDC guidelines recommend to discuss PrEP with HIV uninfected women at high risk of HIV infection who are pregnant or breastfeeding so that an informed decision can be made in awareness of what is known and unknown about benefits and risks of continuing PrEP. [14]

Research continues on the development of the next generation of PrEP. The new research directions include new ARV options, schedules of use and delivery mechanisms aiming to resolve or bypass the critical issue of adherence to the daily oral PrEP schedule [32], and making PrEP easier to use and acceptable to variety of user groups. Future PrEP options may include long-acting injectable ARVs, medicated vaginal rings and condoms, and rectal microbicides, among other. [33]

Other issues which may affect the future implementation of PrEP include those that can influence its uptake, particularly the support from the anticipated target population groups and PrEP providers. Current evidence suggests very low levels of PrEP uptake, even in the US where PrEP is licensed and available. A lack of knowledge in communities about PrEP and varying degrees of community and provider support for PrEP have been reported as obstacles for PrEP implementation there. [34] Importantly, a high cost of TDF/FTC and lack of the TGA approval for its preventive use in Australia may pose important barriers for PrEP implementation.

In Australia, neither TDF/FTC nor any other anti-retroviral agent has been licensed for preventative use. However, Australia maintains high commitment to reducing rates of HIV infection and recognizes that new technological developments should be considered for HIV prevention. The Melbourne Declaration pledged to halve infections in Australia by 2015 and embraced an approach of making HIV PrEP available. The NSW HIV strategy aims to work towards the virtual elimination of HIV transmission by 2020, focusing on reducing the HIV transmission among gay and other homosexually active men by 60% by 2015 (80% by 2020) and heterosexual transmission of HIV by 50% by 2015. [35] During the period of this strategy (2012-2015), NSW Health took a progressive approach to evaluate the mechanisms to most appropriately and efficiently implement PrEP in line with evidence [35] and support the first PrEP implementation study in NSW health care settings designed to establish and evaluate a PrEP implementation model in line with the NSW HIV strategy.

This clinical guidance document outlines the recommendations of the New South Wales Ministry of Health on how to effectively use TDF/FTC as PrEP and integrate it as part of the combination HIV prevention. The guidelines outline the prescription of PrEP and its management in individuals at high risk for HIV infection through sexual contact.

The intended users of this guideline include:

- NSW clinicians who provide care to persons at risk for HIV infection
- Sexual health and HIV treatment specialists who may provide PrEP or serve as consultants to primary care physicians with clients at high risk for HIV infection
- Health program policymakers

Every presentation with request for PrEP should be assessed as to a person's eligibility for PrEP, and the decision to prescribe PrEP should be based on the balance of the potential harms and benefits of using a prescribed, yet unlicensed, medication for primary HIV prevention purposes.

The advice provided is necessarily general. Any unusual or complex case should be discussed with an expert in HIV medicine before deciding whether or not PrEP should be prescribed.

Table 1: Summary of guidance for PrEP use in NSW

	Men Who Have Sex with Men	Heterosexuals	Injection Drug Users (IDU)
When to *offer* PrEP	If the risk of acquiring HIV infection is rated as *high* according to the eligibility criteria in Table 6a on page 12)	If the risk of acquiring HIV infection is rated as *high* according to the eligibility criteria in Table 6b on page 13)	If the risk of acquiring HIV infection is rated as *high* according to the eligibility criteria in Table 6c on page 13)
When to *consider* PrEP	If the risk of acquiring HIV infection is rated as *moderate* according to the eligibility criteria in Table 6a on page 12)	If an HIV negative woman is in serodiscordant heterosexual relationship and is planning natural conception in the next 3 months	
Clinical eligibility	Documented negative HIV test result before prescribing PrEP No signs/symptoms of acute HIV infection Normal renal function (eGFR >60 ml/min) No contraindicated medications		
Prescription	Daily, continuing, oral doses of TDF/FTC (TRUVADA), ≤90-day supply		
Other services	At baseline, documented hepatitis B virus infection and vaccination for those not immune Follow-up visits at month 1 after PrEP initiation and at least every 3 months thereafter to provide the following: HIV testing; medication adherence assessment and support; behavioural risk reduction support; side-effect and concomitant medication assessment; STI symptom assessment and management as required; chronic hepatitis B monitoring and management as required. At 3 months and every 6 months thereafter, assessment of renal function		
Additional testing	Every 3 months, STI testing as per Australian STI testing guidelines	Assess pregnancy intent and conduct pregnancy test every 3 months if appropriate	Test for hepatitis C Access to clean needles/syringes and drug treatment services

II. Assessment of the risk of HIV transmission

The risk of HIV transmission through a single or multiple exposures is determined by:

- The nature of the exposure with its estimated risk per exposure (Table 2)
- The number of such exposures
- The likelihood of the source being HIV positive, if their status is unknown (Table 3)
- Factors associated with the source and exposed individuals (Table 4).

