Journal of Virus Eradication 2017; **3**: 168–184

Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine HIV pre-exposure prophylaxis: clinical guidelines

Edwina Wright[1–3]*, Andrew Grulich[4], Katy Roy[5], Mark Boyd[4,6], Vincent Cornelisse[1,7], Darren Russell[8,9], Darryl O'Donnell[10], Bill Whittaker[11], Levinia Crooks[5,12,13‡] and Iryna Zablotska[4‡]

[1] Department of Infectious Diseases, Alfred Health, Monash University, Melbourne, Australia
[2] Burnet Institute, Melbourne, Australia
[3] Peter Doherty Institute for Infection and Immunity, University of Melbourne, Australia
[4] Kirby Institute, University of New South Wales, Sydney Australia
[5] Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine, Sydney, Australia
[6] University of Adelaide, Lyell McEwin Hospital, Elizabeth Vale, South Australia
[7] Prahran Market Clinic, Victoria, Australia
[8] Cairns Sexual Health Service, Cairns, Australia
[9] College of Medicine and Dentistry, James Cook University, Cairns Australia
[10] Australian Federation of AIDS Organizations, Sydney, Australia
[11] National Association of People with HIV Australia, Sydney, Australia
[12] University of La Trobe, Melbourne, Australia
[13] University of New South Wales, Sydney, Australia
‡Senior co-authors

Abstract

Daily use of coformulated tenofovir and emtricitabine for HIV pre-exposure prophylaxis (PrEP) by populations at high risk of HIV infection is now recommended in guidelines from the United States, Europe and Australia and globally through the 2015 WHO guidelines. These 2017 Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine's (ASHM) PrEP Guidelines are an updated adaptation of the 2014 US Centers for Disease Control's PrEP guidelines and are designed to:

- Support the prescription of PrEP using forms of coformulated tenofovir and emtricitabine that have been registered in Australia by the Therapeutic Goods Administration and other bioequivalent generic drugs that are available in Australia through self-importation, private prescription or Australian PrEP clinical trials
- Assist clinicians in the evaluation of patients who are seeking PrEP
- Assist clinicians in commencing and monitoring patients on PrEP including PrEP dosing schedules, management of side-effects and toxicity, use of PrEP in pregnancy and in chronic hepatitis B infection and how to cease PrEP

Daily PrEP with co-formulated tenofovir and emtricitabine, used continuously or for shorter periods of time, is recommended in these guidelines as a key HIV-prevention option for men who have sex with men (MSM), transgender men and women, heterosexual men and women, and people who inject drugs (PWID) at substantial risk of HIV acquisition.

Keywords: pre-exposure prophylaxis, PrEP, TD*/FTC

Introduction

Co-formulated tenofovir and emtricitabine for use as HIV pre-exposure prophylaxis (PrEP) by populations at high risk of HIV infection is now recommended in guidelines in the United States, Europe and Australia [2–4], as well as globally through the WHO guidelines [5].

These clinical PrEP guidelines update the 2015 Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine's (ASHM) PrEP guidelines and they represent an adaptation and update of the 2014 United States Centers for Disease Control's PrEP guidelines [3].

Between May 2016 and January 2017, the Australian Therapeutic Goods Administration (TGA) approved tenofovir disoproxil fumarate and emtricitabine (TDF/FTC, Truvada), tenofovir disoproxil maleate and emtricitabine (TDM/FTC, Trucitavir) and tenofovir disoproxil phosphate and emtricitabine (TDP/FTC, Tenofovir EMT Lupin) for entry onto the Australian Register of Therapeutic Goods (ARTG). These medications are registered for daily use in individuals aged 18 years and over. However, these medications are not yet subsidised by the Pharmaceutical Benefits Scheme for use as HIV PrEP [6]. Other drugs used for PrEP but not registered in Australia can be legally imported into Australia using the TGA Personal Importation Scheme (PIS) [7]. For simplicity, the form TD* is used to denote the tenofovir disoproxil component present in the three registered drugs.

The recommendations included here are designed to:

- support the prescription of PrEP using the ARTG-listed drugs and other bioequivalent generic drugs that are available in Australia, or are being used in Australian PrEP trials
- assist clinicians in their evaluation of patients who are seeking PrEP
- to assist clinicians in commencing and monitoring their patients on PrEP by providing information on PrEP dosing schedules, management of side-effects and toxicity, use of PrEP in pregnancy and in chronic hepatitis B infection and how to cease PrEP.

Daily PrEP with TD*/FTC is recommended in CDC, WHO and earlier Australian guidelines as a key HIV-prevention option for men who have sex with men (MSM), transgender men and women, heterosexual men and women, and people who inject drugs (PWID) at substantial risk of HIV acquisition. Based on available evidence, this guideline does not recommend the coitally timed use of PrEP. Such use can be considered only for patients at risk of HIV infection who are unable to take daily PrEP, and it is contraindicated for people with chronic hepatitis B infection.

The intended users of this guideline include:

- general practitioners who provide care to persons at risk of acquiring HIV infection

*Corresponding author: Edwina Wright, Department of Infectious Diseases, Alfred Health, Monash University, Melbourne, Australia
Email: edwina.wright@monash.edu

Summary of guidance for PrEP providers

	Men who have sex with men	Trans and gender diverse people	Heterosexuals	People who inject drugs
When to *offer* PrEP	If the risk of acquiring HIV infection is rated as *high* according to the eligibility criteria discussed (see: Behavioural eligibility for PrEP below)			
When to *consider* PrEP	If the risk of acquiring HIV infection is rated as *medium* according to the eligibility criteria discussed (see: Behavioural eligibility for PrEP below)			
PrEP for those not meeting eligibility criteria	In all four scenarios, the individual may not necessarily meet the high- or medium-risk criteria. However, the clinician may deem, after taking a detailed history, that the individual is at high or medium risk, and may recommend or consider PrEP accordingly Note that individuals who inject drugs may have high or medium risk of HIV acquisition through sexual exposure			
Clinical eligibility	Documented negative HIV test result using 4th-generation Ag/Ab test within 7 days of starting PrEP No signs or symptoms of acute HIV infection Normal renal function (eGFR >60 mL/min/1.73 m^2) No contraindicated medications (those that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and emtricitabine: see Patients with chronic renal failure below)			
Prescribe	Daily, continuing, oral dose of coformulated tenofovir and emtricitabine ≤90-day supply Patients need to take a daily dose of PrEP for 7 days before high levels of protection are achieved for both vaginal and rectal exposure to HIV			
Other services	At baseline, document hepatitis B and C infection and vaccinate for hepatitis B for those not immune (see Monitoring HBV and HCV infections below) Follow-up visits at month 1 after PrEP initiation (optional) and at least every 3 months after initiation to provide: • HIV testing using 4th-generation Ag/Ab test (at every follow-up visit), assessment for primary HIV infection if suspected (see Testing for HIV below) • Medication-adherence assessment and support (at every follow-up visit) • Discussion about the reduction of risk of HIV and sexually transmitted infections (STIs) (at every follow-up visit) • Side effects (at every follow-up visit) • STI symptom assessment at every visit and management as required • Complete HBV vaccination if commenced or chronic hepatitis B monitoring and management, as required • Assessment of renal function at 3 months and every 6 months thereafter, or more frequently as indicated • Assessment of hepatitis C status (at least every 12 months or more frequently if necessary)			
Additional testing	**Men who have sex with men** Every 3 months, STI testing as per Australian STI testing guidelines [1]	**Trans and gender diverse people** Every 3 months, STI testing as per Australian STI testing guidelines [1]	**Heterosexuals** Assess pregnancy intent and conduct pregnancy test every 3 months if appropriate	**People who inject drugs** Test for STI if indicated and hepatitis C Access to clean needles/syringes and drug treatment services
Optional testing	HIV testing at 1 month or sooner at clinician's discretion based upon clinician's concerns around adherence, or that a high-risk HIV exposure occurred 3 or more days prior to PrEP initiation Bone mineral density in patients at risk on initial or subsequent assessment Vitamin D levels Proviral DNA testing if early (primary) HIV infection is suspected			

- sexual health physicians who provide care to persons at risk of acquiring HIV infection
- infectious disease and HIV treatment specialists who may provide PrEP, or serve as consultants to primary-care physicians about the use of antiretroviral medications
- trainees and registrars in each of the above categories
- nurse practitioners
- nurses working in nurse-led clinics in consultation with doctors
- peer workers
- counsellors and individuals performing HIV testing, including point-of-care testing
- health program policymakers
- health consumers and others with an interest in HIV PrEP

HIV prevention in Australia

Australia endorsed the 2011 UN Declaration of commitment on HIV/AIDS, and Australian Health Ministers have endorsed the UN Declaration's prevention and treatment targets adapted to the Australian context. These targets informed the development of the Seventh National HIV Strategy 2014–2017 and a number of jurisdictional HIV strategies, with the ambitious goal of virtually eliminating HIV transmission in Australia by 2020 [8].

Primary HIV-prevention strategies in Australia focus on the use of safer sex practices, including condoms, clean needles and biomedical strategies. Other prevention strategies promoted in Australia include HIV testing, immediate HIV treatment to reduce HIV viral load, and HIV post-exposure prophylaxis. Australian testing guidelines recommend that all sexually active MSM test for HIV and retest every 12 months, and that those who are at high risk of HIV infection should retest up to four times a year [9]. Among priority populations considered to be at high risk of HIV infection due to sexual or injecting behaviour, the proportion tested annually has generally been high [10]. Among MSM, both the proportion tested in the last year and the average number of HIV tests per year increased during the period 2011–2015.

Indications for PrEP in Australia

HIV epidemiology

Australia has a concentrated HIV epidemic, with sexual contact between men (with or without injection drug use) accounting for 73% of new HIV diagnoses in 2015 [11]. A further 20% of cases were attributed to heterosexual sex. In these cases, 40% occurred in people from a country with high HIV prevalence, or who had a partner from such a country. Only 3% of new HIV diagnoses were attributable to injecting drug use alone. Other or unknown exposures contributed only 3.8% of infections in 2015 [11].

