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NZAF
Te Tūāpapa Mate
Āraikore o Aotearoa

PREVENT HIV BY PRESCRIBING PrEP

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Content

Glossary

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
GAHT	gender-affirming hormone therapy
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
OST	Opioid Substitution Therapy
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCR	urine protein: creatinine clearance
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
PIS	Personal Importation Scheme
PoCT	point-of-care test
PWID	people who inject drugs
s100	a section of the Pharmaceutical benefits Scheme which provides access to highly specialised drugs
STI	sexually transmissible infection
Takatāpui	Takatāpui is a traditional Māori term meaning 'intimate companion of the same sex.' It has been reclaimed to embrace all Māori who identify with diverse genders and sexualities such as whakawahine, tangata ira tane, lesbian, gay, bisexual, trans, intersex and queer.
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
TGM	Transgender Men
TGW	Transgender Women
WHO	World Health Organization

1. Introduction

Availability and uptake of human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) among people at high risk of acquisition have the potential to significantly reduce HIV transmission in New Zealand (NZ) and globally.

Co-formulated tenofovir and emtricitabine for use as HIV PrEP by people at risk of HIV infection is now recommended as standard care in clinical guidelines in the United States of America, Europe and Australia,[1,2,3] as well as globally through World Health Organization (WHO) guidelines.[4] When used with optimal medication adherence, daily PrEP is a highly effective HIV prevention strategy for men who have sex with men (MSM), heterosexual men and women, transgender people, and people who inject drugs who are at-risk of HIV acquisition.[5-11] In addition, event-driven PrEP is highly effective in cisgender MSM[12-14] and has recently been recommended by the World Health Organization as an option for MSM.[15]

This document serves as a NZ commentary on the ASHM Australian PrEP guidelines.[16]
In 2016, the NZ Medicines and Medical Devices Safety Authority, Medsafe, approved a new indication of Truvada (co-formulated tenofovir disoproxil fumarate and emtricitabine TDF/FTC; Gilead Sciences) for HIV PrEP for people at risk of HIV infection. Since then, generic co-formulations of tenofovir disoproxil* and FTC have been registered by Medsafe for HIV PrEP (for simplicity, TD* is used in these guidelines to denote the tenofovir disoproxil component present in the medicines registered for PrEP use in NZ).

In May 2017, the National HIV and AIDS Forum published and endorsed the *Consensus statement on comprehensive HIV prevention in Aotearoa New Zealand*.[17] The statement recommended providing PrEP to people at high risk of HIV as one of 6 priority actions to reverse the HIV epidemic in NZ. Other actions include the sophisticated promotion of condoms to protect against HIV and other sexually transmissible infections (STIs), timely and more frequent HIV testing, immediate access to HIV treatment on diagnosis (with ongoing retention in health care, to achieve and maintain an undetectable viral load), comprehensive STI screening and ongoing surveillance and research.

From 1 March 2018, TD*/FTC was funded by the NZ Pharmaceutical Management Agency, PHARMAC, for people at high risk of HIV acquisition, initially as the Truvada brand supplied by Gilead Sciences[18] and subsequently as a generic product supplied by Teva Pharma.[19] Whereas previously PrEP was available only through the NZ PrEP study (to assess the feasibility, risks and benefits of prescribing daily Truvada in a sample of men who are at high risk of acquiring HIV), private scripts or personal importation, PHARMAC-funded PrEP can now be prescribed by any relevant prescriber including general practitioners, nurse practitioners and sexual health physicians. People who are ineligible for publicly funded healthcare (e.g. temporary migrants) or who don't meet the PHARMAC behavioural eligibility criteria for funded PrEP can either legally import low-cost generic PrEP (often NZD$20-50 per bottle of 30 pills),[20] or pay the full price with a private script (often NZ$90-110 per bottle of 30 pills, depending on pharmacy mark-up).

The recommendations in these guidelines are designed to:

- support the prescribing of PrEP using either Medsafe-listed and PHARMAC-funded drugs, or the same or other generic drugs that are available through personal importation, or by paying the full price with a private script
- assist clinicians in their evaluation and HIV risk assessment of patients who are seeking PrEP
- assist clinicians in educating their patients about the role that PrEP can play alongside other prevention tools such as condoms
- assist clinicians in initiating their patients on PrEP by providing information on PrEP dosing schedules
- assist clinicians in the monitoring of patients on PrEP, including testing requirements and management of side-effects and toxicity
- assist clinicians to be aware of more complex situations such as the use of PrEP in pregnancy and in chronic hepatitis B infection
- assist clinicians in understanding how to safely cease PrEP.

These guidelines are intended for use by:

- general practitioners who provide care to people at risk of acquiring HIV infection
- sexual health physicians who provide care to people at risk of acquiring HIV infection
- infectious disease and HIV treatment specialists who may provide PrEP for, 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 people performing HIV testing, including point-of-care testing
- health program policymakers
- health consumers and others with an interest in HIV PrEP.