All sexual risk estimations are for unprotected sexual contact. It is assumed that a similar risk is incurred when a condom fails.

Table 2: Exposure and transmission risk/exposure with known HIV positive source (Adopted from the national PEP guidelines. [36] In general, these estimates relate to populations where most individuals were not on ART).

Note: For more information, see Literature Review for the national PEP guidelines, section Transmission risks associated with different exposures [37]

Type of exposure with known HIV positive source	**Estimated risk of HIV transmission/exposure**
Receptive anal intercourse (RAI) – ejaculation – withdrawal	1/70 1/155
Sharing contaminated injecting equipment	1/125
Insertive anal intercourse (IAI) uncircumcised	1/160
Insertive anal intercourse (IAI) circumcised	1/900
Receptive vaginal intercourse (RVI)	1/1250[1] (See next page)
Insertive vaginal intercourse (IVI)	1/1250[1] (See next page)
Receptive or insertive oral intercourse	Unable to estimate risk – extremely low
Needlestick injury (NSI) or other sharps exposure	1/440
Mucous membrane and non-intact skin exposure	< 1/1000

[1] These estimates are based on prospective studies, not cross-sectional data or from modelling

Table 3: HIV seroprevalence in Australian populations (adopted from the national PEP guidelines [36]).

Community group	HIV seroprevalence (%)
Homosexual men (MSM – men who have sex with men)	
• ACT	4.2
• Adelaide	5.4
• Brisbane	8.8
• Melbourne	8.1
• Perth	4.5
• Sydney	11.8
Actual seroprevalence may be higher than reported seroprevalence [8]	
Injecting drug users in Australia	
• homosexual	29.2
• all others	1.0
Heterosexuals in Australia	
• blood donors (% donations)	0.0004
• STI clinic attendees	<0.5
Commercial sex workers (Australia)	<0.1
Overall Australian seroprevalence	0.1

Table 4: Factors known to increase the risk of HIV transmission (adopted from the national PEP guidelines [36]).

- a higher plasma viral load (highest loads occur when seroconverting or with advanced disease);
- a sexually transmissible infection in the source or exposed individual, especially genital ulcer disease and symptomatic gonococcal infections;
- a breach in genital mucosal integrity (e.g., trauma, genital piercing or genital tract infection);
- a breach in oral mucosal integrity when performing oral sex;
- penetrating, percutaneous injuries with a hollow bore needle, direct intravenous or intra-arterial injection with a needle or syringe containing HIV infected blood;
- the uncircumcised status of the insertive HIV negative partner practising IAI or IVI.

Early initiation of antiretroviral therapy, compared with delayed therapy, resulted in a relative reduction of 96% in the number of linked HIV transmissions in serodiscordant heterosexual couples. Therefore the transmission risk for vaginal intercourse with an HIV positive partner with an undetectable viral load may be estimated to be decreased by a factor of 20. [38] As to the transmission risk through anal intercourse, the only evidence at the time of the publication of these guidelines comes from the interim analyses presented by the Partner Study [39]. The latter showed that, in serodiscordant couples, the rate of within-couple HIV transmissions during eligible couple-years was zero, however, the upper limits of the 95%CI were 0.96/100 CYFU for anal sex (in gay and straight

couples combined) and 1.97/100 CYFU for receptive anal sex with or without ejaculation (for gay couples).

III. Determining eligibility for PrEP

PrEP is indicated for HIV-negative adults who are at ongoing high risk for HIV infection.

HIV-negative status should be confirmed as close to initiation of PrEP as possible, ideally on the same day but not more than 7 days before the prescription is given, by using the standard-of-care testing procedures as outlined in section on **Pre-Prescription Assessments, Education, and Laboratory Tests**.

PrEP is meant to be used by people who are at high and ongoing risk of acquiring HIV. Table 5 summarizes different practices and conditions associated with high HIV incidence among men who have sex with men.

Table 5: Different practices and conditions associated with high HIV incidence among MSM

Note: Data for this table were obtained from the Health in Men (HIM) study conducted during 2001-2007. Data were collected for six-month intervals. Due to the specifics of data collection for this study, not all indicators were available to support each individual eligibility criterion, and some indicators were collected in somewhat different form, have a different denominator or reference period.

