May 2017 Dr Michelle Moorhouse

Summary: HIV pre-exposure prophylaxis (PrEP)

Pre-exposure prophylaxis involves taking a pharmaceutical agent prior to an exposure to prevent an outcome, such as antimalarials prior to travelling to a malaria-endemic area. Similarly, PrEP for HIV involves the use of antiretroviral (ARV) medications to prevent HIV infection. This is different to post exposure prophylaxis, where ARVs are taken as soon as possible after (potential) exposure to HIV to prevent infection. Several large studies have demonstrated the efficacy of tenofovir disoproxil fumarate (TDF) alone or in combination with emtricitabine (FTC) in preventing HIV infection in different populations. Currently only oral tenofovir-based PrEP has been approved for use to prevent HIV infection. In the absence of a vaccine to prevent HIV acquisition, oral PrEP is a very effective means to protect individuals at risk of HIV infection. There are ongoing studies looking at different formulations and modalities of PrEP, such as vaginal rings, gels and injectable agents, as well as multipurpose prevention technologies combining PrEP with other interventions such as contraception in a single formulation.

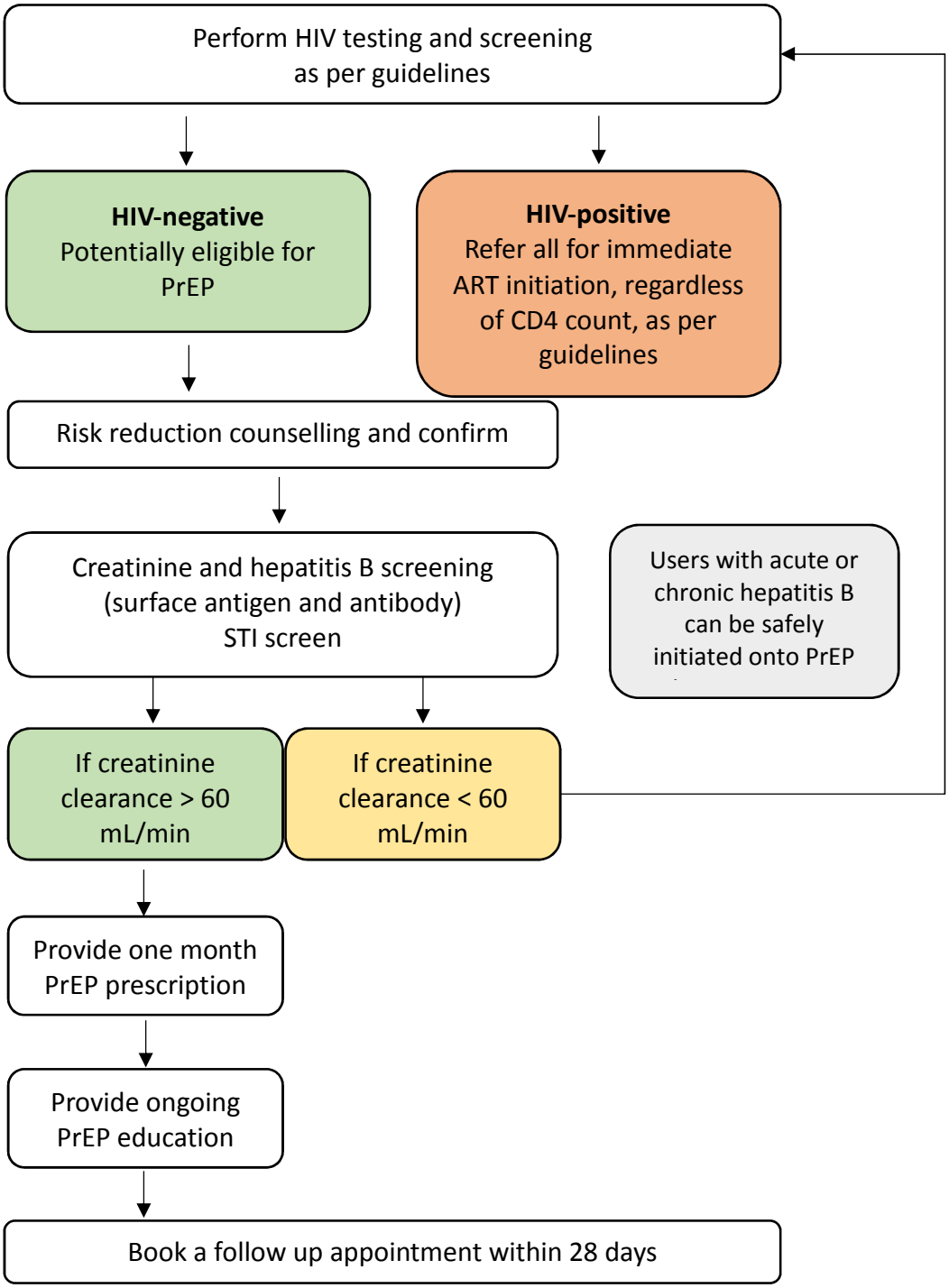
PrEP is recommended for HIV-negative people who are at substantial risk of HIV infection. This may include HIV-negative heterosexual men and women (including adolescents), men who have sex with men (MSM), transgender persons, sex workers and people who inject drugs (PWID). PrEP should be used as part of a package of HIV prevention services (which should include regular HIV testing, condoms, lubrication, contraception, sexually transmitted infection [STI] management and risk reduction counselling). Unlike antiretroviral therapy for people living with HIV, daily oral PrEP may be used intermittently during periods of perceived HIV acquisition risk, rather than continually and lifelong. For this reason, ongoing risk assessment is an essential component of PrEP provision, and not only part of screening for PrEP eligibility.
In some countries, the use of TDF/FTC as PrEP in pregnant or breastfeeding women is contra-indicated. HIV-negative women in serodiscordant relationships are at risk of acquiring HIV infection whilst trying to conceive through unprotected sex. Pregnancy itself is also associated with an increased risk of becoming infected with HIV. Unfortunately, data relating to the safety of PrEP specifically with regard to the developing foetus are limited, and consequently the onus is on the clinician to discuss potential risks and benefits of PrEP initiation or maintenance during pregnancy, allowing these women at high risk of HIV acquisition to make an informed decision regarding PrEP use.

