5. Clinical assessment before starting PrEP

All patients whose sexual or drug injection history indicates the recommendation or consideration of pre-exposure prophylaxis (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, those with acute or chronic human immunodeficiency virus (HIV) infection should be identified through taking a medical history and HIV testing. A negative HIV test result must be documented at the time the patient is evaluated for PrEP as the daily, or on-demand tenofovir disoproxil* and emtricitabine (TD*/FTC) combination alone is insufficient for treatment of acute or chronic HIV infection.

HIV testing must be repeated every 3 months when patients attend for a prescription refill. This requirement for quarterly visits should be explained to patients during the initial discussion about whether PrEP is appropriate for them.

A fourth-generation HIV antibody/antigen venous blood test should be used and should be 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. Failure to detect very early HIV infection by rapid testing in the PrEP context has been reported (1). This includes the Atomo HIV Self-Test, a rapid home-based HIV testing kit which was approved for online purchase in Australia by the TGA in November 2018. However, a rapid PoCT can be used for the same day initiation of PrEP providing that a venous blood test for a fourth generation HIV antibody/ antigen test is obtained and tested simultaneously. 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. Clinicians should not accept patient-reported HIV test results, including home-based HIV 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 non-occupational post-exposure prophylaxis (nPEP) may be required before transitioning to PrEP, in accordance with the PEP and nPEP guidelines (2) if a patient has had a recent high-risk exposure (within 72 hours). See the PEP guidelines for more information.

Patients who have had a recent high-risk exposure outside the 72 hour 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. HIV viral load and HIV proviral DNA tests are not recommended to screen for early HIV infection. These tests are not reimbursed by Medicare and may take 10-14 days for results to be available.

Acute HIV infection should be suspected in individuals at high risk of HIV who may have had recent exposure 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 injecting drug use with shared injection equipment with MSM, or person known to be HIV positive).

In a prospective study of 2,226 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 and signs occurred in 94% of participants with acute HIV infection, just before and around the time of peak HIV viraemia (3). 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 (Table 5.1).

	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	53.5	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

Table 5.1 Symptoms and abnormalities associated with primary or acute HIV infection, overall and by region (3).

[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

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 (4-7).

People 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 (8). Such patients can only be started on PrEP if and when HIV infection is excluded.

Concerns about TD* or FTC resistance

Overall, the risk of developing TD* or FTC resistance among participants on PrEP is low (9). 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 into clinical trials (9). Similar findings were reported in a more recent review of clinical trials and case reports of HIV resistance occurring in the PrEP setting (10). Mathematical modelling shows that the number of HIV-1 infections that would be averted by PrEP greatly exceeds the number of drug-resistant infections that could occur (11).

Assessment of renal function at baseline

In HIV-positive patients, the use of tenofovir was reviewed in a meta-analysis and was associated with a statistically significant loss of renal function, with the effect being judged as clinically modest (12). Tenofovir use was not associated with increased risk of fractures, hypophosphataemia or severe proteinuria (12). Rarely, proximal renal tubular dysfunction (including Fanconi syndrome) may occur with TD* use (12-14).

Overall, tenofovir use in PrEP studies has not been associated with significant clinical renal problems (15-17). The Iniciativa Profilaxis Pre-Exposición (iPrEX) study showed a small but statistically significant mean decline in creatinine clearance (CrCL) from baseline but the decline in CrCL was reversible upon PrEP cessation (15). Factors associated with a decline in estimated Glomerular Filtration Rate (eGFR) include commencement of PrEP at age 40 years or over, a baseline eGFR below 90 mL/min/1.73m^2, and good adherence (17). **There are no data for people using PrEP who have an eGFR below 60 mL/min/1.73m^2 therefore starting PrEP in individuals whose eGFR is well established to be below 60 mL/min/1.73m^2 is not recommended**. However, see comments below on managing individuals who are found to newly have an eGFR around 60 mL/min/1.73m^2 at baseline testing.