Risk factor	**Associated HIV incidence**	
	Per 100 person-years	95% Confidence Interval
All patients regardless of practices	0.78	0.59-1.02
A. **Highest risk**		
A regular sexual partner of or having at least ***one*** episode of unprotected sex with an HIV-infected man with whom condoms were not consistently used in the last six months[2]	5.36	2.78-10.25
At least ***one*** episode of receptive unprotected anal intercourse (CLAI) with any casual HIV-infected male partner or a male partner of unknown HIV status during the last six months	2.31	1.48-3.63
Rectal gonorrhoea diagnosis in last six months	7.01	2.26-21.74
Rectal chlamydia diagnosis in last six months	3.57	1.34-9.52
Methamphetamine use in last six months	1.89	1.25-2.84
B. **Medium to high risk**		
More than one episode of anal intercourse during the last 3 months when proper condom use was not achieved (e.g., condoms slipped off or broke)	1.30	0.95-1.77
A regular sexual partner of or having at least ***one*** episode of insertive CLAI where the serostatus of partner is not known or is HIV-positive[3]	0.94	0.35-2.52
- In uncircumcised men	1.73	0.43-6.90
- In circumcised men (comparison group, low risk, PrEP not recommended)	0.65	0.16-2.61

[2] Data used to generate this estimate did not include the treatment and viral load status of the HIV positive regular partner as this information was not available

[3] The estimates produced by the HIM study cannot account for the treatment and/or viral load status of the HIV positive regular partner as this information was not collected

Providers need to obtain a thorough sexual and drug-use history to determine PrEP eligibility and to regularly discuss high HIV-risk practices with their patients to assess continuing candidacy for PrEP. Eligibility criteria for PrEP prescription are outlined in Table 6.

Individuals who have only infrequent exposures to HIV (e.g., an occasional broken condom or lapse in condom use) may be good candidates for nPEP rather than PrEP. These individuals should be educated about both nPEP and PrEP, and decision about PEP or PrEP use should be made on a case by case basis.

Table 6a: Behavioural eligibility criteria for PrEP MSM

A. High risk - recommend prescribing daily PrEP if the client acknowledges:

being likely to have multiple events of condomless anal intercourse (CLAI), with or without sharing intravenous drug use (IDU), in the next 3 months (indicating sustained risk)

AND

Having any of the following:

- Regular sexual partner of an HIV-infected man with whom condoms were not consistently used in the last 3 months (HIV positive partner is not on treatment and/or has detectable viral load);
- At least ***one*** episode of receptive CLAI with any casual HIV-infected male partner or a male partner of unknown HIV status in the last 3 months;
- Rectal gonorrhoea or chlamydia diagnosis during the last 3 months or at screening;
- Methamphetamine use in the last 3 months

B. Medium risk - consider prescribing daily PrEP if the client acknowledges:

being likely to have multiple events of CLAI, with or without sharing IDU, in the next 3 months (indicating sustained risk)

AND

Any of the following is reported

- More than one episode of anal intercourse in the last 3 months when proper condom use was not achieved (e.g., condoms slipped off or broke);
- if client is uncircumcised and reports more than one episode of insertive CLAI in the last 3 months where the serostatus of partner was not known or was HIV positive and not on treatment.

C. Low risk - PrEP is not recommended for individuals who:

- have no risk exposure other than CLAI with a partner with documented sustained undetectable HIV viral load in the previous 3 months
- are circumcised and report practicing exclusively insertive CLAI in the last 3 months

Table 6b: Behavioural eligibility criteria for PrEP for heterosexual people

A. High risk - recommend prescribing daily PrEP if the client acknowledges:

being likely to have multiple events of condomless anal or vaginal intercourse (CLAI or CLVI, respectively), with or without sharing IDU, in the next 3 months (indicating sustained risk)

AND

- Being a regular sexual partner of an HIV-infected man or woman with whom condoms were not consistently used in the last 3 months (HIV positive partner is not on treatment and/or has detectable viral load);

B. Medium risk - consider prescribing daily PrEP if:

- a female client is in serodiscordant heterosexual relationship and is planning natural conception in the next 3 months

C. Low risk - PrEP is not recommended for individuals who:

- have no risk exposure other than CLVI or CLAI with a partner with documented sustained undetectable HIV viral load in the previous 3 months. However, PrEP may be considered for a female client during a period around attempted conception.
- are a circumcised man who reports practicing exclusively CLVI in the last 3 months

Table 6c: Behavioural eligibility criteria for PrEP for people who inject drugs

A. High risk - recommend prescribing daily PrEP if the client acknowledges:

being likely to have multiple events of sharing needles or injecting equipment with an HIV positive individual or a homosexually active man and has inadequate access to safe injecting equipment in the next 3 months (indicating sustained risk)

AND

- Sharing needles or injecting equipment with an HIV positive individual or with a homosexually active man in the last 3 months

Along with encouraging safer-sex practices and safer injection techniques (if applicable), clinicians should assist their patients in making a decision of when to use PrEP and when to discontinue its use.

The length of PrEP use will depend on the individual's continuing risk practices over time. PrEP should only be prescribed to those patients who are able to adhere to the regimen and express a willingness to do so.