Table 1. Factors associated with elevated risk of HIV acquisition among MSM in the Health in Men (HIM) study, Australia, 2001–2007, and their translation into eligibility criteria for PrEP

Findings of the HIM study		Criteria to identify increased risk of HIV
Risk factor	**HIV incidence per 100 person years (95% confidence interval)**	
All gay and bisexual men regardless of behavioural practices	0.78 (0.59–1.02)	n/a
HIV risk factors: high risk		
A regular sexual partner of an HIV-positive man with whom condoms were not consistently used in the last 6 months	5.36 (2.78–10.25)	A regular sexual partner of an HIV-infected men (***not on treatment and/or detectable viral load***) with whom condoms were not consistently used in the last 3 months
At least one episode of receptive, unprotected anal intercourse with any casual HIV-infected male partner or a male partner of unknown HIV status during the last 6 months	2.31 (1.48–3.63)	At least one episode of receptive condomless anal intercourse (CLAI) with any casual HIV-infected male partner or a male partner of unknown HIV status in the last 3 months
Rectal gonorrhoea diagnosis in last 6 months	7.01 (2.26–21.74)	Rectal gonorrhoea, rectal chlamydia or ***infectious syphilis*** diagnosis in the last 3 months
Rectal chlamydia diagnosis in last 6 months	3.57 (1.34–9.52)	
Methamphetamine use in last 6 months	1.89 (1.25–2.84)	Methamphetamine use in last 3 months
HIV risk factors: medium HIV risk to be used in individual clinical assessment		
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)	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)
A regular sexual partner of CLAI or having at least one episode of insertive CLAI where the serostatus of partner is not known or is HIV-positive	0.94 (0.35–2.52)	n/a
In uncircumcised men having at least one episode of insertive CLAI where the serostatus of partner is not known or is HIV-positive	1.73 (0.43–6.90)	(If patient is uncircumcised) having in the last three months more than one episode of insertive CLAI where the serostatus of partner was not known or was HIV-positive and not on treatment
In circumcised men (comparison group, low risk, PrEP not recommended)	0.65 (0.16–2.61)	n/a

Table 1 summarises the key factors associated with an increased risk of HIV acquisition among gay and bisexually identified men in the Sydney-based Health in Men (HIM) study. Four factors were associated with HIV incidence of above 1.8 per 100 person years; these factors formed a group of criteria for identifying people at high risk of HIV. Two more factors with an HIV incidence above 1.0 and below 1.8 per 100 person years formed this guideline's criteria for medium HIV risk.

The HIM study collected data from 2001 to 2007. While treatment rates are now higher, the annual number of HIV diagnoses has increased by 8% since 2007, and the same risk factors for increased HIV infection risk are likely to remain relevant in Australia today. Therefore, the HIV risk factors reported by the HIM study provided a basis for formulating criteria to identify MSM at increased HIV risk and eligible for PrEP.

Due to the specifics of data collection for the HIM study, not all indicators were available to support each individual eligibility criterion. Some indicators were collected in different forms, or have a different denominator or reference period. Most importantly, the HIV treatment and viral load of HIV-positive regular partners is now known to have a significant impact on HIV transmission; however, these data were not collected in the HIM study. Similarly, infectious syphilis was uncommon and not associated with HIV transmission in the HIM cohort, but its incidence has increased greatly since 2007. Syphilis is associated with an increased risk of HIV among MSM globally, and is therefore included in the risk criteria. Finally, the reference period for PrEP eligibility assessment is set up in these guidelines to reflect behaviour over the previous 3 months.

Note that while the HIM study uses the terminology of 'gay and bisexual men', this guideline uses 'men who have sex with men' (MSM) to focus on behaviour, rather than identity.

Behavioural eligibility for PrEP

Providers need to obtain a thorough sexual and drug-use history at baseline to determine PrEP eligibility. Thereafter, they must regularly discuss HIV-risk practices with their patients to assess their ongoing eligibility for PrEP. Medium-risk behaviours have been included to assist clinicians in the case-by-case approach to assessing eligibility.

These guidelines acknowledge that as an HIV-prevention option, PrEP may be considered by anyone who is at risk of acquiring HIV. Some patients will not fall within the recommended eligibility criteria outlined below, but may still benefit from accessing PrEP. Examples of why a case-by-case approach is important when evaluating a person for PrEP include:

- those patients without recent evidence of sexually transmitted infections (STIs) or high-risk sexual practices, but who report that they have recently left a monogamous relationship and will be having condomless sex with casual partners in the future
- a person whose HIV risk does not meet the high- or medium-risk criteria, but is so anxious about HIV infection that it impedes their quality of life and may prevent them from having regular HIV testing

Clinicians with limited experience in sexual health or management of patients on PrEP are encouraged to discuss cases where PrEP eligibility is not straightforward with a clinician who is experienced in HIV PrEP.

Behavioural eligibility criteria for PrEP for men who have sex with men (Box 1)

Box 1. Risk criteria for MSM to identify their eligibility for PrEP

A. High risk – recommend prescribing daily PrEP if the patient acknowledges

Having had any of the following in the last 3 months	AND	**Being likely to have in the next 3 months** (indicating sustained risk)
• At least one episode of condomless anal intercourse (CLAI) with a regular HIV+ partner (not on treatment and/or detectable viral load) • At least **one** episode of receptive CLAI with any casual HIV+ male partner or a male partner of unknown status • Rectal gonorrhoea, rectal chlamydia or infectious syphilis diagnosis (during the last 3 months or at screening for PrEP) • Methamphetamine use, which may increase the risk of HIV acquisition		• Multiple episodes of CLAI with or without sharing intravenous drug equipment

B. Medium risk – consider prescribing daily PrEP, based on a case-by-case approach if discussion reveals

Having had any of the following in the last 3 months	AND	**Being likely to have in the next 3 months** (indicating sustained risk)
• More than one episode of anal intercourse when proper condom use was not achieved (e.g. condom slipped off or broke) where the serostatus of partner was not known, or was HIV+ and not on treatment or with a detectable viral load • (If patient uncircumcised) more than one episode of insertive CLAI where the serostatus of partner was not known, or was HIV+ and not on treatment or with a detectable viral load		• Multiple episodes of CLAI with or without sharing intravenous drug equipment

Case-by-case approach
Based on a complete sexual and alcohol and other drug-using history and the personal circumstances of the patient, if the clinician is of the opinion that the patient is likely to be at high risk of HIV, then PrEP prescription may be considered despite the absence of reported high- or medium-risk factors above.

PrEP for trans and gender diverse people (Box 2)

Trans and gender diverse individuals have rarely been included in PrEP studies. As a result, limited data are available for these individuals. Incorrect assumptions can be made about trans people and their sexual practices, although they may practice vaginal/neovaginal and anal intercourse, or insertive and receptive sex. Trans and gender diverse people who are at high risk of acquiring HIV on the basis of their sexual history are eligible to access PrEP.

Box 2. Risk criteria for trans and gender diverse people to identify their eligibility for PrEP

A. High risk – recommend prescribing daily PrEP if the patient acknowledges

Having had any of the following in the last 3 months	AND	**Being likely to have in the next 3 months** (indicating sustained risk)
• Being a regular sexual partner of an HIV+ person (not on treatment and/or detectable viral load) with whom condoms have not been consistently used • At least **one** episode of receptive condomless intercourse (CLI) with any casual HIV+ partner or a male partner of unknown status • Rectal or vaginal gonorrhoea, rectal or vaginal chlamydia or infectious syphilis diagnosis (during the last 3 months or at screening for PrEP) • Methamphetamine use, which may increase the risk of HIV acquisition		• Multiple episodes of anal or vaginal CLI with or without sharing intravenous drug equipment

B. Medium risk – consider prescribing daily PrEP, based on a case-by-case approach if discussion reveals

Having had any of the following in the last 3 months	AND	**Being likely to have in the next 3 months** (indicating sustained risk)
• More than one episode of anal or vaginal intercourse when proper condom use was not achieved (e.g. condom slipped off or broke) and where the serostatus of partner was not known, or was HIV+ and not on treatment or with a detectable viral load • (If patient uncircumcised) more than one episode of insertive CLAI where the serostatus of partner was not known, or was HIV+ and not on treatment or with a detectable viral load		• Multiple episodes of anal or vaginal CLI with or without sharing intravenous drug equipment

Case-by-case approach
Based on a complete sexual and alcohol and other drug-using history and the personal circumstances of the patient, if the clinician is of the opinion that the patient is likely to be at high risk of HIV, then PrEP prescription may be considered despite the absence of reported high- or medium-risk factors above.

PrEP for heterosexual people (Box 3)

Box 3. Risk criteria for heterosexual people to identify their eligibility for PrEP

A. High risk – recommend prescribing daily PrEP if the patient acknowledges

Having had any of the following in the last 3 months • Being a regular sexual partner of an HIV+ person (not on treatment and/or with detectable viral load) with whom condoms have not been consistently used • At least **one** episode of receptive anal or vaginal condomless intercourse (CLI) with any casual HIV+ partner or a male homosexual or bisexual partner of unknown status • A female patient in a serodiscordant heterosexual relationship, who is planning natural conception in the next 3 months	AND	**Being likely to have in the next 3 months** (indicating sustained risk) • Multiple episodes of CLI with or without sharing intravenous drug equipment

B. Medium risk – consider prescribing daily PrEP, based on a case-by-case approach if discussion reveals

The patient acknowledges having had any of the following in the last 3 months • At least one episode of CLI with a heterosexual partner, not known to be HIV–, from a country with high HIV prevalence	AND	**Being likely to have in the next 3 months** (indicating sustained risk) • Multiple episodes of CLI with a heterosexual partner, not known to be HIV+, but at high risk of being HIV+ with or without sharing injecting equipment

Case-by-case approach
Based on a complete sexual and alcohol and other drug-using history and the personal circumstances of the patient, if the clinician is of the opinion that the patient is likely to be at high risk of HIV, then PrEP prescription may be considered despite the absence of reported high- or medium-risk factors above. Specific consideration should be given to recommending PrEP to a patient who is travelling to one or more countries with high HIV prevalence and is likely to be sexually active while travelling.

PrEP for people who inject drugs (Box 4)

In the first instance, PWID should be advised of and provided with options for using sterile needles, syringes and other injecting equipment, or offered opioid substitution therapy. PWID can be referred to local needle and syringe programs (NSPs) or the Australian Injecting and Illicit Drug Users League affiliates in their state or territory.

Because PWID may face many health threats, PrEP and other HIV-prevention interventions should be integrated with prevention and clinical care services for hepatitis B and C infection and other infectious diseases services. This includes screening for both viruses and vaccination for hepatitis B where indicated, and injection-related injuries and disease, including abscesses, septicaemia, endocarditis and overdose [12].

The ASHM PrEP guidelines panel is cognisant of the concerns of the International Network of People who Use Drugs. The Network cautions against prioritising PrEP at the expense of other proven interventions as the prime HIV-prevention strategy for PWID, and emphasises that access to harm-reduction services remains a critical component of HIV prevention in PWID [13].

The ASHM PrEP guidelines panel will monitor the outcomes of the few ongoing studies of PrEP in PWID.

PWID may also be at elevated risk of HIV acquisition through sexual exposure. Therefore, they should be evaluated for PrEP using risk criteria outlined in Boxes 1, 2 and 3.

