6. Providing PrEP

Goals of PrEP

The ultimate goal of HIV pre-exposure prophylaxis (PrEP) is to reduce the acquisition of HIV infection and its resultant morbidity, mortality and associated 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 people who are suitable for PrEP to reduce their risk of HIV acquisition. Only co-formulated tenofovir and emtricitabine (TD*/FTC) is licensed in Australia for use as PrEP and is the only regimen that should be used.
- educate patients about the medications and the dosing regimen (daily for all patients, or on-demand for cis-gender men who have sex with men (MSM)) to optimise safe medication use.
- provide counselling on sexually transmissible infections (STIs) and their prevention.
- provide medication-adherence support and counselling to help patients achieve and maintain protective levels of medication.
- provide HIV risk-reduction support and offer harm reduction including referrals to help patients minimise their risk of acquiring HIV, viral hepatitis B and C and STIs.
- provide effective contraception to women who are taking PrEP and who do not wish to become pregnant.
- monitor patients on a quarterly basis to screen for HIV infection, STIs and toxicity and to determine whether PrEP remains indicated.

PrEP licensing in Australia

Co-formulated TD*/FTC is registered by the Therapeutic Goods Administration (TGA) for daily use and is subsidised by the Pharmaceutical Benefits Scheme (PBS) in Australia.

Daily PrEP

Daily PrEP is the most commonly prescribed PrEP regimen in Australia. Daily use of TD*/FTC is highly efficacious at preventing HIV transmission in MSM (1, 2), heterosexuals (3), transgender women (4) and people who inject drugs (PWID) (5) in the setting of high medication adherence. A detailed review of these and other studies that have demonstrated the efficacy and effectiveness of daily PrEP is beyond the scope of these guidelines. For more information see PrEP efficacy.

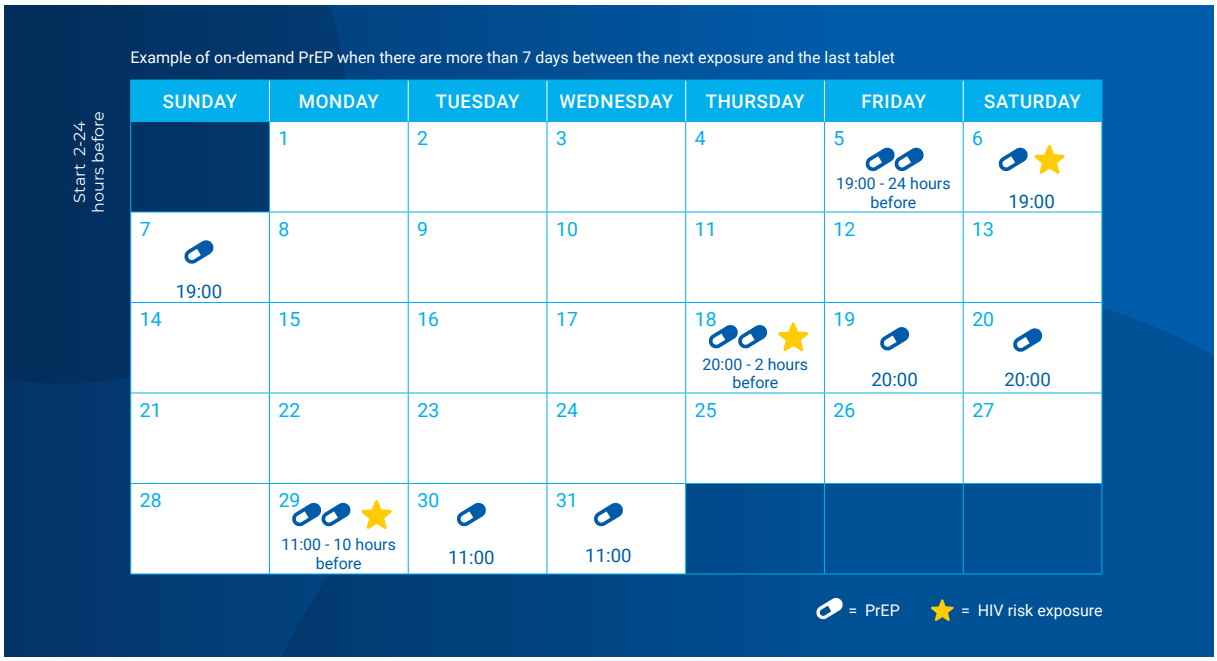
The ASHM PrEP Guidelines Panel continues to recommend that daily TD*/FTC should be offered to all populations at risk of HIV infection.