Eligibility criteria	Contra-indications to PrEP
1. Anyone identified as being at high risk for HIV exposure	1. HIV-1 infected or evidence of possible acute infection
2. No contraindications to FTC/TDF FDC	2. Suspicion of window period following potential exposure
3. HIV-negative / not thought to be in the window period	3. Adolescents <35 kg or <15 years who are not ≥Tanner stage 3
4. Absence of symptoms of acute HIV infection	4. Poor renal function (creatinine clearance <60 mL/min)
5. Willing and able to attend 3-monthly visits	5. Other nephrotoxic drugs (eg aminoglycosides, NSAIDS)
6. Understands that PrEP only protects against HIV	6. Unwilling or unable to return for 3-monthly visits
7. Recurrent use of PEP	7. pregnant or breastfeeding women

When prescribing PrEP, and at every visit, it is critical to confirm the HIV-negative status of the PrEP user. This is very important, as if PrEP is prescribed during the window period, during active viral replication, providing PrEP which would be suboptimal ART, could result in the development of resistance. For this reason, it is important to understand which HIV test is being used. Ideally, a fourth-generation laboratory ELISA should be used, which detects both antibodies and antigen and has a shorter window period than third-generation or earlier tests. In addition, a careful history of potential recent exposure to HIV should be elicited, and careful screening for symptoms and signs which could indicate acute HIV infection are important components of determining HIV status. PrEP users should be educated about the clinical features of acute HIV infection, and advised to return to the clinic promptly should they experience any of these symptoms.