IV. Prescribing PrEP and managing patients on PrEP

Ultimately, the decision to prescribe PrEP needs to be made on a case-by-case with a full consideration of its benefits and harm. Situations where there is greater uncertainty or complexity should be discussed with a physician experienced in this area.

a. Clinical assessment

In making a clinical assessment health practitioners should consider the gender, culture, behaviour, language and literacy level of the patient, and their intellectual capacity.

The following steps should be made to determine the suitability for PrEP prescription

- Conduct HIV testing and document negative antibody test result no more than 7 days prior to initiating PrEP including 4th generation serology test plus Western Blot for confirmation.

  Note: existing POC rapid tests to date have been insufficient to detect early infection. Therefore a fourth generation antibody antigen test is recommended.

- Provide patient education regarding acute HIV infection symptoms and direct them to seek urgent medical attention if they believe they may be experiencing acute HIV infection

- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection. Negative results of this testing should be documented before PrEP is commenced.

  Note: Table 7 provides clinical signs and symptoms of acute (primary) HIV infection and their frequencies

- Confirm that patient is at substantial, ongoing, high risk for acquiring HIV infection. Use algorithm in Table 6a, 6b or 6c as guidance (depending on the patient's identification as a homosexual man, a heterosexual men or woman, or an individual injecting drugs, respectively).

  Note: If the partner of a patient who presents for PrEP is HIV positive and has consistently undetectable viral load (as established by test results), the risk of HIV acquisition from such a partner does not warrant the use of PrEP. However, the patient may be requesting PrEP due to sex with other partners; therefore, assessment against all eligibility criteria should be carefully conducted.

- Confirm that calculated creatinine clearance is ≥60 mL per minute (via estimated glomerular filtration rate [eGFR]).

Other recommended actions:

- Screen for hepatitis B infection. Vaccinate if non-immune.

- Screen for STIs.
- Inform patient about the symptoms of HIV seroconversion illness

Table 7: Clinical Signs and Symptoms of Acute (Primary) HIV Infection [38]

Features	**Overall frequency, (%) (n = 375)**
Fever	75
Fatigue	68
Myalgia	49
Skin rash	48
Headache	45
Pharyngitis	40
Cervical lymphadenopathy	39
Arthralgia	30
Night sweats	28
Diarrhoea	27

Table 8 lists all details that should be documented in the patient's history.

Table 8: Details to be documented

1. Information about the candidate for PrEP
    - most recent HIV test and result;
    - test results for rectal and/or vaginal STIs; hepatitis B infection;
    - creatinine clearance;
    - history of post-exposure prophylaxis;
    - medical history, as related to prescription of TDF/FTC (allergies, current use of medications known to interact with TDF or FTC);
    - pregnancy risk, intention or status; lactation (women).

2. Candidate's awareness and knowledge about HIV:
    - knowledge about HIV risk factors and practices at high risk for HIV;
    - awareness of risk reduction approaches;
    - knowledge of symptoms of HIV seroconversion.

3. Details about HIV risk and risk reduction practices:
    - sexual partnerships and practices as related to behavioural eligibility criteria for PrEP;
    - drug use (particularly, methamphetamines and injection drug practices);
    - currently used risk reduction practices, willingness to use condoms
    - probable exposure to HIV in the preceding month (or the length of the HIV-screening window period?);
    - high-risk event of exposure to HIV in the preceding 72 hours (for triage of patients to PEP or PrEP)

4. Knowledge about PrEP and PEP:
    - knowledge about effectiveness of PrEP and PEP and recommended schedule of use;
    - awareness of PrEP adherence requirements and willingness to adhere to the prescribed schedule of use;
    - knowledge of side-effects associated with PrEP use;
    - knowledge about HIV and STI testing requirements.

b. PrEP discussion

An explanation of PrEP, how it works, its indications and limitations, effectiveness, risks and benefits, need for adherence and common side-effects are provided to all potential candidates. Discussion of HIV, including risk assessment, is part of every clinical assessment *(see 2011 National HIV testing policy*).

Clinicians must inform patients who are prescribed PrEP of the partial efficacy of this intervention, the importance of adherence, and the potential adverse effects associated with the use of the medication. Other key information includes preventive measures and description of HIV seroconversion symptoms.

c. Initiation of PrEP

Initiation of PrEP should be made only upon confirmation of HIV-negative status of the patient in the previous 7 days using the 4th generation of HIV antibody/antigen test. If the test result is negative and the patient is free of any symptoms consistent with HIV seroconversion illness, they can start on PrEP immediately and no later than within 7 days..

If concern about the recent risk of HIV seroconversion is high, conduct a seroconversion screening.

If HIV test is indeterminate or there has been a high likelihood of exposure to HIV in the last 30 days, such patient should be retested to confirm HIV negative status. In the event of high risk exposure to HV within the last 72 hours, the patient can start with a course of PEP as per national guidelines for PEP after non-occupational and occupational exposure to HIV. [36] After completing the PEP course, the patient can immediately transition to PrEP if HIV test result is confirmed negative.