Box 4. Risk criteria for PWID to identify their eligibility for PrEP

A. High risk – recommend prescribing daily PrEP if the patient acknowledges

Having in the last 3 months • Shared injecting equipment with an HIV+ individual or with a gay or bisexual man of unknown HIV status	AND	**Being likely to have in the next 3 months** (indicating sustained risk) • Multiple events of sharing injecting equipment with an HIV+ individual or a gay or bisexual man of unknown HIV status • Inadequate access to safe injecting equipment

Case-by-case approach
Based on a complete sexual and alcohol and other drug-using history and the personal circumstances of the patient, if the clinician is of the opinion that the patient is likely to be at high risk of HIV, then PrEP prescription may be considered despite the absence of reported high- or medium-risk factors above.

Clinical assessment before starting PrEP

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

HIV testing

For patients' safety, ***a negative HIV test result must be performed and documented at the time that the patient is evaluated for PrEP***. This is because daily TD*/FTC combination alone is insufficient for treatment of undiagnosed acute or chronic HIV infection.

HIV testing should be repeated every 3 months (before prescriptions are refilled or reissued). This requirement should be explained to patients during the discussion about whether PrEP is appropriate for them.

A fourth-generation HIV antibody/antigen test should be used, and performed within 7 days of the patient being evaluated

for PrEP. Clinicians should tell patients to start PrEP within 7 days of the day that their HIV-negative test was performed.

Rapid, point-of-care tests (PoCT) should not be used alone to screen for HIV infection when considering PrEP, because they are less sensitive than blood tests [14]. A PoCT can exclude potential PrEP users who are found to be HIV-positive, and any reactive PoCT should be confirmed by conventional laboratory testing in line with the Australian HIV Testing Policy. Seroconversions to HIV have been described in the published literature that appeared to be related to stage 0 or pre-seroconversion HIV, and were acquired very soon before testing for the trial entry, but could not be detected by PoCT [15,16]. Clinicians should not accept patient-reported test results, or documented anonymous test results.

Any positive HIV antibody test result must be managed according to the Australian HIV Testing Policy and local management guidelines (www.testingportal.ashm.org.au/).

A course of nPEP may be required before transitioning to PrEP, in accordance with the PEP and nPEP Guidelines [17] if a patient had a recent high-risk exposure (within 72 hours). See nPEP and PrEP for more information.

Patients who have had a recent high-risk exposure outside the window for the commencement of nPEP should be started on PrEP and closely monitored for seroconversion using a fourth-generation HIV test for the next 2–8 weeks before reverting to standard PrEP monitoring.

Acute HIV infection should be suspected in individuals at high risk of HIV who have been exposed recently to HIV (e.g. no condom or a condom broke during sex with an HIV-positive partner not on treatment, or casual partner of MSM; recent injection drug use with shared injection equipment with MSM, or person known to be HIV-positive).

In a prospective study of 2226 people at high risk of HIV infection who underwent twice-weekly HIV nucleic acid testing, 50 people were evaluated for their clinical signs and symptoms during acute HIV infection. Symptoms occurred in 94% of participants with acute HIV infection, just before and around the time of peak HIV viraemia [18]. Importantly, when individuals were examined during study visits during the period of acute infection, 71% reported no symptoms and 50% reported no symptoms or signs. Hence, clinical detection of acute HIV infection may not be possible in all patients who present for PrEP. The most common symptoms were fever, headache and malaise, while the most common signs were related to the head, eyes, ears, nose, throat, tachycardia and lymphadenopathy (see Table 2).

Initiation of TD*/FTC PrEP in individuals with undiagnosed primary or acute (symptomatic) HIV infection has been associated with the development of resistance to TD*/FTC, mostly commonly to the FTC component [19–22].

Individuals who present with signs or symptoms consistent with acute HIV infection should not be commenced on PrEP until HIV infection has been excluded.

Patients with indeterminate HIV test results at baseline should not be started on PrEP. They should be assessed for early HIV infection and treated according to local antiretroviral treatment guidelines [23]. Such patients can only be started on PrEP if and when HIV infection is excluded.

Table 2. Symptoms and abnormalities associated with primary or acute HIV infection, overall and by region [18]

	Africa (*n*=31)		Thailand (*n*=17)		Overall (*n*=48)	
	n	**%**	***n***	**%**	***n***	**%**
Symptom						
Fever	18	55	7	41	25	50
Headache	17	52	6	35	23	46
Feeling of illness	14	42	5	29	19	38
Coughing	10	30	9	535	19	38
Abnormality						
HEENT[a]	6	18	16	94	22	44
Lymphadenopathy[b]	9	9	16	94	19	38
Tachycardia	11	33	5	29	16	32

[a] Head, ears, eyes, nose and throat
[b] A condition or disease affecting the lymph glands of the body resulting in lymph nodes that are abnormal in size, consistency or number

Concerns about TD* or FTC resistance

Overall, the risk of developing TD* or FTC resistance among participants on PrEP is low [24]. According to a World Health Organization (WHO) meta-analysis of HIV resistance data from randomised clinical trials of PrEP, participants on PrEP versus placebo who started PrEP at the time of acute HIV infection had a higher risk of developing resistance, with more cases of resistance developing to FTC than to TD*. Only a few TD* or FTC mutations were recorded among participants who seroconverted after randomisation [24].

Assessment of renal function at baseline

In a meta-analysis, tenofovir use in HIV-positive patients was associated with a statistically significant loss of renal function, with the effect being judged as clinically modest [25]. Tenofovir use was not associated with increased risk of fractures, hypophosphataemia or severe proteinuria [25]. Rarely, proximal renal tubular dysfunction (including Fanconi's syndrome) may occur with TD* use [25–27].

Overall, tenofovir use in PrEP studies has not been associated with significant renal problems, although some patient populations may be at a higher risk for renal decline while taking TD*/FTC for PrEP. In the US PrEP Demo Project, 23 occurrences of elevated creatinine levels were seen in 13 of 557 individuals (2.3%), including 22 grade 1 and one grade 2 events [28]. On repeat testing, only three elevations among three participants were confirmed, and all episodes of creatinine elevation resolved within 2–20 weeks without stopping PrEP [29]. In a recent conference report that updated the US PrEP Demo Project findings, the median decline in creatinine clearance was 6 mL/min (5%) from baseline to week 12. It then remained stable through to week 48 (P=0.96), with no differences by race/ethnicity, weight or use of non-steroidal agents. However, new-onset estimated glomerular filtration rate (eGFR) <70 mL/min/1.73 m^2 was more common in those with baseline eGFR <90 mL/min/1.73 m^2, and was seen more obviously in people over the age of 45 [28]. However, in a multivariable analysis, the following factors were independently associated with greater creatinine clearance loss: age younger than 25 years, use of medications for hypertension or diabetes, and red blood cell tenofovir diphosphate (TFV-DP) levels consistent with taking two or more doses/week of TD*/FTC. The authors reported that younger PrEP users may warrant increased monitoring of renal function [28]. In another study, factors associated with greater

odds of the eGFR falling below 60 mL/min/1.73 m^2 were: age greater than 40 years, a baseline creatinine clearance of less than 90 mL/min and evidence of good adherence [30]. Finally, older age was associated with greater decline in renal function in the Bangkok Tenofovir study [31].

For all patients considered for PrEP, their risk factors for renal disease should be assessed. These include diabetes, hypertension, smoking, concurrent medications and a known history of renal impairment. Measurements of baseline serum creatinine, eGFR, urine protein: creatinine ratio (PCR) and blood pressure should also be taken. The Cockcroft–Gault formula (see Appendix 1) is regarded as the ideal way to measure the eGFR. However, for most practitioners, this is not practical. Instead, it is reasonable to measure the patient's renal function using the eGFR. A patient with an eGFR of less than 60 mL/min/1.73 m^2 should not be prescribed PrEP.

These guidelines recommend that individuals' creatinine, eGFR and urinary PCR are evaluated at 3 months after commencing PrEP then 6 monthly thereafter, while they receive PrEP. However, based on currently available evidence, more intensive monitoring may be warranted in individuals under the age of 25 years or over the age of 40 years, and in those with a baseline eGFR of less than 90 mL/min/1.73 m^2.

Assessment for and management of sexually transmissible infections at baseline

Individuals at high risk for HIV infection are also at high risk for STIs. Clinicians should screen for STIs (specifically gonorrhoea, chlamydia and infectious syphilis) using the standard of care tests and procedures, and manage any detected STI as recommended by the Australian STI Management Guidelines [9]. The presence of an STI at baseline should not delay the commencement of PrEP.

Patients starting on PrEP should be informed about:

- prevention of STI acquisition and transmission
- frequency of STI testing
- signs and symptoms of STIs
- the need to present for testing and treatment whenever signs or symptoms of STIs appear

Assessment for hepatitis B and C status

Patients assessed as high or medium risk for HIV can also be at risk of acquiring hepatitis B virus (HBV) [32] and hepatitis C virus (HCV) [33] infection. HBV and HCV infection status should be documented by screening serology when PrEP is initiated.

Vaccination against HBV is recommended for all susceptible priority populations, which include MSM; sex workers; people from countries with a high HIV, HBV or HCV prevalence, and their sexual partners; and PWID [34,35]. Individuals identified at baseline as having undiagnosed chronic hepatitis B should be referred to a clinician experienced in the management of hepatitis B for treatment assessment. Individuals on TD*/FTC for HIV PrEP should be counselled on the importance of strict adherence to PrEP to prevent both a flare in their hepatitis B infection and the development of hepatitis B resistance to TD*/FTC. Individuals identified at baseline with undiagnosed hepatitis C infection should be referred to a clinician experienced in hepatitis C management for consideration of hepatitis C treatment. A diagnosis of hepatitis B or hepatitis C is not an impediment to HIV PrEP initiation.

Other considerations and testing before commencement of PrEP

Additional testing may be warranted in some special subpopulations.

Assessment of bone health

Low bone mineral density (BMD) has been observed at baseline in approximately 10% of individuals receiving TD*/FTC for PrEP in two studies [28,36]. Hence, individuals should be counselled about the effects of TD* on BMD and counselled to decrease alcohol and cigarette use, undertake weight-bearing exercise and ensure their diet provides adequate amounts of calcium and vitamin D [36]. A clinician may suspect that an individual is vitamin D deficient and may wish to test their vitamin D levels. There is no evidence that over-the-counter vitamin D supplements reduce tenofovir-related BMD changes.

A small but significant decline in BMD has been observed in three studies using TD* or TD*/FTC for PrEP. The decline in BMD correlates directly with levels of intracellular TD*-DP and is reversible following PrEP cessation [36]. A person with a history of osteoporosis will require careful monitoring while on PrEP. If the clinician suspects that a person may have osteoporosis, they may recommend BMD testing. BMD testing is rebated in Australia under specific clinical circumstances (more information about BMD rebates can be found at: www.health.gov.au/internet/main/publishing.nsf/content/diagnosticimaging-bd.htm).