Key recommendations from the NZ commentary

The NZ authors of this commentary advise that daily PrEP should be recommended by clinicians as an important HIV-prevention strategy for people who meet the PHARMAC eligibility criteria and people who might be considered at moderate risk (see chapter 4. Eligibility for PrEP). The authors emphasise that PrEP ought to be provided as part of a wider suite of sexual health and STI prevention strategies that includes continued promotion of condoms to prevent HIV and other STIs, timely and more frequent HIV testing, immediate access to HIV treatment on diagnosis and comprehensive STI screening.

Event-driven PrEP should be considered as an alternative option for cis-gender MSM in cases where daily PrEP is not acceptable, sex is infrequent, or a person feels they can plan their sexual activity.

Caution should be used in recommending event-driven PrEP to adolescent MSM because there have been no trials of event-driven PrEP in adolescent MSM and because adherence rates to daily PrEP have been consistently low in studies of adolescent MSM.[21,22]

Event-driven PrEP is contraindicated in people with chronic hepatitis B infection

Of note, the authors will continue to monitor the data on the efficacy of event-driven PrEP for MSM who use PrEP less frequently than fortnightly.[14,23]

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2. PrEP safety and efficacy

For a full review of PrEP safety and efficacy please see the “Pre-exposure prophylaxis for the prevention of HIV Infection in the United States– 2017 update” starting from page 16:
https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

3. Indications for PrEP in Aotearoa New Zealand

This chapter replaces *Indications for PrEP in Australia* in the Australian guidelines. It provides New Zealand-specific HIV epidemiology and prevention.

It also differs from the Australian guidelines by positioning PrEP as part of a combination approach to prevention that includes continued promotion of condoms to prevent human immunodeficiency virus (HIV) and sexually transmissible infection (STIs), timely and more frequent HIV testing, immediate access to HIV treatment on diagnosis and comprehensive STI screening.

HIV epidemiology

New Zealand (NZ) has a concentrated HIV epidemic. In 2018, 78% of those newly diagnosed with HIV with a known mode of transmission were men who had sex with men (MSM), 19% contracted HIV heterosexually, 0.7% acquired HIV through injecting drug use (IDU), 0.7% were perinatal (overseas) and 2% obtained the infection through other means. Around 1.7% were transgender.[1] Overall MSM are estimated to be 187 times more likely to be living with diagnosed HIV than heterosexual men and women.[2] This trend has continued since 1996 when enhanced surveillance began.[3]

A substantial proportion of diagnoses were previously diagnosed overseas (23% in 2018) or were newly diagnosed in NZ but HIV infection was believed to have been acquired overseas (28%).[1] Within NZ, HIV transmission is even more concentrated: MSM accounted for 88% of NZ-acquired HIV with a known mode of transmission in 2018, which includes 9% MSM and IDU and 6% heterosexual transmission.[4] No children have ever contracted HIV during childbirth in NZ from mothers with a known HIV status at the time of birth.[1]

After a decade of relative stability, in 2016 NZ recorded the highest number of new HIV diagnoses ever, including the number of NZ -acquired infections (110).[1] That increase was largely driven by infection among MSM. Since 2016, trends in annual HIV diagnoses among MSM, including those that were NZ acquired, have declined by 39% between 2016 and 2018 and by 27% in 2018 compared to the previous 5year average.[5] The number of NZ -acquired HIV diagnoses through heterosexual contact has also declined. HIV transmission via IDU in NZ is rare, with an average of 1 per annum through IDU and 1 per annum where the mode of transmission was MSM and IDU over the period 1996-2018.[4]

The most recent estimate of undiagnosed HIV is among a community sample of MSM in Auckland in 2011, which found an undiagnosed HIV prevalence of 1.3% overall, or 1 in 5 (21%) of those living with HIV.[6] Almost a third (30%) of new HIV diagnoses among MSM between 2010 and 2014 were late presentations (CD4 count < 350 cells/μL),[7] living a median 4 years with unrecognised infection. This proportion has not improved.5 Late diagnosis is more common among heterosexually-acquired HIV, in whom over half (52%) of cases between 2014 and 2018 had a CD4 count below 350 cells/μL at the time of diagnosis.[5] A study of HIV prevalence in sexual health clinics over a 12-month period in 2005-2006 found no HIV cases, diagnosed or undiagnosed, among current sex workers.[8]

Among Māori, the majority of HIV diagnoses occur among takatāpui (Māori MSM).[3,9] Evidence from 2011 suggests Māori MSM have the same prevalence of HIV as other NZ MSM, although proportionately less of that is diagnosed.[6] HIV diagnosis in this group may therefore occur later, supported by surveillance data showing Māori MSM being more likely than other NZ MSM to present with advanced HIV disease (CD4 < 200 cells/μL).[7] Over time the proportion of new HIV diagnoses among MSM who were Māori has remained relatively stable at around 10%,[3] although in 2018 this was higher at 27%, which occurred in a context when the number of HIV diagnoses among other NZ MSM was declining.[5] There has been a doubling over time in the proportion of MSM newly diagnosed with HIV reporting an Asian ethnicity, that may partly reflect demographic changes in Auckland as well as other factors.[3,5]

Combination HIV prevention

NZ has a successful history of HIV prevention grounded in principles of science, pragmatism, partnerships, equity and leadership. Notwithstanding recent increases in HIV diagnoses, HIV prevalence and incidence in NZ is among the lowest in the world. These same principles guide our recommendations for pre-exposure prophylaxis (PrEP).