Both the clinician and the patient should be aware that the first month on PrEP is the period of the high risk of HIV seroconversion from risk exposures preceding PrEP. The patient should be informed about this period as well as the symptoms of seroconversion illness and should notify the clinician when such symptoms occur.

d. Duration of treatment

Decision about the duration of PrEP prescription should be made based on the patient's continuing eligibility for PrEP, as well as willingness and ability to adhere to the prescribed schedule of PrEP use.

Initial prescription should start with a 30-day supply to assess adherence. In general, it is recommended to prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected.

e. Prescribed regimen

Currently recommended regimen is TRUVADA (a fixed co-formulation of tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg), 1 tablet PO daily with or without food. No antiretroviral regimens should be used for PrEP other than a daily oral dose of TDF/FTC.

Other medications and other dosing schedules have not yet been shown to be safe or effective in preventing HIV acquisition.

Do not provide PrEP as expedited partner therapy (i.e., do not prescribe for an uninfected person not in your care).

f. PrEP medication drug interactions

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 9 for PrEP medication drug interactions).

Table 9: PrEP Medication Drug Interactions (adopted from 2014 US Clinical Practice Guideline[14])

	Tenofovir	**Emtricitabine**
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

g. Follow-up schedule

The first follow-up visit should be conducted one month following PrEP initiation, to assess PrEP adherence, followed by regular visits at no more than 90-day intervals.

Adherence to PrEP should be assessed at each follow-up visit. Suboptimal adherence should be based on the clinician's judgement, in light of available evidence. [14] PrEP users who otherwise declare to the site investigator non-adherence, but are willing and eligible to

continue on PrEP, should receive reinforced adherence education. Those who are due for a new PrEP prescription should be given only a one month prescription, and should be scheduled for a visit one month later to reassess adherence before providing further prescriptions for PrEP.

If adherence is sufficiently suboptimal as to compromise PrEP efficacy and patient's safety, the clinician should discontinue prescribing PrEP.

h. Laboratory assessment and follow-up

Table 10 below sets out the recommended schedule of testing and follow-up for individuals who are prescribed PrEP

The symptoms of seroconversion should be explained to all patients, with advice to present if these symptoms occur.

Table 10: Laboratory evaluation of individuals who are prescribed PrEP

Test	**Baseline (Week 0)**	**About day 30 after initiating PrEP**	**90 days after initiating PrEP**	**Every subsequent 90 days on PrEP**
HIV testing	**X**	**X**	**X**	**X**
Hepatitis B serology	**X**			
Hepatitis C serology	**X**			
STI screen	**X**		**X**	**X**
Serum creatinine and proteinuria	**X**			**X**[1]
Pregnancy test (for women of child-bearing potential)	**X**	**X**	**X**	**X**

1 – at three months following PrEP initiation and then every 6 months on PrEP

Routine dual-energy x-ray absorptiometry (DXA) scans or other assessments of bone health before the initiation of PrEP or for the monitoring of patients taking PrEP are not mandatory. DXA and assessment for secondary causes of osteoporosis may be appropriate for individuals with a history of pathological or fragility bone fracture or who have significant risk factors for osteoporosis. The optimal interval for these assessments is unknown.

i. Immediate management of an individual with known or suspected exposure to HIV and missed daily dose/s of PrEP

The number and pattern of missed doses of daily oral PrEP which may undermine the protective effect of PrEP are still poorly understood. Therefore, patients reporting a known or suspected exposure to HIV within 72 hours who missed their daily doses of TRUVADA within 24 hours before and/or after the event may require post-exposure prophylaxis (PEP) of HIV. If indicated, they should be transitioned to the standard-of-care PEP course (which may include 3 drugs rather than only 2 drugs) according to the national PEP guidelines.

j. Immediate management of an individual with symptoms suggestive of primary HIV infection

- Determine HIV exposure risk over preceding 3 months
- Suspend PrEP until HIV status determined
- Advise patient to eliminate all HIV risk behaviours until HIV status determined
- Order HIV antibody (4th-generation assay), and consider HIV proviral DNA
- Recommence PrEP once confirmed HIV-negative (may require more than one episode of testing)

k. Immediate management of an individual on PrEP who is diagnosed with HIV infection

- Suspend PrEP immediately
- Advise patient to eliminate all HIV risk behaviours
- Confirm HIV status by repeat testing: antibody (4th-generation assay), p24 antigen, HIV western blot and either HIV proviral DNA or viral load
- If HIV infection confirmed, discuss with patient further plan for HIV management
- Perform tests for HIV viral load, HIV genotype and ARV resistance, and other tests routinely indicated for a newly-infected patient

l. Management of possible exposure to other conditions

i. Hepatitis B

All individuals presenting for PrEP are assessed for hepatitis B infection.