Assessment for pregnancy (in women of child-bearing age, where applicable or suspected)

PrEP can be used in pregnancy. In observational studies of HIV-positive women treated throughout pregnancy with TD*-containing regimens, TD* during pregnancy has not been associated with adverse outcomes, but lowered BMD was observed in their newborns [37]. In HIV-negative women in PrEP trials, PrEP was promptly discontinued for those who became pregnant. Therefore, the safety for exposed fetuses could not be adequately assessed. Some women with an HIV-positive partner may prefer to continue PrEP while pregnant, due to increased risk of acquisition of HIV during pregnancy.

Providing PrEP

Goals of PrEP

The ultimate goal of PrEP is to reduce the acquisition of HIV infection and 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 HIV-negative persons who meet recommended criteria to reduce their risk of HIV acquisition
- educate patients about the medications and the regimen to maximise their safe use
- provide medication-adherence support and counselling 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 minimise their risk of acquiring HIV
- provide effective contraception to women who are taking PrEP and do not wish to become pregnant
- monitor patients to detect HIV infection, medication toxicities, STIs and levels of risk behaviour, make indicated changes in strategies to support patients' long-term health, and initiate timely treatment of infections.

The choice of PrEP schedule

Daily PrEP

Daily PrEP should be recommended to people who have ongoing high or medium risk of acquiring HIV. In Australia, TD*/FTC has been registered for use as a daily medication.

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

Non-daily PrEP

Some individuals may express interest in taking PrEP on a non-daily or intermittent basis. This is because they may have reasons not to take medication on a daily basis, may engage in risk practices for only short periods of time, or have infrequent exposures to HIV.

Data on the efficacy of non-daily PrEP dosing are available only for MSM and transgender women, and only from a single randomised, placebo-controlled trial by IPERGAY and its open-label extension. IPERGAY evaluated the efficacy of a coitally timed regimen comprising two pills of TD*/FTC (versus placebo) taken 2–24 hours before potential sexual exposure to HIV, followed by single doses 24 and 48 hours following the initial dose. The incidence of HIV was high in the placebo group, and a risk reduction of 86% and 97% was reported in the randomised and open-label phases, respectively [38,39]. The IPERGAY participants reported using a median of 15 PrEP doses per month (interquartile range 9–21), which is approximately four tablets per week. Previously, the results from a pharmacological TD*/FTC dosing study in 21 HIV-negative volunteers were extrapolated to the Pre-exposure Prophylaxis Initiative (iPrEx) study participants who had taken TD*/FTC daily. The results suggested that four daily TD*/FTC doses per week were highly protective for MSM and transgender women [40]. Of note, 16% of individuals may not reach the highly protective drug levels after four doses of TD*/FTC [38].

Additionally, the feasibility of different TD*/FTC dosing methods was investigated in a single phase II, randomised, open-label trial of pharmacokinetics and behaviour – the HIV Prevention Trials Network HPTN 067 (also known as the ADAPT study). ADAPT compared three medication regimens in two population groups, MSM (in Thailand and Harlem) and women (in South Africa), as follows:

i. daily

ii. twice weekly (3–4 days apart and a dose after sex)

iii. coitally timed dosing, with doses taken before and after sex [41]

MSM had better adherence to daily and coitally timed dosing than women. In women, the daily dosing covered significantly more sex acts and provided significantly higher drug levels than other regimens [42].

Combined, this evidence suggests that:

- four doses per week of TD*/FTC taken as daily doses, or as a coitally timed regimen, are highly protective from HIV infection in MSM
- full adherence to coitally timed regimens is critical
- the efficacy of a coitally timed regimen in MSM who have infrequent HIV exposure (less than one episode per week) is not strong
- individuals taking coitally timed PrEP must anticipate sex to employ this dosing regimen appropriately

The efficacy of coitally timed dosing has not yet been determined in heterosexual men and women.

Therefore, the ASHM PrEP guidelines panel continues to recommend daily TD*/FTC dosing for all population groups eligible for PrEP. The panel will monitor this area and provide updated advice if and when additional evidence becomes available.

Duration of PrEP use and follow-up schedule

Along with encouraging safer sex practices and safer injection techniques (if applicable), clinicians should help their patients decide when to use PrEP and when to discontinue its use.

The duration of PrEP use will depend on whether the individual's risk of HIV continues over time. PrEP should only be prescribed to those patients who are able to adhere to a regimen that has been shown to be efficacious and express a willingness to do so.

Initial prescription should offer a 90-day medication supply.

Extensions of PrEP prescriptions should cover no more than 90 days of TD*/FTC supply at a time, renewable only after HIV testing confirms that a patient remains HIV-uninfected and still eligible for PrEP.

The recommended schedule of testing and follow-up is outlined in Table 3.

Adherence to PrEP should be assessed at each follow-up visit. PrEP users who otherwise declare non-adherence, but are willing and eligible to continue on PrEP, should be offered additional adherence education (see Improving medication adherence, including offering referral to peer-based support services). If a patient repeatedly reports adherence that is sufficiently suboptimal to compromise both PrEP's efficacy (i.e. fewer than four pills per week) and the patient's safety, the clinician should discontinue prescribing PrEP. See also nPEP and PrEP for the course of action if a patient was not adherent to PrEP and had a risk of exposure in the last 72 hours.

Indicated medication

The medications proven safe and effective, and currently approved by the TGA for PrEP in healthy adults at risk of acquiring HIV infection, are the fixed-dose combination of TD* and FTC in a single daily dose. Therefore, TD*/FTC or other generic versions of TD*/FTC are the recommended medications that should be prescribed for PrEP for MSM, trans and gender diverse individuals heterosexuals, and PWID who meet recommended criteria. TDF alone has been proven effective in trials with PWID and heterosexuals (with efficacy comparable to TDF/FTC [24]). As a result, WHO recommends that TDF alone can be considered as an alternative regimen in these specific populations. TDF alone is not recommended as PrEP for MSM, because no trials have been performed to assess the efficacy of this regimen in MSM.

There have been some recent overseas reports of HIV seroconversion in MSM taking unprescribed antiretroviral medication for PrEP [43].

What not to use for PrEP

DO NOT use:

- other antiretroviral medications, either in place of, or in addition to TD* or FTC
- other than daily dosing, such as intermittent, coitally timed, or episodic (pre/post sex only)

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

PrEP medication side effects

Patients taking PrEP should be informed of TD*/FTC side effects experienced by participants in PrEP trials. These include headache, nausea, flatulence, and the potential for renal injury or hepatotoxicity. 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 counselled about signs or symptoms that indicate a need for urgent evaluation (e.g. those suggesting possible acute renal injury or acute HIV infection).

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 performed in small numbers of HIV-uninfected, healthy adults. No significant effect was seen and no dosage adjustment was necessary for TD*, but there are no data on FTC [44,45].

FTC and TD* are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Since both drugs are primarily eliminated by the kidneys, co-administration of TD*/FTC with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of TD* and FTC, and those of other renally eliminated drugs. Examples include (but are not limited to) cidofovir, aciclovir, valaciclovir, ganciclovir, valganciclovir, aminoglycosides and high-dose or multiple non-steroidal anti-inflammatory drugs [44].

Cocaine, methamphetamine and alcohol use was not seen to influence the concentrations of PrEP drugs [46].

Time to achieving and maintaining protection

The pharmacokinetics of TD* and FTC vary by tissue [47]. Data from exploratory pharmacokinetic studies conducted with HIV-uninfected men and women [48,49] suggest that maximum intracellular concentrations of TFV-DP are reached in blood after approximately 20 days of daily oral dosing. Current evidence suggests that for both rectal and vaginal exposures, high protection is achieved after 7 days of daily dosing [50]. Women need to have high adherence to daily dosing of TD*/FTC to maintain adequate drug levels in vaginal/cervical tissues [50]. 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. Limited data exist for trans and gender diverse people; therefore (similarly to women), extra attention to daily dosing is recommended.

Intermittent (coitally timed or on-demand) PrEP was assessed among MSM in the IPERGAY study, and has been recommended as an acceptable regimen for this population group in France. The high frequency with which this dosing was performed afforded blood levels similar to daily dosing levels. Patients who would only like to use PrEP on rare occasions may not reach the therapeutic (protective) drug level after a long period without PrEP, and may not maintain these levels long enough to prevent HIV infection. In the absence of strong evidence of efficacy of intermittent PrEP dosing in such users, the ASHM guidance panel has taken the more cautious approach of recommending only daily dosing as described in the section on Indicated medication.

Clinicians should familiarise themselves with the reasons for this recommendation, because it is likely that patients will want to experiment with less rigorous dosing and reduce their pill burden. Therefore, it may be necessary to explore the frequency with which patients will begin to use PrEP for HIV prevention. For example, if an MSM patient wants to take PrEP while on an overseas trip, he can be advised to start daily PrEP a week before departure and to cease PrEP once it is no longer needed (i.e. 28 days after the last high-risk episode).

Taking a break and discontinuing PrEP

Starting and stopping PrEP

For some patients, HIV exposure may be episodic, and people who start PrEP may stop and restart it periodically. Learning when and how to start and stop PrEP is important for effective PrEP use [51]. The need for PrEP may end when a partner with HIV achieves viral suppression, or when a patient enters a mutually monogamous relationship with a seroconcordant partner.

Patients may want to restart PrEP when:

- entering a period of engaging in condomless sex
- leaving a long-term relationship
- starting a new relationship with an HIV-positive partner who is not on antiretroviral treatment, or a partner whose HIV status is unknown
- moving to a new region or country with high or unknown prevalence of HIV and unknown sex partners
- entering the field of sex work

Discontinuing PrEP

It is important to note that protective levels of the PrEP drugs are thought to persist only for up to 7 days after ceasing PrEP. One US study recommends that people continue to take daily PrEP for 28 days after the last sexual exposure that put them at high risk of HIV infection [52] and we recommend that clinicians should offer this advice until more information is available.

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

- HIV status at the time of discontinuation
- reasons for PrEP discontinuation
- recent medication adherence and reported sexual risk behaviour

Any person who wishes to restart taking PrEP medications should repeat the baseline evaluations (see sections on Eligibility for PrEP based on risk exposure and Assessment before starting PrEP). Previous discontinuation of PrEP for any reason (except seroconversion to HIV) should not exclude the person from restarting PrEP.

Clinical follow-up and monitoring of patients on PrEP

Recommended schedule of testing and follow-up for individuals on PrEP (Box 5)

Once PrEP is initiated, patients should return for follow-up 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. Table 3 and Box 5 set out the recommended schedule of testing and follow-up for individuals who are prescribed PrEP.