Figure 6.1 Daily PrEP

On-demand PrEP

On-demand PrEP involves taking two tablets of TD*/FTC 2–24 hours before a potential sexual exposure to HIV, followed by a third tablet 24 hours after the first dose and a fourth tablet 48 hours after the first dose. If sex continues beyond one day, a user of on-demand PrEP can stay protected by continuing to take a pill every 24 hours for each day that sex occurs. A PrEP pill should be taken each day for the two days following the last day that sex occurred.

Figure 6.2 On-demand PrEP



The World Health Organization (WHO) recently released a technical brief recommending the use of on-demand PrEP for cis-gender men who have sex with men (MSM) (6). **The 2019 ASHM PrEP Guidelines Panel endorses WHO's recommendation that on-demand PrEP should be offered to cis-gender MSM**. On-demand PrEP is recommended only for cis-gender MSM because its efficacy is yet to be determined in all other populations at risk of HIV infection. The ASHM PrEP guidelines panel recommends that caution be used in recommending on-demand versus daily PrEP to adolescent MSM because there have been no trials of on-demand PrEP in adolescent MSM and because adherence rates to daily PrEP have been consistently low in studies of adolescent MSM (7, 8). **Of note, on-demand PrEP is contraindicated in people with chronic hepatitis B infection.**

Evidence in support of on-demand PrEP dosing

Data on the efficacy of non-daily PrEP dosing are available for cis-gender MSM. Very few transgender women have been evaluated in randomised controlled trials of on-demand PrEP (9-11); nor have such trials been undertaken in cis-gender women or cis-or transgender men, or in people whose principal HIV exposure risk is injecting drug use. Pharmacological studies in cis-gender women suggest that on-demand PrEP does not provide adequate tissue levels of PrEP to provide high levels of HIV protection and on-demand PrEP should not be recommended for cis-gender women.

Data on how efficacious on-demand PrEP is for MSM in reducing HIV transmission came initially from the randomised, placebo-controlled trial, IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les Gays) (12). This study evaluated the efficacy of on-demand PrEP comprising two tablets of TDF/FTC (versus placebo) taken 2–24 hours before potential sexual exposure to HIV, followed by a third tablet 24 hours after the first dose and a fourth tablet 48 hours after the first dose. If multiple episodes of sex occurred, the participants were advised to continue to take one tablet daily until the last sex act then take the two final doses, 24 hours apart. If sexual activity was resumed within a week, a single, rather than a double dose before sex was recommended. If sexual activity resumed more than a week later, the loading dose schedule (two tablets) was recommenced. The incidence of HIV was high in the placebo group (6.6 per 100 person-years) and a risk reduction in the TDF-FTC group of 86% [95% confidence interval (CI), 40 to 98; p = 0.002] was observed (12).

Demonstration studies have been undertaken to determine how effective on-demand PrEP is when used in community settings. In an open-label extension study of the IPERGAY study, an HIV risk reduction of 97% (95% CI, 81–100) with on-demand PrEP was reported in 361 participants with a median follow-up of 18 months (10). In a study of 1,069 people commencing PrEP in a single clinic in France, four HIV infections were diagnosed over 486 years of person follow-up (9). In the French Prévenir study, an interim analysis presented in July 2019 at the IAS conference on HIV science showed that of 2,143 participants, 47% took daily PrEP and 52% took on-demand PrEP (11). The median number of partners in the 3 months before PrEP commencement was 15 (IQR: 7-25) in the daily group and 10 (IQR 5-15) in the on-demand group (p < 0.001). The median number of condomless sex events in the previous 4 weeks was 2 (0 to 8) and 2 (0 to 4), in the daily and on-demand participants, respectively (p = 0.04). Follow-up in the daily and on-demand groups was 744 and 830 person-years, respectively. The HIV-1 incidence was 0 (95% CI: 0-0.5) and 0 (95% CI: 0-0.4) per 100 person-years in the daily and on-demand groups, respectively (11).

The efficacy of on-demand PrEP in people who use it infrequently

To address the question of whether on-demand PrEP is efficacious for people using it infrequently, the IPERGAY study team undertook a post-hoc analysis of IPERGAY study participants who reported relatively infrequent sex (13). Overall, IPERGAY participants reported using a median of 15 PrEP tablets per month (interquartile range (IQR 9–21). The post-hoc study looked at the follow-up time between two consecutive visits during which participants in the placebo and active study arms used ≤ 15 tablets per month and reported they used PrEP 'systematically or often' and not 'from time to time or never". During these periods of lower PrEP use, participants had a median of five episodes of sex per month (IQR 2-10) and used a median of 9.5 tablets per month (IQR 6-13). Six HIV infections occurred in the placebo arm (incidence: 9.3 per 100 person-years, total follow-up time: 64.8 person-years) and 0 in the TDF/FTC arm (incidence: 0 per 100 person-years, total follow-up time: 68.9 person years, p = 0.013). The relative reduction of HIV incidence in the treatment group was 100% (95% CI, 20-100). The study investigators concluded that an on-demand PrEP strategy remains highly effective in MSM even when they have infrequent sex (13).

