7. Clinical follow-up and monitoring of patients on PrEP

Recommended schedule of testing and follow-up for people on PrEP

Once pre-exposure prophylaxis (PrEP) is initiated, patients should return for follow-up every 3 months. Clinicians may wish to see patients more frequently in the period after PrEP initiation (e.g. 1 month after initiation) to:

- assess and re-confirm human immunodeficiency virus (HIV)-negative test status in patients with a recent pre-PrEP HIV exposure
- assess side effects
- monitor renal function in patients at particular renal risk
- assess adherence
- answer questions.

Some jurisdictions recommend a visit at month one. The Table 7.1 and Box 7.1 set out the recommended schedule of testing and follow-up for people who are prescribed PrEP.

Table 7.1
Laboratory evaluation and clinical follow-up of individuals who are prescribed PrEP

Test	Baseline (Week 0)	About day 30 after initiating PrEP (optional but recommended in some jurisdictions)	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 Vaccinate if non-immune	Y	N	N	N	Y If patient required hepatitis B vaccine at baseline, confirm immune response to vaccination 1 month after last vaccine dose
Hepatitis C serology	Y	N	N	N	12 monthly but, more frequently if ongoing risk e.g. non-sterile injection drug use and MSM with sexual practices that pre-dispose to anal trauma
STI (i.e. syphilis, gonorrhoea, chlamydia) as per Australian STI Management Guidelines *	Y	N	Y	Y	N
eGFR at 3 months and then every 6 months	Y	N	Y	N	At least every 6 months or according to risk of CKD
Urine protein creatinine ratio (PCR) baseline	Y	N	Y	N	Every 6 months
Pregnancy test (for women of child-bearing age , not on effective contraception)	Y	Y	Y	Y	N

CKD: chronic kidney disease; eGFR: estimated glomerular. filtration rate;
PrEP: pre-exposure prophylaxis; PWID: people who inject drugs
STI: sexually transmissible infection

* http://www.sti.guidelines.org.au/

Box 7.1 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. Rapid point-of-care tests (POCTs) are not recommended for monitoring patients receiving PrEP
- Test for sexually transmissible infections (STIs). This involves PCR tests for chlamydia (first-pass urine, pharyngeal swab and anal swab) and *Neisseria gonorrhoea*, (pharyngeal swab and anal swab) and a blood test for syphilis serology (1)
- Assess side-effects, PrEP adherence and ongoing PrEP suitability
- Provide an authority streamlined (PBS) prescription or a private prescription of daily TD*/FTC for 90 days (see Providing PrEP for exceptions to this script duration)
- Respond to questions and provide any new information about PrEP use
- Provide support for medication adherence and risk-reduction behaviours.

In addition:

- Repeat pregnancy testing for women of child bearing age
- Test for hepatitis C virus (HCV) in people who inject drugs (PWID) who report continued sharing of injecting equipment and men who have sex with men (MSM) with elevated risk of HCV acquisition (e.g. sexual practices that pre-dispose to anal trauma).

At least every 6 months:

- Monitor estimated glomerular. filtration rate (eGFR), creatinine and urine protein/creatinine ratio
- If the patient has risk factors for renal impairment (e.g. hypertension, diabetes), renal function may require more frequent monitoring and/or may need to include additional tests (e.g. urine protein/creatinine ratio)
- A rise in serum creatinine is not always a reason to withhold treatment if the eGFR remains at or above 60 mL/min/1.73 m^2 but an acute rise in the serum creatinine in a patient on PrEP would need full clinical evaluation and sometimes a review by a renal specialist
- If eGFR is declining steadily (but still at or above 60 mL/min/1.73 m^2), consultation with a renal specialist or other evaluations of possible causes for declining renal function may be indicated.

At least every 12 months:

- Test for hepatitis C
- Test for hepatitis B serology if the patient has not been vaccinated.

Patients who access PrEP through the Personal Importation Scheme of the Therapeutic Goods Administration (TGA) should allow a lead time of 2–6 weeks for the drug to arrive in Australia and pass customs clearance.

Testing for HIV

HIV testing should be repeated every 3 months using a fourth generation HIV antibody and antigen test via a venous blood draw. Rapid point-of-care tests, including the recently approved home testing HIV diagnostic kit, the Atomo HIV Self Test, should not be used for monitoring patients receiving PrEP.

A patient's ongoing HIV risk and adherence to PrEP should be established when requesting the patient presents for their quarterly clinical visit including the HIV test and PrEP script (see Improving medication adherence). Patients should be familiar from their baseline visit with the requirement for quarterly clinical visits to obtain ongoing PrEP prescriptions. Clinicians should consider writing on ongoing PrEP prescriptions a date past which dispensing the script should not occur without the pharmacist talking to both the patient and the prescribing doctor about the reasons for the delay in filling the script. This approach may help ensure that patients who have had intermittent PrEP adherence and who have unknowingly acquired HIV infection do not receive 3 months of suboptimal antiretroviral treatment.

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 (2).

A positive HIV test result

Any positive HIV test result should be managed urgently by appropriate counselling and referral to an HIV prescriber. Assistance can be sought via telephone from a local sexual health clinic. It is very important for the clinician to recognise that HIV acquisition in a person who is using PrEP is a highly significant event and that the emphasis should be on supporting the person initially rather than focusing on how the infection occurred. If a patient is diagnosed with HIV infection while taking PrEP, their current health and wellbeing should be the chief immediate priority as opposed to enquiries about their adherence to PrEP.