Patients who are accessing PrEP through the PIS should allow a lead time of up to 4–6 weeks if ordering online to allow for the drug to arrive in Australia and pass customs clearance.

Testing for HIV

HIV testing should be repeated every 3 months (before prescriptions are refilled or reissued). Risk practices and adherence to PrEP should also be ascertained when requesting an HIV test (see section on Improving medication adherence). Patients should be familiar with this requirement for subsequent PrEP prescriptions from the discussion conducted when starting PrEP. Clinicians should consider writing on the prescription a date past which dispensing the script should not occur. This may help ensure that patients who have poor medication adherence, or who have only used PrEP intermittently and have unknowingly become infected with HIV, do not receive three months of dual antiretroviral therapy.

See Appendix 2 for up-to-date HIV tests approved in Australia (K Wilson, National Serum Reference Library, personal communication) and time to detection of HIV infection [53].

Table 3. Laboratory evaluation and clinical follow-up of individuals who are prescribed PrEP

Test	Baseline (Week 0)	About day 30 after initiating PrEP (optional)	90 days after initiating PrEP	Every subsequent 90 days on PrEP	Other frequency
HIV testing and assessment for signs or symptoms of acute infection	Y	Y	Y	Y	N
Assess side effects	N	Y	Y	Y	N
Hepatitis B serology	Y	N	N	N	N
Hepatitis C serology	Y	N	N	N	At least every 12 months
STI (i.e. syphilis, gonorrhoea, chlamydia) as per Australian STI Management Guidelines [9]	Y	N	Y	Y	N
eGFR and urine protein: creatinine ratio (PCR) at 3 months and then every 6 months	Y	N	Y	N	At least every 6 months
Pregnancy test (for women of child-bearing potential)	Y	Y	Y	Y	N

Box 5. PrEP follow-up procedures

At least every 3 months:

- Repeat HIV testing and assess for signs or symptoms of acute infection to document that patients are still HIV-negative
- Repeat pregnancy testing for women who may become pregnant
- Provide a prescription or refill authorisation of daily TD*/FTC for no more than 90 days (until the next HIV test)
- Assess side effects, adherence and HIV risk behaviours
- Provide support for medication adherence and risk-reduction behaviours
- Respond to new questions and provide any new information about PrEP use
- Test for STIs
- Evaluate the need to continue PrEP as a component of HIV prevention
- Test for HCV in PWID who report continued sharing and MSM with elevated risk of HCV acquisition

At least every 6 months:

- Monitor eGFR, creatinine and urinary PCR
- If other conditions are present that may impair renal function (e.g., hypertension, diabetes), renal function may require more frequent monitoring or may need to include additional tests
- A rise in serum creatinine is not a reason to withhold treatment if the eGFR remains ≥60 mL/min/1.73 m^2
- If eGFR is declining steadily (but still ≥60 mL/min/1.73 m^2), consultation with a nephrologist or other evaluations of possible causes for declining renal function may be indicated

At least every 12 months:

- Evaluate the need to continue PrEP as a component of HIV prevention
- Test for hepatitis C, in those not tested more frequently

A positive HIV test result must be managed as per HIV Testing Policy and local management guidelines.

A course of nPEP may be required if a patient had a recent high-risk exposure (within 72 hours) but only if they did not take PrEP during those days. See section on nPEP and PrEP below for management of such cases.

Acute HIV infection should be suspected in individuals at high risk for HIV who have been exposed recently (e.g. no condom or a condom broke during sex with an HIV-positive partner who is not on antiretroviral treatment, or has a detectable HIV viral load; recent injection drug use with shared injection equipment with an HIV-positive partner) ***and were not taking PrEP during that time***. Also, infection with TD* and/or FTC resistant HIV is extremely rare but possible while on PrEP, with two cases reported internationally [54,55]. Therefore, in addition to sexual behaviour and injecting drug use, clinicians should solicit a history of non-specific signs or symptoms of viral infection during the preceding month, or on the day of evaluation. See Table 2 for clinical symptoms and abnormalities of acute (primary) HIV infection. If a patient is diagnosed with HIV infection while taking PrEP, their health and wellbeing rather than the emphasis on what their medication adherence was like and how they acquired HIV, should be the chief priority. HIV drug resistance testing should be performed in all cases and if the individual reports high PrEP adherence they may agree to have their blood, or hair tested for tenofovir and emtricitabine drug levels. In this setting referral to an HIV specialist is recommended.

Indeterminate HIV test results in the first 3 months on PrEP

There is a potential for PrEP to delay or attenuate seroconversion in people who may have been exposed just before starting PrEP [56,57]. As yet, there has been little consideration, and no common recommendations of how to manage these patients. Patients with an indeterminate HIV test result while on PrEP (particularly, with repeated indeterminate test results) should be closely monitored in conjunction with an HIV specialist. Proviral DNA testing should be considered. The ASHM PrEP guidelines panel will continue to monitor this issue with a view to providing further guidance.

Monitoring of renal function

Renal function should be monitored at 3 months and 6 monthly thereafter, or more frequently in certain populations (see Assessment of renal function at baseline). The management of individuals at high and ongoing risk of HIV infection, but whose eGFR has declined below 60 mL/min/1.73 m^2 since commencing TD*/FTC, is challenging. This situation typically requires consultation with a physician who is expert in PrEP. Cessation of TD*/FTC for 1 month may restore eGFR to above 60 mL/min/1.73 m^2, following which TD*/FTC may be recommenced with cautious monitoring. In these circumstances, consideration should be given to using coitally based TD*/FTC, or possibly second-daily TD*/FTC. However, there are no data to show that either of these options will stabilise the eGFR above 60 mL/min/1.73 m^2.

Testing for and management of STI

Because PrEP users are at high risk for STIs, clinicians should screen for STIs (specifically gonorrhoea, chlamydia and infectious syphilis) every 3 months using the standard of care tests and procedures, and manage any detected STI as recommended by the Australian STI Management Guidelines [9]. At each follow-up visit, patients taking PrEP should be reminded about:

- prevention of STI acquisition and transmission
- the need for quarterly STI testing
- the need to present for testing and treatment whenever signs or symptoms of STI appear

The presence of an STI at follow-up testing should not prevent the ongoing prescription of PrEP.

Monitoring HBV and HCV infections

HBV monitoring

Both TD* and FTC are active against HBV [58]. If people living with chronic HBV infection stop taking these medications, hepatic flares can occur, which can be severe [58]. A person taking PrEP who has chronic HBV infection should be assessed by a clinician experienced in the management of hepatitis B before ceasing PrEP. If PrEP is discontinued, close monitoring is strongly advised.

For additional guidance about the management of PrEP in persons with chronic active HBV infection, see the section on Special clinical considerations.

HCV monitoring

MSM and trans and gender diverse people should be monitored for HCV if they engage in sexually adventurous sex. The incidence of HCV has currently been low at ~1% per annum in PrEP studies of MSM [38,59], and higher in HIV-positive MSM [60,61]. However, there is concern that HCV incidence may increase following changes in sexual and sero-sorting behaviour in the era of PrEP. Therefore, in this context, HCV should be viewed as an STI. It should be tested at least annually, and more frequently if necessary, following sexual history taking.

Managing side effects

Patients taking PrEP should be assessed for common side effects associated with TD*/FTC use, most importantly those suggesting possible acute renal injury or hepatotoxicity. A recent review of symptoms experienced in the iPrEx study showed that potential PrEP-associated symptoms peaked at 1 month, when 39% of participants reported symptoms, compared with 22% at baseline. Gastrointestinal (GIT) symptoms occurred in a median of 28% of individuals across study sites (range 11–70%) and non-GIT symptoms occurred in a median of 24% of individuals (range 3–59%). The odds of GIT symptoms were higher in those with evidence of high adherence to PrEP. By 3 months, symptoms had returned to pre-PrEP levels.

Bodybuilding increases muscle mass, which may result in increased creatinine levels in blood. When evaluating and managing PrEP users with creatinine clearance changes, clinicians should solicit and take into consideration the history of steroid use and bodybuilding.

The ASHM PrEP guidance panel will monitor evidence in this area and update the guidelines as appropriate.

Optional assessments

Therapeutic drug monitoring

As for HIV treatment, the limited availability of clinical laboratories that can quantify TD*/FTC concentrations under rigorous quality assurance and quality control standards prevents the routine use of therapeutic drug monitoring in PrEP.

Initial demonstration projects in Australia conducted therapeutic drug monitoring as part of research protocols to understand why seroconversions occur among study participants. Their results revealed a high correlation between self-reports of pill taking and blood concentrations of TD* and FTC, and high adherence to PrEP at >90% [62,63].

Therapeutic drug monitoring is unlikely to become available in routine clinical practice.

Special clinical considerations

Women taking PrEP during conception, pregnancy and breastfeeding

Conception in serodiscordant couples

Serodiscordant couples may desire pregnancy. Women without HIV infection who have sex partners with documented HIV infection are at substantial risk of HIV acquisition during natural attempts to conceive (i.e. without a condom) if their HIV-positive partner has a detectable or variably detectable plasma viral load. Providers should discuss the available information about the potential risks and benefits of PrEP in these circumstances.

Pregnancy

Among HIV-uninfected women, pregnancy is a period of elevated risk of HIV infection. In addition, infection acquired during pregnancy may be more likely to be transmitted to the infant than a pre-existing infection.

PrEP exposure among couples desiring pregnancy was not associated with adverse pregnancy outcomes in the Partners PrEP study [19]. TD* use for HIV treatment has not been associated with adverse pregnancy outcomes, although lower BMD in newborns is observed if the mother received antiretroviral therapy during pregnancy, especially if regimens containing TD* are used. Providers should discuss available information about potential risks and benefits of beginning or continuing PrEP during pregnancy so that patients can make an informed decision. After weighing the risks and benefits, PrEP may be continued during pregnancy in women at substantial risk for HIV acquisition.

Breastfeeding

Although experience with PrEP during breastfeeding is still lacking, there is substantial experience with the use of TD*/FTC during the breastfeeding period by women with HIV taking TD*/FTC based ART. TD* and FTC are secreted in breast milk, although at very low concentrations (0.3 and 2%, respectively, of the doses recommended for treatment of HIV infection in infants [64]). If a woman becomes infected with HIV during breastfeeding, the risk of transmission to her infant is higher than in an established infection, because of high viral load soon after seroconversion. Therefore, PrEP may be continued during breastfeeding in women at substantial risk for HIV acquisition.

Patients with chronic active HBV infection

Both TD* and FTC are active against HIV and HBV infections. They may prevent the development of significant liver disease by suppressing HBV replication. Only TD*, however, is currently approved for this use in Australia. Therefore, ongoing treatment with TD*/FTC may be especially indicated in persons with substantial risk of both HIV acquisition and active HBV infection.