Notably, of concern to the ASHM PrEP Guidelines Panel were the wide 95% confidence intervals of the relative risk reduction in this group of IPERGAY participants practising infrequent sex. However, the recently updated data from the Prévenir study (11) are reassuring in terms of the efficacy of less frequent use of on-demand PrEP. These updated data show that the median number of partners in the previous 3 months for participants using on-demand PrEP was 10 (IQR 5-15) and the median number of condomless sex events in the previous 4 weeks was 2 (0 to 4) (p = 0.04) with an associated HIV incidence in the on-demand participants of 0 (95% CI: 0-0.4) (11).

Toxicity and on-demand PrEP

There are few data available to determine whether on-demand PrEP offers less toxicity. In the IPERGAY study, no significant decline in the mean slope of estimated glomerular filtration rate (eGFR) in the TD*/FTC versus placebo arms was observed over a median of 9.3 months follow-up (14). In the HIV Prevention Trials Network (HPTN) study 067, the Alternative Dosing to Augment PrEP Pill Taking (ADAPT) study, 9% of 178 participants at one study site had creatinine elevation, but this was not significantly different between participants in the daily, time-driven and on-demand PrEP study arms (p = 0.05) (15).

Preference for on-demand versus daily PrEP

In the ongoing French Prévenir study, in which MSM are offered the choice of daily or on-demand PrEP, approximately half of the participants opt for each regimen (11). In the AM PrEP (the Netherlands) and Be PrEPared (Belgium) implementation studies, approximately one-third of men opted to take PrEP on-demand (16). In a report from the PRELUDE study from New South Wales, one third of participants enrolling in the study expressed a preference for non-daily PrEP (17). Recent data from previous participants of the Victorian PrEPX study showed that 48% would be interested in participating in an on-demand PrEP study (18) and this interest was most strongly associated with having sex infrequently and concerns about long-term toxicity) (18).

The choice of PrEP schedule: daily versus on-demand PrEP

Daily PrEP is suitable for all people who are at risk of HIV. Daily PrEP is the only PrEP regimen that is recommended for cis-gender and transgender women, for transgender men who have vaginal sex, for men who have anal or vaginal sex with women, PWID and for people with chronic hepatitis B (6).

Only cis-gender MSM have a choice between daily and on-demand PrEP. In this setting, daily PrEP would be preferential for those MSM who cannot predict when sex will occur, who cannot delay sex for more than 2 hours and for those whose potential exposure to HIV occurs more than twice a week. Daily PrEP is the only suitable regimen for cis-gender MSM with chronic hepatitis B infection to maintain virological suppression, prevent drug resistance and hepatitis flares.

On-demand PrEP would be suitable for those MSM whose preference is for the on-demand regimen, who have sex less than twice a week, and who can plan ahead for sex at least 2 hours in advance. Other reasons that MSM may choose or merit on-demand PrEP include side-effects from daily PrEP, poor kidney function or financial constraints.

The ASHM PrEP Guidelines Panel will continue to monitor HIV incidence in MSM using on-demand PrEP, including those who use on-demand PrEP less than fortnightly (11).

Summary of when to recommend daily and on-demand PrEP

Based on the evidence, the ASHM PrEP Guidelines Panel continues to recommend daily TD*/FTC dosing for all populations suitable for PrEP. The ASHM PrEP Guidelines Panel recommends that on-demand PrEP should be offered to cis-gender MSM. For cis-gender MSM, on-demand PrEP should be offered when this preference is expressed, when the person has at-risk sex less than twice a week, when the at-risk sex is unpredictable, and when sex can be delayed for 2 hours. Daily PrEP is the only suitable regimen for cis-gender MSM with chronic hepatitis B infection.

Other PrEP dosing schedules

There is some online guidance currently available that recommends that MSM taking PrEP can use a dosing schedule where they take a single dose of PrEP on Tuesdays, Thursdays, Saturdays and Sundays, known as 'the Ts and Ss'. While the motive for simplifying the PrEP dosing schedule is laudable the ASHM PrEP Guidelines Panel does not recommend the 'Ts and Ss' dosing schedule as it has not been tested in a clinical trial to demonstrate its efficacy in preventing HIV transmission.