Data from the iPrEx open-label extension (iPrEX-OLE) study found a significant increase in both urine alpha-1 microglobulin, a urine marker of impaired tubular reabsorption, and proteinuria after 6 months of TDF/FTC exposure suggesting that subclinical tubular injury occurs on PrEP (18).

There are limited data regarding whether on-demand versus daily PrEP reduces the likelihood of renal toxicity. However, in the Intervention Préventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY) study, no significant decline was observed in the mean slope of eGFR in the tenofovir and emtricitabine versus placebo arms over a median of 9.3 months follow-up (19), suggesting that on-demand PrEP may not influence renal function. In the ADAPT study, a creatinine elevation was observed in 9% of 178 participants evaluated, but creatinine elevation did not differ between participants in the daily, time-driven and on-demand PrEP study arms (P = 0.05) (20).

Recent data from the DISCOVER study where MSM and transgender women at risk of HIV were randomised to TDF/FTC versus tenofovir alafenamide (TAF)/FTC reported a significant difference in change in eGFR and tubular proteins during the study favouring TAF/FTC (21). More broadly the DISCOVER study found that

TAF/FTC was non-inferior to TDF/FTC in terms of preventing HIV infection (21), however TAF/FTC has not been licensed yet in Australia for use as PrEP.

For all patients considered for PrEP, their risk factors for chronic kidney disease (CKD) should be assessed at baseline. These risk factors include diabetes, hypertension, smoking, concurrent medications and a known history of renal impairment or history of kidney injury or structural abnormality and Aboriginal and Torres Strait Islander status. Measurements of baseline serum creatinine, eGFR, the urine protein: creatinine ratio (PCR) and blood pressure should also be taken. The Cockcroft–Gault formula for estimating creatinine clearance (CrCl) (see Appendix 2) 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 as reported by the laboratories.

For individuals who are found to newly have an eGFR around 60 mL/min/1.73m^2 at baseline, the eGFR should be repeated within 7 days because clinical situations occur when the eGFR may be unreliable, e.g. recent consumption of cooked meat. In this setting the clinician should ask the individual to fast or avoid a cooked meat meal within 4 hours of repeat eGFR testing. Exceptional dietary intake e.g. vegetarian diet, high protein diet, creatine supplements, and extremes of body size (e.g. high muscle mass) may underestimate eGFR. Being underweight or having low muscle mass may overestimate eGFR.

If after repeat testing an individual's eGFR remains just below or just above 60 mL/min/1.73m^2, it is recommended that the clinician speak to a specialist in PrEP as these patients may still be able to commence PrEP with close monitoring. Of note, this setting on-demand PrEP may be a suitable option if the patient is a cis-gender MSM.

These guidelines recommend that creatinine, eGFR and urinary PCR measurements for each person are evaluated at baseline. The eGFR should be repeated 3 months after commencing PrEP then 6 monthly thereafter. However, based on currently available evidence, more intensive monitoring may be warranted in the following individuals:

- those over the age of 40 years
- those with a baseline eGFR of less than 90 mL/min/1.73 m^2
- those with other comorbidities (e.g. hypertension, diabetes)
- those taking nephrotoxic drugs.

A minority of individuals may experience a decline in eGFR; the Australian CKD Management in General Practice recommends further investigations and consideration of a referral to a specialist renal service when there is sustained decrease in eGFR of 25% or more or a sustained decrease in eGFR of 15 mL/min/1.73 m^2 (22).

Assessment and management of sexually transmissible infections at baseline

Individuals at 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 (23). Importantly the presence of an STI at baseline should not delay the commencement of PrEP. Of note, in the PrEPX study it was reported that 10.2% of 1,774 evaluable study participants tested positive for STIs

at baseline (24).

Patients starting on PrEP should be informed about:
- prevention of STI acquisition and transmission
- frequency of STI testing
- signs and symptoms of STIs.