Of note are two case reports of patients who were receiving TD* for treatment of hepatitis B and acquired HIV infection [65]. Plasma levels of tenofovir and prescription refills suggested that the patients' medication adherence was good. These guidelines recommend that individuals with established hepatitis B infection who require treatment for hepatitis B infection receive combined TD*/FTC and have ongoing monitoring for HIV PrEP and hepatitis B infection.

All persons 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 liver specialist should be considered.

People living with chronic HBV infection should be tested for HBV DNA by the use of a quantitative assay to determine the level of HBV replication [66] before PrEP is prescribed, and at regular intervals (e.g. every 3–6 months) while taking PrEP. TD* 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 TD*/FTC to prevent reactivation of HBV infection with the attendant risk of hepatic injury, and to minimise the possible risk of developing TD*-resistant HBV infection [67]. Patients with chronic hepatitis B should be strongly advised against intermittent PrEP for these reasons.

If PrEP is no longer needed to prevent HIV infection, a separate determination should be made about whether the patient requires ongoing treatment for HBV infection. Acute flares resulting from the reactivation of HBV infection have been seen in HIV-infected and HIV-uninfected persons after stopping TD* and other medications used to treat HBV infection. When people living with chronic hepatitis B elect to discontinue PrEP, they should first be evaluated by a clinician experienced in the management of HBV infection to ascertain their need for ongoing HBV treatment, and to monitor for any hepatic flares that occur if PrEP is ceased.

Patients with chronic renal failure

HIV-uninfected patients with an eGFR of less than 60 mL/min/1.73 m^2 should not be prescribed PrEP. The only PrEP regimen proven effective to date is TD*/FTC and approved by the TGA for PrEP is not indicated for persons with chronic renal failure [44].

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 or guardian involvement in an adolescent's health care is often desirable, but is sometimes contraindicated for the safety of the adolescent, and can compromise full disclosure.

Clinicians should carefully consider the lack of data on safety and effectiveness of PrEP taken by persons under 18 years of age, including the possibility of BMD loss or other toxicities among youth who are still growing, and the safety evidence available when TD*/FTC is used in treatment regimens for HIV-infected youth [68]. Adherence to PrEP in adolescents may be suboptimal; a PrEP demonstration program for 18–22-year-old HIV-negative MSM reported that TFV-DP intracellular levels consistent with good adherence peaked at 56% at month 1, and declined thereafter [69]. A recent study of 15–22-year-old HIV-negative MSM demonstrated that over 48 weeks, TD*/FTC was not associated with a decline in eGFR, but was associated with a significant decline in BMD [70]. However, another study has suggested that age younger than 25 years is associated

with a more rapid decline in eGFR in individuals receiving TD*/FTC for PrEP [29].

The above factors should be weighed against the potential benefit of providing PrEP for an individual adolescent at substantial risk of HIV acquisition. Clinicians are encouraged to seek expert advice in complex cases. Of note PrEP is approved for use by the TGA for individuals aged 18 years and older.

nPEP and PrEP

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 [17].

If the exposure is isolated (e.g. sexual assault, infrequent condom failure), nPEP should be prescribed, but continued antiretroviral medication is not indicated after completion of the 28-day nPEP course.

If such exposures are not isolated, and the person is determined not to have an HIV infection, clinicians should consider beginning PrEP immediately (or prescribe nPEP immediately followed by PrEP) if the individual needs a three-drug nPEP regimen.

The decision to commence nPEP should be made in line with local nPEP Guidelines [17]. The decision to transition to PrEP should rely on eligibility for PrEP (including confirmatory HIV test result) and willingness to continue taking daily TD*/FTC.

A course of nPEP may be required if a PrEP user had a recent high-risk exposure (within 72 hours), but only if they did not take PrEP during those days. The decision to return to PrEP should rely on eligibility for PrEP (including confirmatory HIV test result) and willingness to continue taking daily TD*/FTC.

Improving medication adherence

Medication adherence is critical to achieving the maximum prevention benefit of PrEP and reducing the risk of selecting for a drug-resistant virus in the event of HIV acquisition [71,72].

Medication education and adherence counselling (also called medication self-management) will need to be provided to support daily PrEP use (Box 6).

Various approaches can be used to effectively support medication adherence [73]. These include:

- educating patients about the medications
- helping patients anticipate and manage side effects
- helping patients 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
- facilitating social support

When initiating a PrEP regimen, clinicians must educate patients about how to take their medications (i.e. when to take them, how many pills to take) and what to do if they experience problems (e.g. what constitutes a missed dose [i.e. number of hours after the failure to take the daily 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 (<12 hours), patients should skip the missed dose and continue with the regular dosing schedule.

Side effects can lead to non-adherence. Clinicians should inform 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 emphasised.

Box 6. Key components of medication-adherence counselling

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 taking to patient's daily routine (e.g. with tooth brushing, before bed)
- Identify reminders and devices to minimise forgotten doses
- Identify and address barriers to adherence

Monitor medication adherence in a non-judgemental manner

- Normalise 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 these

Assess side effects and plan how to manage them

Behavioural strategies to risk reduction

In the era of PrEP, behavioural methods of risk reduction – including condom use – retain their importance in preventing HIV infection and remain the pillar of STI prevention (Box 7).

Box 7. Discussion points on behavioural reduction of HIV and STI risk

Establish trust and two-way communication

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

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

Support risk-reduction efforts

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

Monitor medication adherence in a non-judgemental manner

- Acknowledge the effort required for behaviour change
- Reinforce success

If not fully successful, assess factors interfering with completion of planned actions and help patient identify the next steps (including PrEP prescriptions)

How to access PrEP in Australia

At the time of writing, PrEP has not been approved for subsidy by the Pharmaceutical Benefits Advisory Committee. Availability in Australia is limited to personal importation and the state government medical trials listed below:

NSW	Epic Trial	www.endinghiv.org.au/nsw/stay-safe/epic/
QLD	QPrEP Study	www.comeprepd.info/accessing-prep/
SA	PrEPX-SA	www.samesh.org.au/prep.html
VIC	PrEPX	www.alfredhealth.org.au/research/research-areas/infectious-diseases-research/prepx-study
WA	Trial coming soon	www.waaids.com/hiv/prep-easier-than-you-think.html

Other jurisdictions are in the process of negotiating access to demonstration projects and clinical trials. This section will be updated as changes come into place.

The WA Department of Health provides advice to clinicians supporting patients to import PrEP: www.waaids.com/hiv/prep-easier-than-you-think.html

Information about personal importation is provided at the following links:

www.tga.gov.au/personal-importation-scheme

www.ashm.org.au/hiv/PrEP

www.endinghiv.org.au/nsw/wp-content/uploads/2015/02/PrEP_Access_Options_Paper1.pdf#page=2

Acknowledgements

The Australian PrEP guidelines panel wishes to acknowledge and thank the CDC PrEP guidelines project manager, Dawn Smith, for allowing us to use and adapt the structure and content of the 2014 US Public Health Service Pre-exposure prophylaxis for the prevention of HIV infection in the United States – 2014 clinical practice guidelines.

Contributors

Alfred Health, Monash University (VIC): Christina Chang; Michelle Giles

Australian Federation of AIDS Organisations: Heath Paynter

Australian Injecting and Illicit Drug Users League: Angella Duvnjak

Centers for Disease Control and Prevention (USA): Silvina Masciotra

Centre Clinic – St Kilda: Pauline Cundall

Peter Doherty Institute for Infection and Immunity WHO Collaborating Centre for Viral Hepatitis: Ben Cowie

Gender Centre: Phinn Borg

Harm Reduction Victoria: Jenny Kelso

Holdsworth House Medical Practice (Sydney): Mark Bloch

Kirby Institute: Lisa Maher

National Association of People with HIV Australia: Aaron Cogle

National HIV Reference Laboratory (NRL): Kim Wilson

Peer Advocacy Network for the Sexual Health of Trans Masculinities: Ted Cook

Positive Women Victoria: Alison Broughy

Prahan Market Clinic: Vincent Cornelisse

Queensland AIDS Council: Michael Scott

Royal Prince Alfred Hospital: David Gracey

St Vincent's Hospital: Phillip Cunningham

Sydney Sexual Health Centre: Anna McNulty

Taylor Square Private Clinic: Robert Finlayson

Western Sydney Sexual Health Centre: Cationa Ooi

Abbreviations

AIDS: acquired immunodeficiency syndrome

ART: antiretroviral therapy

ARTG: Australian Register of Therapeutic Drugs

ASHM: Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine

BMD: bone mineral density

eCrCl: estimated creatinine clearance rate

eGFR: estimated glomerular filtration rate

FTC: emtricitabine (trade name Emtriva)

HBV: hepatitis B virus

HCV: hepatitis C virus

HIV: human immunodeficiency virus

iPrEx: Pre-exposure Prophylaxis Initiative

MSM: men who have sex with men

nPEP: non-occupational post-exposure prophylaxis

NSP: needle and syringe program

PEP: post-exposure prophylaxis

PIS: Personal Importation Scheme

PoCT: point-of-care tests

PWID: people who inject drugs

PrEP: pre-exposure prophylaxis

PCR: urine protein: creatinine clearance

STI: sexually transmitted infection

TD*: tenofovir disoproxil maleate or fumarate or phosphate

TDF: tenofovir disoproxil fumarate (trade name Viread)

TDM: tenofovir disoproxil maleate (trade name Trucitavir)

TDP: tenofovir disoproxil phosphate (trade name Tenofovir EMT Lupin)

TDF/FTC: tenofovir disoproxil fumarate coformulated with emtricitabine (trade name Truvada, or in generic form Tenvir). In Australia, the TGA has also approved the generic Trucitavir, which is coformulated tenofovir disoproxil maleate and emtricitabine and Tenofovir EMT Lupin which is co-formulated tenofovir disoproxil phosphate and emtricitabine