Other laboratory investigations which are required prior to initiating include creatinine (to calculate creatinine clearance); hepatitis B screen (at least HBsAg, but preferably HBsAb too and where possible, if both are negative, HBV vaccine should be given); STI screen (symptom screen, examination, urine dipstix, rapid syphilis or where

possible full STI panel); and pregnancy test. Providing the creatinine clearance (CrCl) or eGFR is greater than 60 mL/min, and there are no other contra-indications, PrEP can be prescribed. It is important to note, that the presence of HBV infection or any STIs are not contra-indications or reasons to delay PrEP initiation. HBV-infected individuals may require LFT monitoring of their HBV, and should not interrupt PrEP once started without consulting their healthcare provider, as there is a risk of acute hepatitis flare (both TDF and FTC treat HBV). Any STIs should be managed according to local guidelines. Below is an algorithm for PrEP screening and initiation.



The schedule of events for PrEP visits, including laboratory monitoring, is in the table below. It is imperative to emphasis at every visit that PrEP is part of a combination prevention package which should include condoms, lubricant provision, VMMC, STI screening and other interventions shown to be effective in preventing HIV infection.

Visit	Recommended procedures
Screening	Educate about the risks and benefits of PrEP
	Assess risk and eligibility
	Conduct HIV counselling and testing, serum creatinine level, hepatitis B and STI screen, pregnancy test
	Contraceptive counselling and offer services
	Arrange follow-up visit
PrEP initiation	Conduct HIV counselling and testing
	Confirm eligibility (including investigation results and creatinine clearance calculation)
	Commence hepatitis B vaccination if indicated
	Provide STI treatment if indicated
	Pregnancy test
	Educate client about PrEP side-effects and management
	Educate client about signs and symptoms of acute HIV infection
	Discuss behaviours that promote bone health, such as weight-bearing exercise and avoiding alcohol, tobacco and recreational drugs
	Initiate a medication effective use plan
	Provide condoms and lubricant
	Contraceptive counselling and offer services as appropriate
	Provide one-month TDF/FTC (FDC) prescription and follow-up date
One-month follow-up	PrEP initiation visit, PLUS:
	• Assess tolerability, side-effects and effective use
	• Actively manage side-effects
	• Measure serum creatinine and calculate creatinine clearance
	• Contraceptive services
	• Provide three-month TDF/FTC (FDC) prescription and follow-up date
Four-month follow-up and 3-monthly maintenance visits	Repeat procedures done at one-month follow-up
	Measure serum creatinine and calculate creatinine clearance at four-month follow-up, and 12-monthly thereafter
	Conduct 6-monthly STI screen, including urine dipstix and rapid syphilis test
	Complete hepatitis B immunisation at 6 months

FDC, fixed-dose combination; FTC, emtricitabine; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TDF, Tenofovir.

In case of abnormalities in CrCl, both at screening or whilst on PrEP, PrEP should be withheld. It is important to identify potential causes, such as acute events, hypertension, diabetes, medications etc. Ensure any acute issues such as dehydration are identified and addressed, and repeat CrCl in two weeks. If the CrCl is > 60 mL/min, PrEP can then be (re-)initiated.

Up to 10% of PrEP users may experience some side-effects on PrEP. These are usually mild, non-specific and self-limiting, and can often be managed by reassurance or active management such as anti-emetics for nausea. Some PrEP users may experience a decline in renal function or bone mineral density as a result of the TDF component of PrEP. PrEP studies to date have shown that these declines are usually mild, but more importantly, that they are reversible when TDF is stopped.

PrEP users need to be made aware that the protection offered by PrEP is only against HIV, and that PrEP will not protect against other STIs or pregnancy. They also need to be informed that protection is not immediate, and that 7 days of daily PrEP dosing are required to protect against HIV acquisition via anal sex, and 20 days for vaginal sex. Prior to this, they may not be fully protected and condom use is essential. When stopping PrEP, 28 days of daily dosing following the last exposure are needed to ensure adequate cover (similar principle to PEP). With PrEP, daily dosing is required; however, PrEP is not expected to be lifelong and so users may cycle on and off PrEP according to their risk. It is important that they understand that if they have stopped PrEP, they must not initiate without first having an HIV test to ensure that they have remained HIV-negative.

There are many aspects to prescribing PrEP, and the SA HIV Clinicians Society guidelines includes many useful tools to support effective PrEP use and prescribing. This includes guidance on supporting effective use of PrEP (effective use is preferred to the term adherence, as PrEP is a preventive intervention, like condoms and not a treatment).