- Determine HBV exposure risk over preceding 3 months
- Determine HBV immune status based on prior known infection or vaccination
- Continue PrEP until HBV status determined
- Advise patient to eliminate all HBV risk behaviours until HBV status determined
- Order testing for HBV according to the standard-of-care.
- Document HBV infection status before TRUVADA is prescribed as PrEP.
- Order testing for HCV infection depending on risk factors and document HCV infection positive status if detected before TRUVADA is prescribed as PrEP.

- For patients determined to be susceptible to HBV infection, order HBV vaccination if not immune
- 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, a hepatologist or a sexual health specialist should be considered.
- While on PrEP, patients with chronic hepatitis B need routine hepatitis B monitoring every 6-12 months as recommended by the ASHM guidelines. [39]
- TDF and FTC are each active against HBV infection and thus may prevent the development of significant liver disease by suppressing the replication of HBV. Reinforce to the patient the need for consistent adherence to daily TRUVADA to prevent reactivation of HBV infection with the attendant risk of hepatic injury, and to minimize the possible risk of developing TDF or FTC-resistant HBV infection.

ii. Sexually transmissible infections

Individuals presenting for PrEP initiation or follow-up should be screened and treated for chlamydia, gonorrhoea and syphilis as recommended by STI screening guidelines. If symptoms are present, further appropriate tests and follow-up should be performed.

iii. Pregnancy and breastfeeding

TRUVADA has been evaluated in a limited number of women during pregnancy and postpartum. Safety for infants exposed to TRUVADA during pregnancy is not fully assessed, but available human and animal data suggest that TRUVADA does not increase the risk of major birth defects overall compared to the background rate. Therefore, planning to become pregnant, currently being pregnant or breastfeeding are not exclusion criteria for PrEP.

Clinicians should discuss PrEP with HIV-uninfected women at high risk of HIV infection who are pregnant or breastfeeding so that an informed decision can be made in full awareness of what is known and unknown about benefits and risks of continuing PrEP. [14] The potential risks of taking TRUVADA should be weighed against the benefits of taking it as PrEP to reduce the risk of acquiring HIV during pregnancy and, in case of infection, passing HIV from an infected mother to her infant(s). The decision to continue PrEP should be made jointly by the patient and the clinician based on their discussion of potential risks and benefits.

m. Additional clinical management issues

i. Preventive behaviours whilst being on PrEP

Use TRUVADA for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, including safer sex practices, because TRUVADA is not always effective in preventing the acquisition of HIV-1

- Counsel uninfected individuals about safer sex practices that include
    - consistent and correct use of condoms

    - knowledge of their HIV-1 status and that of their partner(s), and
    - regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhoea)
- Inform uninfected individuals about and support their efforts in reducing sexual risk behaviour.
- Inform individuals who inject drugs about access to clean needles/syringes and drug treatment services

ii. Individuals at risk of HIV transmission who discontinue PrEP

Education about preventive behaviours and HIV seroconversion is provided to these individuals. PrEP is recommended to be stopped no earlier than 28 days after the last event that would merit initiation of NPEP. It is important that patients maintain a positive relationship with their health service so that they are monitored clinically and tested for HIV after discontinuing PrEP.

iii. Individuals who re-present for PrEP after a break

Re-assess risk of HIV infection and HIV status and offer PrEP if the individual meets the eligibility criteria for PrEP.

Assess the reasons why the patient stopped PrEP with a view to improving adherence when PrEP is re-initiated.

Individuals who request PrEP after completion of a 28-day course of PEP as per standard of care can start taking daily oral PrEP immediately upon the completion of PEP, provided that they continue to satisfy the eligibility criteria for PrEP.

V. Information about PrEP

US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States – 2014 Clinical practice guideline. Centres for Disease Control and Prevention. 14 May 2014.
Available at: *http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf*

World Health Organization. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. July 2014.
Available at: http://www.who.int/hiv/pub/guidelines/

TRUVADA Risk Evaluation and Mitigation Strategy (REMS) Materials developed by Gilead Inc. and FDA:
Available at: www.truvadapreprems.com/truvadaprep-resources

TRUVADA prescription guide:
Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2013/021752s042lbl.pdf

AIDS Vaccine Advocacy Coalition (AVAC) website: Pre-Exposure Prophylaxis

PrEP Watch: www.prepwatch.org/

Further information about PrEP and antiretroviral prescribing is available on the ASHM website at www.ashm.org.au/HIVguidelines

Local information may be found on the NSW Ministry of Health websites:
http://www.health.nsw.gov.au

Information for patients

Further information about PrEP may be found on the websites of:

ASHM: http://www.ashm.org.au

ACON: http://www.acon.org.au

AFAO: http://www.afao.org.au

VI. References

1. Cardo, D.M., et al., *A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group.* N.Engl.J.Med., 1997. 337(21): p. 1485-1490.
2. Connor, E.M., et al., *Reduction of Maternal-Infant Transmission of Human-Immunodeficiency-Virus Type-1 with Zidovudine Treatment.* New England Journal of Medicine, 1994. 331(18): p. 1173-1180.
3. Subbarao, S., et al., *Chemoprophylaxis with tenofovir disoproxil fumarate provided partial protection against infection with simian human immunodeficiency virus in macaques given multiple virus challenges.* Journal of Infectious Diseases, 2006. 194(7): p. 904-911.
4. Garcia-Lerma, J.G., et al., *Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir.* Plos Medicine, 2008. 5(2): p. 291-299.
5. Denton, P.W., et al., *Antiretroviral pre-exposure prophylaxis prevents vaginal transmission of HIV-1 in humanized BLT mice.* Plos Medicine, 2008. 5(1): p. 79-89.
6. Grant, R.M., et al., *Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.* N.Engl.J.Med., 2010. 363(27): p. 2587-2599.
7. Baeten, J.M., et al., *Antiretroviral prophylaxis for HIV prevention in heterosexual men and women.* N Engl J Med, 2012. 367(5): p. 399-410.
8. Thigpen, M.C., et al., *Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana.* N Engl J Med, 2012. 367(5): p. 423-34.
9. Choopanya, K., et al., *Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial.* Lancet, 2013. 381(9883): p. 2083-90.
10. van der Helm, J.J., et al., *The hepatitis C epidemic among HIV-positive MSM: incidence estimates from 1990 to 2007.* Aids, 2011. 25(8): p. 1083-1091.
11. Grohskopf, L.A., et al. *Preliminary analysis of biomedical data from the phase II clinical safety trial of tenofovir disoproxil fumarate (TDF) for HIV-1 pre-exposure prophylaxis (PrEP) among US men who have sex with men (MSM).*
12. Administration, U.S.F.a.D., *FDA approves first drug for reducing the risk of sexually acquired HIV infection. Press release. July 16 2012. Availalbe online at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm*.
13. Veronese, F., et al., *Implications of HIV PrEP Trials Results.* AIDS Res.Hum.Retroviruses, 2011. 27(1): p. 81-90.
14. *US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States – 2014 Clinical practice guideline. Centres for Disease Control and Prevention. 14 May 2014.*
15. Gilead, *Truvada: Medication Guide #21-752-GS-026.* June 2013: https://www.gilead.com/~/media/Files/pdfs/medicines/hiv/truvada/truvada_pi.pdf.
16. Prevention, C.f.D.C.a., *Update to interim guidance for pre-exposure prophylaxis (PrEP) for the prevention of HIV infection: PrEP for injecting drug users.* Morb Mortal Wkly Rep 2013. 62.
17. Van Damme, L., et al., *Preexposure prophylaxis for HIV infection among African women.* N Engl J Med, 2012. 367(5): p. 411-22.
18. Marrazzo, J., Ramjee, G, Nair, G, Palanee, T, Mikhize, B, Nakabiito, C, Taljaard, M, Piper, J, Gomez Feliciano, K, *Pre-exposure prophylaxis for HIV in women: Daily oral tenofovir, oralntenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE study (MTN 003) (Papern #26LB). Oral abstract presentation. CROI 2013.* 2014.