Evaluation of the need for ongoing PrEP

Along with encouraging safer sex practices and safer injecting techniques, as needed, clinicians should support their patients to decide when to commence PrEP and when to discontinue its use.

The duration of PrEP use will depend on whether the person'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 who express a willingness to do so.

Adherence to PrEP should be assessed at each follow-up visit. PrEP users who explain that they have had suboptimal adherence, but who are willing and suitable to continue on PrEP, should be offered additional adherence education (see Medication adherence, including offering referral to peer-based support services). If a PrEP user repeatedly reports adherence that is sufficiently suboptimal to compromise both PrEP's efficacy (i.e. fewer than four tablets per week when taking a daily regimen) and the patient's safety, the clinician should discontinue prescribing PrEP. See also Chapter 9. *nPEP and PrEP* for the course of action to follow if a patient is not adherent to PrEP and has had a risk of exposure in the last 72 hours.

PrEP script duration including extension of PrEP scripts

The initial and ongoing prescriptions should offer a 90-day medication supply. PrEP scripts can be dispensed and filled on the same day as the baseline HIV test is done as long as the clinician is confident that the pathology service they use will provide a 4th generation HIV test result within 24-48 hours, at which time HIV antiretroviral treatment can be offered if the HIV test is found to be positive.

Typically, PrEP prescriptions should cover no more than 90 days of TD*/FTC supply at a time. Scripts can be provided and dispensed before the repeat quarterly HIV test results are available. However, people who are travelling overseas for prolonged periods may be given more than 90 days supply of PrEP, but the patient should agree to undergo HIV and STI testing at the usual 90-day period when they are overseas and to provide the results to their PrEP prescriber in Australia. People who use on-demand PrEP should also present for HIV and STI testing on a quarterly basis even if they do not need a prescription refill at that time.

Laboratory and clinical follow-up schedule at baseline and follow-up

The recommended schedule of testing and follow-up of people on PrEP is outlined in the Table 7.1 in Clinical follow-up and monitoring of patients on PrEP.

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, transgender and gender-diverse people, heterosexuals and PWID who meet recommended criteria. TDF alone has been proven effective in trials with people who inject drugs and heterosexuals (with efficacy comparable to TDF/FTC) (19). 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 overseas reports of HIV seroconversion in MSM taking unprescribed antiretroviral medication for PrEP (20).

What not to use for PrEP

DO NOT use any HIV antiretroviral medications, either in place of, or in addition to TD* or FTC.
Do not provide PrEP as expedited partner therapy (i.e. do not prescribe for a person who is not in your care).

PrEP dosing schedule

A daily PrEP regimen involves the person taking a single daily tablet at approximately the same time each day. Taking the tablet some hours earlier or later than usual will not adversely influence the levels of the drug. If the person forgets to take a tablet for one day, there is no need to take two tablets the next day.

The on-demand PrEP regimen, which is recommended for cis-gender MSM only involves the person taking a loading dose of PrEP where two tablets of PrEP are taken together as early as 24 hours before sex, or as late as 2 hours before sex. After sex, another PrEP tablet is taken 24 hours after the loading dose and then a final PrEP tablet is taken 48 hours after the loading dose. This 2+1+1 method for the use of on-demand PrEP for an isolated act of sex was recently endorsed by WHO (6).

If more sex acts take place over the following days, a single PrEP pill can be continued daily for as long as sex continues, with a single daily pill taken for each of two days after the last sex act.

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. Hepatotoxicity can occur but it is very uncommon. In these trials, side-effects were uncommon and usually resolved within the first month of taking PrEP (known as '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 symptoms that indicate a need for urgent evaluation (e.g. those suggesting possible acute renal injury or acute HIV infection). See Clinical assessment before starting PrEP for a review of the signs and symptoms of acute HIV infection.

PrEP medication drug interactions

In addition to the safety data obtained in PrEP clinical trials, data on drug-drug interactions and longer-term toxicities have been obtained by studying the component drugs individually for their use in treatment of people with HIV infection. Studies have also been performed in small numbers of healthy adults without HIV infection. No significant effect was seen, and no dosage adjustment was necessary for TD*, but there are no data on FTC (21, 22).

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*, FTC and other renally eliminated drugs including (but not limited to) cidofovir, aciclovir, valaciclovir, ganciclovir, valganciclovir, aminoglycosides and high-dose or multiple non-steroidal anti-inflammatory drugs (21).