Acute HIV infection should be suspected in people at risk for HIV who were not taking PrEP at the time that they were recently exposed to HIV (e.g. no condom, or a condom broke during sex with an HIV-positive partner who was not on antiretroviral treatment, or has a detectable HIV viral load; condomless anal sex with a casual partner; recent injecting drug use with shared injection equipment with an HIV-positive partner). Also, infection with tenofovir disoproxil* (TD*)- and/or emtricitabine (FTC)-resistant HIV is possible, however, it is very uncommon while on PrEP, with only a few cases reported internationally (3). Therefore, in addition to sexual behaviour and injecting drug use, clinicians should elicit a history of any signs and symptoms of viral infection during the preceding month, including the day of PrEP evaluation. See the Table for clinical symptoms and abnormalities of acute (primary) HIV infection.

In this setting HIV drug resistance testing should be performed in all cases and if the patient reports high PrEP adherence they may agree to have their blood, and hair tested for tenofovir and emtricitabine drug levels. In this setting urgent referral to an HIV specialist is recommended. If urgent review by an HIV specialist is not possible, then the diagnosing clinician may wish to phone ASHM who will be able to help coordinate the patient and a clinical advisor.

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 to HIV just before starting PrEP, or who acquire HIV infection while taking PrEP (e.g. due to poor adherence or transmitted drug resistant virus) (4-6). There is not a broad international agreement on how to manage these patients. Patients who have an indeterminate HIV test result while on PrEP (particularly, those with repeated indeterminate test results) should be closely monitored in conjunction with an HIV specialist and in consultation with a diagnostic laboratory scientist who should be informed that the patient is taking PrEP. The ASHM PrEP Guidelines Panel will continue to monitor this issue with a view to providing further guidance.

A recent high-risk exposure (within 72 hours)

A course of non-occupational post exposure prophylaxis (nPEP) may be required if a patient is on daily PrEP, or on-demand PrEP and had a recent high-risk exposure (within 72 hours) but only if they did not take PrEP during those days. This nPEP may need to consist of a three-drug regimen, depending on the nature of the exposure. See section on nPEP and PrEP for management of such cases.

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 people with high and ongoing risk of HIV infection, but whose eGFR has declined below or around 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 on-demand 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 STIs

As PrEP users are at increased risk for STIs (7) 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 (1). Partner notification should be undertaken using the most appropriate available resources.

It is important to note, that for MSM and other groups where relevant, STI tests must include a throat swab and anal swab for chlamydia and gonorrhoea and vaginal swab should also be taken.

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 an STI appear.

Clinicians should ensure that the pathology service provider that they use has these swabs available.

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

Monitoring HBV Hepatitis B and HCV Hepatitis C virus infections

Hepatitis B virus monitoring

For people who are hepatitis B virus (HBV) non-immune at baseline, clinicians should provide hepatitis B vaccination and confirm their immune response 1 month after the last vaccine dose.

For people who state that they have been vaccinated for hepatitis B at baseline, clinicians should test for hepatitis B surface antibody; if their hepatitis B surface antibody is below 10 IU/mL, they should be vaccinated with one dose of hepatitis B vaccine and their hepatitis B surface antibody titre should be checked 1 month later. If their titre does not rise above 10 IU/mL their hepatitis B vaccination should then be completed.

Both TD* and FTC are active against HBV (8). If people living with chronic HBV infection stop taking these medications, hepatic flares can occur, which can be severe (8). Patients with chronic HBV need to be counselled regarding the risks of poor adherence and the risks of self-ceasing PrEP medication. Patients

who are known to have chronic HBV and are already taking treatment for this condition should consult their liver specialist before commencing PrEP. 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.

Only daily PrEP should be offered to people with chronic HBV. For additional guidance about the management of PrEP in people with chronic hepatitis B, see Special clinical considerations.

Hepatitis C virus monitoring

All people who inject drugs including MSM, trans and gender diverse and heterosexual people should be monitored for Hepatitis C virus (HCV), as should MSM and trans and gender diverse people who engage in sexual contact that may pre-dispose to anal trauma. The incidence of HCV has currently been low at approximately 1% per annum in PrEP studies of MSM (9, 10), and higher in HIV-positive MSM (11, 12). However, there is concern that HCV incidence may increase following changes in sexual and sero-sorting behaviour in the era of PrEP. In this context, HCV can be sexually acquired and is considered as an STI. It should be tested at least annually, and more frequently if necessary, following sexual history taking and review of injecting practices (13).

Managing side-effects

Patients taking PrEP should be assessed for side-effects associated with TD*/FTC use, most importantly those suggesting possible acute renal injury. A review of symptoms experienced in the iPrEx (Iniciativa Profilaxis Pre-Exposición) study showed that potential PrEP-associated symptoms peaked at 1 month, when 39% of participants reported symptoms, compared with 22% at baseline. Gastrointestinal (GI) symptoms occurred in a median of 28% of participants across study sites (range 11–70%) and non-GI symptoms occurred in a median of 24% of participants (range 3–59%). The odds of GI symptoms were higher in those with evidence of high adherence to PrEP. By 3 months, symptoms had returned to pre-PrEP levels (14).

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 take into consideration the history of steroid, protein, creatine powder use (which also increases blood creatinine levels) and bodybuilding. A wash-out period of 14 days cessation of creatine before renal function assessment may be recommended.

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

Optional assessments

Therapeutic drug monitoring

Initial demonstration projects in Australia conducted therapeutic drug monitoring as part of research protocols to evaluate medication adherence and HIV seroconversions among study participants. Their results revealed a high correlation between self-reports of tablet taking and blood concentrations of TD* and FTC, and high adherence to PrEP (over 90%) (15, 16). However, in Australia there are no clinical laboratories that quantify TD*/FTC concentrations in plasma, cells or urine for therapeutic drug monitoring (TDM) in the setting of PrEP (17) and it is likely that therapeutic drug monitoring is likely to be used primarily for research including evaluations of people who acquire HIV infection while taking PrEP.

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