Patients should be encouraged to present for testing and treatment whenever signs or symptoms of STIs appear.

Assessment of hepatitis A, B and C status

Patients being suitable for PrEP can also be at risk of acquiring hepatitis A, hepatitis B virus (HBV) infection (25) and hepatitis C virus (HCV) [infection (26). Hepatitis A, HBV and HCV infection status should be documented by screening serology when PrEP is initiated.

Vaccination against hepatitis A and 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 people who inject drugs (27, 28). 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 with chronic hepatitis B infection should only be offered daily PrEP and not on-demand PrEP. They should also 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 obstacle to HIV PrEP initiation.

Assessment of bone health

Low bone mineral density (BMD) was observed at baseline in approximately 10% of individuals receiving TD*/FTC for PrEP in the IPREX study (29). Individuals should be counselled about the effects of TD* on BMD and counselled to decrease alcohol and cigarette use, to undertake weight-bearing exercise and ensure their diet provides adequate amounts of calcium and vitamin D (30). 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 statistically significant decline in BMD was observed by week 24 in participants of the iPrEX study. The decline in BMD correlated directly with levels of intracellular TD*-DP and was found to be reversible once PrEP was ceased (31).

There are no data available on whether on-demand PrEP is less likely to cause a decline in BMD.

Recent data from the DISCOVER study, found that TAF/FTC versus TDF/FTC was associated with less decline in BMD (21).

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; information about BMD rebates can be found at: www.health.gov.au/internet/main/publishing.nsf/content/diagnosticimaging-bd.htm. In those people over the age of 40 years thought to be at risk of having reduced BMD, a FRAX® tool to evaluate fracture risk can be used to assess the need for dual-energy X-ray absorptiometry (DXA) scanning. For further information see https://www.sheffield.ac.uk/FRAX/tool.aspx?country=31.

Assessment for pregnancy in women of childbearing age

The risk of HIV transmission to women increases by over two-fold when they are pregnant (32). As reviewed recently, current evidence suggests that PrEP can be used safely during pregnancy and breastfeeding (33).

The use of TD*-containing regimens by HIV positive women throughout pregnancy has not been associated with adverse pregnancy outcomes, but lowered BMD has been observed in newborns exposed to TD* in utero (34, 35) as has a lower length and head circumference at 1 year of age (35).

In the Partners PrEP study, which compared the efficacy of TDF/FTC versus TDF versus placebo to reduce HIV transmission in African heterosexual HIV-serodifferent couples, 431 pregnancies occurred; the average duration of in utero PrEP exposure was 5 weeks. There was no difference in the incidence of pregnancy, birth outcomes or infant growth in women who received TDF or TDF/FTC versus placebo PrEP (36). However, as noted by the authors, the confidence intervals for these findings were wide and therefore definitive statements about the safety of TDF/FTC as PrEP during pregnancy could not be made based on this study's findings. A subsequent study from this group examined the pregnancy outcomes of 30 women who continued to use PrEP during pregnancy compared to 96 pregnancies without PrEP exposure. The authors found that there was no increase in adverse pregnancy outcomes or restrictions in infant growth between the two groups (37). The World Health Organization has included PrEP as an HIV prevention strategy during pregnancy (38) and a number of other jurisdictions recommend PrEP for safe conception and for use during pregnancy and breastfeeding (39).

Some women with an HIV-positive partner may prefer to continue PrEP while pregnant, due to an increased risk of acquisition of HIV if their partner is not reliably virologically supressed during pregnancy (39). The lead in time for PrEP to reach highly effective levels in women is 7 days (40). A study evaluating antiretroviral excretion in breast milk and infant absorption suggests PrEP can be safely used during breastfeeding with minimal infant drug exposure (41).

The ASHM PrEP Guidelines Panel will continue to monitor the safety of TD*/FTC PrEP regimens when used during pregnancy and breastfeeding.

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