TFV-DP: tenofovir diphosphate

TGA: Therapeutic Goods Administration

WHO: World Health Organization

References

1. STIs in Gay Men Action Group. Australian sexually transmitted infection and HIV testing guidelines 2014. 2014. Available at: stipu.nsw.gov.au/wp-content/uploads/STIGMA_Testing_Guidelines_Final_v5.pdf (accessed June 2017).
2. ASHM. PrEP update for HIV clinicians. 2015. Available at: www.ashm.org.au/PrEP (accessed June 2017).
3. Centers for Disease Control. Preexposure prophylaxis for the prevention of HIV infection in the United States – 2014. A clinical practice guideline. 2014. Available at: www.cdc.gov/hiv/pdf/prepguidelines2014.pdf (accessed June 2017).
4. European AIDS Clinical Society. Guidelines version 8. 2015. Available at: www.eacsociety.org/files/guidelines_8_0-english_web.pdf (accessed June 2017).
5. World Health Organization. WHO guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. 2012. Available at: www.who.int/hiv/pub/guidance_prep/en/ (accessed June 2017).
6. Pharmaceutical Benefits Advisory Committee (PBAC). July 2016 PBAC outcomes – 1st time decisions not to recommend. 2016. Available at: www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2016-07/first-time-decisions-not-to-recommend-2016-07.pdf (accessed June 2017).
7. Therapeutic Goods Administration. Personal importation scheme. 2015. Available at: www.tga.gov.au/personal-importation-scheme (accessed June 2017).
8. Australian Government Department of Health. Seventh National HIV Strategy 2014–2017. Available at: www.health.gov.au/internet/main/publishing.nsf/Content/8E87E65EEF535B02CA257BF0001A4EB6/$File/HIV-Strategy2014-v3.pdf (accessed June 2017).
9. ASHM. Australian STI management guidelines. 2014. Available at: www.ashm.org.au/Pages/STIs/sti-guidelines.aspx (accessed June 2017).
10. Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2016. Available at: kirby.unsw.edu.au/surveillance/2016-annual-surveillance-report-hiv-viral-hepatitis-stis (accessed June 2017).
11. Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2015. 2015. Available at: kirby.unsw.edu.au/report/annual-surveillance-report-hiv-viral-hepatitis-stis-2015 (accessed June 2017).
12. Integrated prevention services for HIV infection, viral hepatitis, sexually transmitted diseases, and tuberculosis for persons who use drugs illicitly: summary guidance from CDC and the U.S. Department of Health and Human Services. *MMWR Recomm Rep* 2012; **61**: 1–40.
13. International Network of People who Use Drugs (INPUD). Position paper: pre-exposure prophylaxis (PrEP) for people who inject drugs. 2015. Available at: www.inpud.net/INPUD_PositionPaper_Pre-exposure_prophylaxis_PrEP_April15.pdf (accessed June 2017).
14. ASHM. HIV testing policy. 2016. Available at: www.testingportal.ashm.org.au/hiv/types-of-hiv-diagnostic-tests (accessed June 2017).
15. Murnane PM, Celum C, Mugo M *et al.* Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. *AIDS* 2013; **27**: 2155–2160.
16. Grohskopf LA, Chillag KL, Gvetadze R *et al.* Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. *J Acquir Immune Defic Syndr* 2013; **64**: 79–86.
17. ASHM. Post-exposure prophylaxis after non-occupational and occupational exposure to HIV: Australian guidelines. 2016. Available at: www.ashm.org.au/pep-guidelines (accessed June 2017).
18. Robb ML, Eller LA, Kibuuka H *et al.* Prospective study of acute HIV-1 infection in adults in East Africa and Thailand. *N Engl J Med* 2016; **374**: 2120–2130.
19. Baeten JM, Donnell D, Ndase P *et al.* Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367**: 399–410.
20. Grohskopf LA, Chillag KL, Gvetadze R *et al.* Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. *J Acquir Immune Defic Syndr* 2013; **64**: 79–86.
21. Marrazzo JM, Ramjee G, Richardson BA *et al.* Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2015; **372**: 509–518.
22. Thigpen MC, Kebaabetswe PM, Paxton LA *et al.* Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* 2012; **367**: 423–434.
23. ASHM. Antiretroviral guidelines: US DHHS guidelines with Australian commentary. 2014. Available at: www.arv.ashm.org.au (accessed June 2017).
24. Fonner VA, Dalglish SL, Kennedy CE *et al.* Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *AIDS* 2016; **30**: 1973–1983.
25. Cooper RD, Wiebe N, Smith N *et al.* Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 2010; **51**: 496–505.
26. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. *Am J Kidney Dis* 2011; **57**: 773–780.
27. Phair J, Palella F. Renal disease in HIV-infected individuals. *Curr Opin HIV AIDS* 2011; **6**: 285–289.
28. Liu AY, Cohen SE, Vittinghoff E *et al.* Preexposure prophylaxis for HIV infection integrated with municipal- and community-based sexual health services. *JAMA Intern Med* 2016; **176**: 75–84.
29. Liu AY, Vittinghoff E, PL A. Changes in renal function associated with TDF/FTC PrEP use in the US Demo Project. *Conference on Retroviruses and Opportunistic Infections.* Boston, MA, USA. Abstract 867.
30. Gandhi M, Glidden DV, AY L. Higher cumulative TFV/FTC levels in PrEP associated with decline in renal function. *Conference on Retroviruses and Opportunistic Infections.* February 2016. Boston, MA, USA. Abstract 866.
31. Martin M, Vanichseni S, Suntharasamai P *et al.* Renal function of participants in the Bangkok tenofovir study–Thailand, 2005–2012. *Clin Infect Dis* 2014; **59**: 716–724.
32. Wolitski RJ, Fenton KA. Sexual health, HIV, and sexually transmitted infections among gay, bisexual, and other men who have sex with men in the United States. *AIDS Behav* 2011; **15 Suppl 1**: S9–17.
33. van der Helm JJ, Prins M, del Amo J *et al.* The hepatitis C epidemic among HIV-positive MSM: incidence estimates from 1990 to 2007. *AIDS* 2011; **25**: 1083–1091.
34. Australian Government Department of Health. Second National Hepatitis B Strategy 2014–2017. 2016. Available at: www.health.gov.au/internet/main/publishing.nsf/content/ohp-bbvs-hepb#7. (accessed June 2017).
35. Australian Government Department of Health. The Australian Immunisation Handbook. 10th edn. 4.5 Hepatitis B. 2017. Available at: www.immunise.health.gov.au/internet/immunise/publishing.nsf/content/Handbook10-home~handbook10part4~handbook10-4-5 (accessed June 2017).
36. Grant R, Mulligan K, McMahan V. Recovery of bone mineral density after stopping oral HIV preexposure prophylaxis. *Conference on Retroviruses and Opportunistic Infections.* February 2016. Boston, MA, USA. Abstract 48LB.
37. Siberry GK, Jacobson DL, Kalkwarf HJ *et al.* Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate during pregnancy. *Clin Infect Dis* 2015; **61**: 996–1003.
38. Molina JM, Capitant C, Spire B *et al.* On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med* 2015; **373**: 2237–2246.
39. Molina JM, Charreau I, Spire B *et al.* Efficacy of on demand PrEP with TDF-FTC in the ANRS IPERGAY open-label extension study. *International AIDS Conference.* July 2016. Durban, South Adrica. Abstract WEAC0102.
40. Glidden DV, Anderson PL, Grant RM. Pharmacology supports on-demand PrEP. *Lancet HIV* 2016; **3**: e405–406.
41. Anderson PL, Garcia-Lerma JG, Heneine W. Nondaily preexposure prophylaxis for HIV prevention. *Curr Opin HIV AIDS* 2016; **11**: 94–101.
42. Bekker LG, Hughes J, Amico R *et al.* HPTN 067/ADAPT Cape Town: a comparison of daily and nondaily PrEP dosing in African women. *Conference on Retroviruses and Opportunistic Infection.* February 2015. Seattle, WA, USA. Abstract 978LB.
43. Buttram ME, Kurtz SP. Preliminary evidence of HIV seroconversion among HIV-negative men who have sex with men taking non-prescribed antiretroviral medication for HIV prevention in Miami, Florida, USA. *Sex Health* 2016.
44. Gilead Sciences. Package insert 2013. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2013/021752s035lbl.pdf (accessed June 2017).
45. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-Infected adults and adolescents. Available at: www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf (accessed June 2017).
46. Grant RM, Anderson PL, McMahan V *et al.* Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* 2014; **14**: 820–829.
47. Patterson KB, Prince HA, Kraft E *et al.* Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. *Sci Transl Med* 2011; **3**: 112re114.
48. Anderson PL. Pharmacology considerations for HIV prevention. *International Workshop on Clinical Pharmacology of HIV.* April 2012. Barcelona, Spain.
49. Anderson PL, Kiser JJ, Gardner EM *et al.* Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection. *J Antimicrob Chemother* 2011; **66**: 240–250.
50. Cottrell ML, Yang KH, Prince HM *et al.* A translational pharmacology approach to predicting outcomes of preexposure prophylaxis against HIV in men and women using tenofovir disoproxil fumarate with or without emtricitabine. *J Infect Dis* 2016; **214**: 55–64.
51. Haberer JE, Bangsberg DR, Baeten JM *et al.* Defining success with HIV pre-exposure prophylaxis: a prevention-effective adherence paradigm. *AIDS* 2015; **29**: 1277–1285.
52. Seifert SM, Glidden DV, Meditz AL *et al.* Dose response for starting and stopping HIV preexposure prophylaxis for men who have sex with men. *Clin Infect Dis* 2015; **60**: 804–810.
53. Masciotra S, McDougal JS, Feldman J *et al.* Evaluation of an alternative HIV diagnostic algorithm using specimens from seroconversion panels and persons with established HIV infections. *J Clin Virol* 2011; **52 Suppl 1**: S17–22.
54. Grossman H, Anderson P, Grant R *et al.* Newly acquired HIV-1 infection with multi-drug resistant (MDR) HIV-1 in a patient on TDF/FTC-based PrEP. *HIV R4P.* October 2016. Chicago, IL, USA. Abstract OA03.06LB.
55. Knox DC, Tan DH, Harrigan PR, PL A. HIV-1 infection with multiclass resistance despite preexposure prophylaxis (PrEP. *Conference on Retroviruses and Opportunistic Infections.* February 2016. Boston, MA, USA. Abstract 169aLB.
56. de Souza MS, Pinyakorn S, Akapirat S *et al.* Initiation of antiretroviral therapy during acute HIV-1 infection leads to a high rate of nonreactive HIV serology. *Clin Infect Dis* 2016; **63**: 555–561.
57. Laeyendecker O, Redd AD, Nason M *et al.* Antibody maturation in women who acquire HIV infection while using antiretroviral preexposure prophylaxis. *J Infect Dis* 2015; **212**: 754–759.
58. ASHM. B positive: all you wanted to know about hepatitis B. A guide for primary care. 2014. Available at: www.hepatitisb.org.au (accessed June 2017).
59. Grant RM, Lama JR, Anderson PL *et al.* Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363**: 2587–2599.
60. Danta M, Brown D, Bhagani S *et al.* Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS* 2007; **21**: 983–991.