19. *R Grant, V McMahan, R Amico, et al (iPrEx Study Team). Drug detection during open-label extension of the iPrEx trial indicates sustained and appropriate interest in PrEP among men who have sex with men. 7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. Kuala Lumpur, June 30-July 3, 2013. Abstract WELBC02.*
20. Anderson, P.L., et al., *Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection.* J.Antimicrob.Chemother., 2010.
21. Abbas, U.L., et al., *Antiretroviral Therapy and Pre-exposure Prophylaxis: Combined Impact on HIV Transmission and Drug Resistance in South Africa.* Journal of Infectious Diseases, 2013. 208(2): p. 224-234.
22. Celum, C., T.B. Hallett, and J.M. Baeten, *HIV-1 Prevention With ART and PrEP: Mathematical Modeling Insights Into Resistance, Effectiveness, and Public Health Impact.* Journal of Infectious Diseases, 2013. 208(2): p. 189-191.
23. Anderson, P.L., et al., *Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men.* Sci Transl Med, 2012. 4(151): p. 151ra125.
24. Mutua, G., et al., *Safety and Adherence to Intermittent Pre-Exposure Prophylaxis (PrEP) for HIV-1 in African Men Who Have Sex with Men and Female Sex Workers.* Plos One, 2012. 7(4).
25. Yin, M.T. and E.T. Overton, *Increasing Clarity on Bone Loss Associated With Antiretroviral Initiation.* Journal of Infectious Diseases, 2011. 203(12): p. 1705-1707.
26. Liu, A.Y., et al., *Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco.* PLoS.One., 2011. 6(8): p. e23688.
27. Schneider, K., R.T. Gray, and D.P. Wilson, *A Cost-effectiveness Analysis of HIV Preexposure Prophylaxis for Men Who Have Sex With Men in Australia.* Clinical Infectious Diseases, 2014. 58(7): p. 1027-1034.
28. Smith, D.K., et al., *Development of a Clinical Screening Index Predictive of Incident HIV Infection Among Men Who Have Sex With Men in the United States.* Jaids-Journal of Acquired Immune Deficiency Syndromes, 2012. 60(4): p. 421-427.
29. Buchbinder, S.P., et al., *HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial.* Lancet Infectious Diseases, 2014. 14(6): p. 468-475.
30. Kahle, E.M., et al., *An Empiric Risk Scoring Tool for Identifying High-Risk Heterosexual HIV-1-Serodiscordant Couples for Targeted HIV-1 Prevention.* Jaids-Journal of Acquired Immune Deficiency Syndromes, 2013. 62(3): p. 339-347.
31. Matthews, L.T., et al., *Antiretrovirals and safer conception for HIV-serodiscordant couples.* Current Opinion in Hiv and Aids, 2012. 7(6): p. 569-578.
32. Amico, K.R., *The key role of adherence for the effectiveness of antiretroviral-based prevention: State of the science and implications for Asia Pacific.* Sexual Health, 2014.
33. *PrEP Pipeline: Ongoing research. Available at http://www.prepwatch.org/prep-research/prep-pipeline-ongoing-research/ Last accessed 10 May 2014.*
34. Balthazar C, D.L., *A community Perspective on PrEP (Paper #xx). Oral presentation. CROI 2014*
35. NSW Government Ministry of Health. *NSW HIV strategy 2012-2015: A new era.* Sydney, NSW, 2012, 2012.
36. ASHM *Post-Exposure Prophylaxis after Non-Occupational and Occupational Exposure to HIV: National Guidelines*. Australian Government Department of Health and Aging, 2013.

37. *Savage J and the National PEP Guidelines Reference Group. Literature review for the National guidelines for post-exposure prophylaxis after non-occupational and occupational exposure to HIV. [monograph on the internet] Australasian Society for HIV Medicine: Sydney, 2012. Available from www.ashm.org.au/pep-guidelines.*
38. Daar, E.S., C.D. Pilcher, and F.M. Hecht, *Clinical presentation and diagnosis of primary HIV-1 infection.* Current Opinion in Hiv and Aids, 2008. 3(1): p. 10-15.
39. *Chronic Hepatitis B Management Recommendations, GESA Digestive Health Foundation, 2009/10.*
40. Murnane, P.M., et al., *Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial.* Aids, 2013. 27(13): p. 2155-2160.
41. Peterson, L., et al., *Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial.* PLoS.Clin.Trials, 2007. 2(5): p. e27.

APPENDICES

Appendix 1: Summary of human trials of the safety and efficacy of PrEP (Adopted from the US Public Health Service/CDC 2014 Clinical practice guideline on PrEP [14])

PUBLISHED TRIALS OF ANTIRETROVIRAL PREEXPOSURE PROPHYLAXIS AMONG MEN WHO HAVE SEX WITH MEN

IPREX (PREEXPOSURE PROPHYLAXIS INITIATIVE) TRIAL

The iPrEx study [6] 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). [11] 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[3,40] 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 [8], 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 [17] 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). [41] 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) [18] 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 [9] 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 A1.1: Evidence Summary—Overall Evidence Quality (per GRADE Criteria)

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 A1.2: 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 A1.3: 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 A1.4: 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 A1.5: 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.

Appendix 2: Summary of side effects associated with the use of emtricitabine and tenofovir by HIV-negative individuals

SIDE EFFECTS OBSERVED IN HIV-NEGATIVE INDIVIDUALS WHO USED **EMTRICITABINE**:

- Headache
- Dizziness
- Tiredness
- Inability to sleep, unusual dreams
- Loose or watery stools
- Upset stomach (nausea) or vomiting
- Abdominal pain
- Rash, itching, which sometimes can be a sign of an allergic reaction
- Skin darkening of the palms and/or soles
- Increased cough
- Runny nose
- Abnormal liver function tests, which could mean liver damage
- Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas
- Increased triglycerides
- Increased creatine phosphokinase, which could mean muscle damage

SIDE EFFECTS OBSERVED IN HIV-NEGATIVE INDIVIDUALS WHO USED **TENOFOVIR**:

- Upset stomach, vomiting, gas, loose or watery stools
- Generalized weakness
- Dizziness
- Depression
- Headache
- Abdominal pain
- Worsening or new kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas and liver
- Shortness of breath
- Rash
- Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage
- Muscle pain and muscle weakness