Cocaine, methamphetamine and alcohol use were not seen to influence the concentrations of PrEP drugs (23) but use of these drugs may have an effect on the person's ability to maintain full adherence to PrEP.

Time to achieving and maintaining protection

The pharmacokinetics of TD* and FTC vary by tissue (24). Data from exploratory pharmacokinetic studies conducted with men and women without HIV infection suggest that maximum intracellular concentrations of tenofovir diphosphate are reached in blood after approximately 20 days of daily oral dosing (25, 26). Current evidence suggests that for both rectal and vaginal exposure, high protection is achieved after 7 days of daily dosing (27). Women need to maintain high adherence to daily dosing of TD*/FTC to maintain adequate drug levels in vaginal/cervical tissues (27). 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 transgender and gender-diverse people therefore extra attention to daily dosing is recommended.

Recently WHO recommended that because MSM achieve highly protective levels of PrEP medications with a single loading dose of two PrEP tablets (28, 29), they can take this PrEP loading dose whether they intend to commence daily, or on-demand PrEP (6). **The ASHM PrEP Guidelines Panel agrees with this recommendation on PrEP dosing initiation for MSM whether they are commencing daily or on-demand PrEP**

PrEP and travel

PrEP can play an important role in preventing HIV infection in people travelling outside of Australia, along with other measures to reduce HIV and STIs (30). If an MSM patient wants to take daily PrEP while on an overseas trip, he can commence two tablets on the day of departure and cease PrEP once it is no longer needed (see section below on ceasing PrEP). Alternatively, the MSM patient can take a double-dose 2-24 hours before sex and then use the on-demand regimen outlined above during the overseas trip. Cis - and transgender heterosexual men and women including those who inject drugs who want to take PrEP while on an overseas trip should commence PrEP 7 days before their departure.

nPEP use and PrEP

If a person is not taking PrEP but presents within 72 hours of a potential HIV exposure, they should be assessed for non-occupational post-exposure prophylaxis (nPEP) as a matter of urgency and should be offered nPEP immediately according to current nPEP guidelines if appropriate if HIV acquisition risk is likely to continue into the future, PrEP should be offered.

Discontinuing PrEP

Clinicians should regularly advise people using PrEP about how to discontinue PrEP. The need for PrEP may end when a partner with HIV achieves sustained HIV viral suppression after at least 6 months of antiretroviral therapy, when a patient enters a mutually monogamous relationship with a seroconcordant partner, or when other social circumstances change.

Discontinuing daily PrEP in MSM

There is now substantial clinical evidence that cis-gender MSM can safely cease daily PrEP by taking a dose of PrEP 24 and 48 hours after their last at-risk sexual exposure (9-11). Recently WHO recommended that MSM who take either daily or on-demand PrEP can safely cease PrEP by taking a dose of PrEP 24 and 48 hours after the first two pills if taking event based or if taking daily PrEP they can cease PrEP by taking a single daily pill for each of two days after the last sex act (6). **The ASHM PrEP Guidelines Panel agrees with this recommendation.**

Discontinuing daily PrEP for other populations

One US study recommends that PrEP should be continued for 28 days after the last at-risk sexual exposure (31). The ASHM PrEP Guidelines Panel recommends that clinicians should offer this advice for all people other than cis-gender MSM using daily PrEP until more information is available.

Discontinuing on-demand PrEP

On-demand PrEP can be ceased by taking a single daily PrEP tablet for 2 days after the last sex act, as described above.

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.

Recommencing PrEP

Clinicians should advise any patient who has discontinued PrEP on how to safely recommence PrEP. Clinicians should advise that if and when a patient decides to recommence PrEP that they must first have repeat HIV testing in case they have acquired HIV infection during the time that they were not taking PrEP. All other baseline clinical and laboratory evaluations need to be repeated also when a patient recommences PrEP and quarterly visits for PrEP scripts and ongoing evaluations must follow thereafter.

Patients may want to recommence 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
- travelling to or moving to a new region or country with high or unknown prevalence of HIV during which time they anticipate that they will be having condomless sex with casual partners, or using injectable drugs
- commencing, or recommencing sex work
- returning home to an overseas country which has a high HIV prevalence during which time they anticipate that they may have condomless sex, or injecting drug use with HIV-positive partners not on antiretroviral treatment or partners whose HIV status is unknown
- entering, or leaving institutional or correctional facilities with the anticipation that they may have condomless sex, or injecting use with HIV-positive partners not on antiretroviral treatment or partners whose HIV status is unknown.

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