61. Rauch A, Rickenbach M, Weber R *et al.* Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: the Swiss HIV Cohort Study. *Clin Infect Dis* 2005; **41**: 395–402.
62. Lal L, Audsley J, Murphy D *et al.* Medication adherence, condom use and sexually transmitted infections in Australian PrEP users: interim results from the Victorian PrEP Demonstration Project. *AIDS* 2017 (doi: 10.1097/QAD.0000000000001519).
63. Zablotska-Manos I. Targeted implementation of PREP in NSW. *Australasian HIV and AIDS Conference*. November 2016. Adelaide, Australia.
64. Benaboud S, Pruvost A, Coffie PA *et al.* Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. *Antimicrob Agents Chemother* 2011; **55**: 1315–1317.
65. Fox J, Brady M, Alexander H *et al.* Tenofovir disoproxil fumarate fails to prevent HIV acquisition or the establishment of a viral reservoir: two case reports. *Infect Dis Ther* 2016; **5**: 65–71.
66. ASHM. Assessment and management of hepatitis B: 6.0 Clinical assessment of patients with hepatitis B virus infection. 2014. Available at: www.hepatitisb.org.au/6-0-clinical-assessment-of-patients-with-hepatitis-b-virus-infection#6-1-initial-assessment-of-patients-with-chronic-hepatitis-b-virus-infection (accessed June 2017).
67. Hongthanakorn C, Chotiyaputta W, Oberhelman K *et al.* Virological breakthrough and resistance in patients with chronic hepatitis B receiving nucleos(t)ide analogues in clinical practice. *Hepatology* 2011; **53**: 1854–1863.
68. Purswani M, Patel K, Kopp JB *et al.* Tenofovir treatment duration predicts proteinuria in a multiethnic United States Cohort of children and adolescents with perinatal HIV-1 infection. *Pediatr Infect Dis J* 2013; **32**: 495–500.
69. Hosek SG, Rudy B, Landovitz R *et al.* An HIV preexposure prophylaxis demonstration project and safety study for young MSM. *J Acquir Immune Defic Syndr* 2017; **74**: 21–29.
70. Havens PL, Stephensen CB, Van Loan MD *et al.* Decline in bone mass with tenofovir disoproxil fumarate/emtricitabine is associated with hormonal changes in the absence of renal impairment when used by HIV-uninfected adolescent boys and young men for HIV preexposure prophylaxis. *Clin Infect Dis* 2017; **64**: 1–9.
71. Abbas UL, Glaubius R, Mubayi A *et al.* Antiretroviral therapy and pre-exposure prophylaxis: combined impact on HIV transmission and drug resistance in South Africa. *J Infect Dis* 2013; **208**: 224–234.
72. Celum C, Hallett TB, Baeten JM. HIV-1 prevention with ART and PrEP: mathematical modeling insights into resistance, effectiveness, and public health impact. *J Infect Dis* 2013; **208**: 189–191.
73. Koenig LJ, Lyles C, Smith DK. Adherence to antiretroviral medications for HIV pre-exposure prophylaxis: lessons learned from trials and treatment studies. *Am J Prev Med* 2013; **44**: S91–98.

Appendix 1

Cockcroft–Gault formula

Basic formula [1]

$eCrCl_{CG}$=[[(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/100 mL

Optional adjustment for low actual body weight [2]

If the actual body weight is less than the IBW use the actual body weight for calculating the eCrCl.

Optional adjustment of high actual body weight [2]

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) [3]

Can be used if actual body weight is greater or less than IBW $eCrClBSAadj=1.73\ m^2 \times eCrCl_{CG}$ (mL/min)÷BSA of the patient (m^2)

BSA (DuBois and DuBois formula [4])=(height (m) 0.725×weight (kg) 0.425)÷139.2

References

1. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.
2. Wargo KA, Eiland EH, 3rd, Hamm W *et al.* Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. *Ann Pharmacother* 2006; **40**: 1248–1253.
3. Rostoker G, Andrivet P, Pham I *et al.* Accuracy and limitations of equations for predicting the glomerular filtration rate during follow-up of patients with non-diabetic nephropathies. *BMC Nephrol* 2009; **10**: 16.
4. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 1989; **5**: 303–311; discussion 312–303.

Appendix 2

This appendix contains the TGA-approved products for HIV tests.

TGA-approved HIV rapid tests typically used for point-of-care testing or in clinicians' offices

Inverness Medical Innovations Australia Pty Ltd T/A Alere

- **ARTG ID:** 276049
- **Product name:** Alere HIV Combo – HIV1/HIV2 antigen/antibody IVD, kit, immunochromatographic test (ICT), rapid
- **Sponsor:** Inverness Medical Innovations Australia Pty Ltd T/A Alere

Immuno Pty Ltd

- **ARTG ID:** 240814
- **Product name:** Uni-Gold HIV – HIV1/HIV2 antibody IVD, kit, immunochromatographic test (ICT), rapid
- **Sponsor:** Immuno Pty Ltd

Integrated Sciences Pty Ltd

- **ARTG ID:** 240813
- **Product name:** OraQuick ADVANCE Rapid HIV-1/2 Antibody Test and Kit Controls – HIV1/HIV2 antibody IVD, kit, immunochromatographic test (ICT), rapid
- **Sponsor:** Integrated Sciences Pty Ltd

Inverness Medical Innovations Australia Pty Ltd T/A Alere

- **ARTG ID:** 232594
- **Product name:** Determine HIV-1/2 – HIV1/HIV2 antibody IVD, kit, immunochromatographic test (ICT), rapid
- **Sponsor:** Inverness Medical Innovations Australia Pty Ltd T/A Alere

TGA-approved diagnostic laboratory-based hiv antibody tests

DiaSorin Australia Pty Ltd

- **ARTG ID:** 279803
- **Product name:** LIAISON XL MUREX HIV Ab/Ag HT – HIV1/HIV2 antigen/antibody IVD, kit, chemiluminescent immunoassay
- **Sponsor:** DiaSorin Australia Pty Ltd

Ortho-Clinical Diagnostics Australia Pty Ltd

- **ARTG ID:** 251957
- **Product name:** VITROS Anti-HIV 1+2 – HIV1/HIV2 antibody IVD, kit, chemiluminescent immunoassay
- **Sponsor:** Ortho-Clinical Diagnostics Australia Pty Ltd

Siemens Healthcare Pty Ltd

- **ARTG ID:** 239117
- **Product name:** ADVIA Centaur HIV 1/O/2 Enhanced (EHIV) – HIV1/HIV2 antibody IVD, kit, chemiluminescent immunoassay
- **Sponsor:** Siemens Healthcare Pty Ltd

Biomerieux Australia Pty Ltd

- **ARTG ID:** 233218
- **Product name:** bioMerieux SA VIDAS HIV DUO Ultra – HIV1/HIV2 antigen/antibody IVD, kit, enzyme immunoassay (EIA)
- **Sponsor:** Biomerieux Australia Pty Ltd

Bio-Rad Laboratories Pty Ltd

- **ARTG ID:** 229064
- **Product name:** Geenius™ HIV 1/2 Confirmatory Assay – HIV1/HIV2 antibody IVD, kit, immunochromatographic test (ICT), rapid
- **Sponsor:** Bio-Rad Laboratories Pty Ltd

Roche Diagnostics Australia Pty Limited

- **ARTG ID:** 226069
- **Product name:** Elecsys HIV Combi PT – HIV1 antigen/antibody IVD, kit, chemiluminescent immunoassay
- **Sponsor:** Roche Diagnostics Australia Pty Limited

Bio-Rad Laboratories Pty Ltd

- **ARTG ID:** 220632
- **Product name:** Genscreen ULTRA HIV Ag-Ab – HIV1/HIV2 antigen/antibody IVD, kit, enzyme immunoassay (EIA)
- **Sponsor:** Bio-Rad Laboratories Pty Ltd

Bio-Rad Laboratories Pty Ltd

- **ARTG ID:** 220068
- **Product name:** Genscreen HIV-1 Ag Confirmatory Assay – HIV1 antigen neutralization IVD, kit, enzyme immunoassay (EIA)
- **Sponsor:** Bio-Rad Laboratories Pty Ltd

Bio-Rad Laboratories Pty Ltd

- **ARTG ID:** 220067
- **Product name:** Genscreen HIV-1 Antigen Assay – HIV1 antigen IVD, kit, enzyme immunoassay (EIA)
- **Sponsor:** Bio-Rad Laboratories Pty Ltd

Bio-Rad Laboratories Pty Ltd

- **ARTG ID:** 220061
- **Product name:** Genscreen™ HIV-1/2 Version 2 – HIV1/HIV2 antibody IVD, kit, enzyme immunoassay (EIA)
- **Sponsor:** Bio-Rad Laboratories Pty Ltd

Abbott Australasia Pty Ltd Diagnostic Division

- **ARTG ID:** 213306
- **Product name:** ARCHITECT HIV Ag/Ab Combo assay – HIV1/HIV2 antigen/antibody IVD, kit, chemiluminescent immunoassay
- **Sponsor:** Abbott Australasia Pty Ltd Diagnostic Division

Abbott Australasia Pty Ltd Diagnostic Division

- **ARTG ID:** 212528
- **Product name:** PRISM HIV Ag/Ab combo assay – HIV1/HIV2 antigen/antibody IVD, kit, chemiluminescent immunoassay
- **Sponsor:** Abbott Australasia Pty Ltd Diagnostic Division

MP Biomedicals Australasia Pty Ltd

- **ARTG ID:** 212462
- **Product name:** MP Diagnostics HIV Blot 2.2 assay – HIV1/HIV2 antibody IVD, kit, immunoblot
- **Sponsor:** MP Biomedicals Australasia Pty Ltd

DiaSorin Australia Pty Ltd

- **ARTG ID:** 212434
- **Product name:** LIAISON XL MUREX HIV Ab / Ag – HIV1/HIV2 antigen/antibody IVD, kit, chemiluminescent immunoassay
- **Sponsor:** DiaSorin Australia Pty Ltd

Siemens Healthcare Pty Ltd

- **ARTG ID:** 205090
- **Product name:** ADVIA Centaur HIV Ag/Ab Combo (CHIV) – HIV1/HIV2 antigen/antibody IVD, kit, chemiluminescent immunoassay
- **Sponsor:** Siemens Healthcare Pty Ltd

Bio-Rad Laboratories Pty Ltd

- **ARTG ID:** 207994
- **Product name:** Access HIV Combo – HIV1/HIV2 antigen/antibody IVD, kit, chemiluminescent immunoassay
- **Sponsor:** Bio-Rad Laboratories Pty Ltd

TGA-approved diagnostic laboratory-based HIV NAT tests

Gen-Probe Australia Pty Ltd

- **ARTG ID:** 269680
- **Product name:** Aptima HIV-1 Quant DX Assay Kit, PRD-03000 – HIV1 nucleic acid IVD, kit, nucleic acid technique (NAT)
- **Sponsor:** Gen-Probe Australia Pty Ltd