The HIV and sexual health sector in NZ has been an early adopter and advocate of PrEP, resulting in its public funding on 1 March 2018 for people with a higher probability of acquiring HIV.

The indication, availability and funding of PrEP is an essential part of the 2017 Consensus Statement on Comprehensive HIV Prevention in Aotearoa New Zealand.[10] This Consensus Statement recognises that: HIV transmission in NZ remains too high; HIV transmission is preventable by using existing and new biomedical interventions; and these interventions should be deployed in combination and at scale. The goal of this strategy is to eliminate HIV transmission in NZ.[11] This comprehensive approach is supported by the National HIV and AIDS Forum, a multidisciplinary collective of parties working in HIV prevention, care, policy and research in Aotearoa/New Zealand, and is being implemented by organisations for example in NZ AIDS Foundation's Ending HIV strategy.[12]

PrEP is identified as one of 6 priority actions in the Consensus Statement (Box 3.1).[10]

Box 3.1 Priority actions from the Consensus Statement.[10] Adapted from Saxton et al. 2015[11]

Action	Purpose
(1) Sophisticated promotion of condoms to protect against HIV and STIs during anal and vaginal intercourse, and continuation of needle and syringe exchange programs	To interrupt HIV and STI transmission
(2) Timely, more frequent and widespread HIV testing by improving access to testing services in clinical and community settings	To reduce the number with undiagnosed HIV infection
(3) HIV antiretroviral treatment to be offered following diagnosis, and ongoing retention in health care, to achieve and maintain an undetectable viral load	To minimise transmission and maximise personal wellbeing of people with confirmed HIV infection
(4) Pre-exposure prophylaxis (PrEP) and quarterly STI screening to be made available to people without HIV at high risk and unable to sustain behavioural risk reduction	To target the most vulnerable people who also play a disproportionate role in onward HIV transmission
(5) Improved access to comprehensive STI vaccination, screening and treatment	To control resurgent STI epidemics which synergise with HIV control
(6) Ongoing surveillance and research into HIV and STI infections and risk behaviours	To enable evidence-based decision making, evaluate progress and prompt agile responses

Furthermore, the Consensus Statement recommends that to be successful, comprehensive HIV prevention in NZ should be guided by the full spectrum of public health activity, skills and strategy:[10]

- public health actions range from individual interventions to policy reform, using approaches such as sexuality education, health education, community development, health promotion, harm reduction and social marketing[13] responses should be targeted to the most at-risk populations, especially MSM, migrant communities, people who inject drugs and sex workers
- services should be inclusive and respect diversity, and recognise the importance of peer-delivered services including Māori-led responses and the involvement of people living with HIV
- HIV stigma must be challenged to improve the lives of people living with HIV and to motivate engagement in HIV prevention and care
- health workforce capacity, training and guidelines need to keep pace with demand, especially in specialist sexual health services and primary care
- new prevention efforts should be carefully crafted and coordinated to minimise risk compensation and to ensure the effects are additive. For example, PrEP should not displace condoms and the outcome should be a net gain (i.e. the prevention of more HIV infections).

PrEP in NZ is therefore seen as part of a wider suite of sexual health and STI prevention strategies. Our most at-risk communities suffer from (1) an ongoing epidemic of syphilis (including a resurgence of congenital syphilis cases); (2) increasing rates of gonorrhoea (including drug-resistant cases); and (3) stubbornly high chlamydia rates.[14] The sexual and mental health (including drug and alcohol addiction) of our gender and sexually diverse minorities remain poor. Free access to quality bloodborne virus and sexual health care remains problematic for Māori, Pasifika, regional and remote areas, recent immigrants and other culturally and linguistically diverse communities. Transgender and other gender diverse people face barriers accessing basic services like gender-affirming surgery and, in some areas, gender-affirming hormonal therapy or mental health support.

With this wider context in mind, all interventions such as PrEP, condoms, HIV testing and early HIV treatment will have both benefits and drawbacks for different people.

Important issues to consider about PrEP and other interventions in the Aotearoa New Zealand context are listed here:

An enduring and effective public health response to HIV and STIs in Aotearoa New Zealand will require maintaining high rates of condom use for sex among MSM and other important affected communities. Care should be taken to position PrEP as a universal prevention strategy for all. Both condoms and PrEP are highly effective in preventing HIV, with condoms also providing broad protection against other STIs.[15]

Early and sustained antiretroviral treatment that leads to viral suppression (sometimes referred to by communities as undetectable or undetectable viral load [UVL]) benefits the health of people living with HIV, reduces stigma and prevents the sexual transmission of HIV.[15] The confidence in UVL as an effective tool to prevent onward transmission is such that having a partner with UVL is an exclusion criterion to access funded PrEP in Aotearoa New Zealand.

Like other biomedical interventions, PrEP risks privileging those with higher health literacy and access. To be an effective public health intervention, PrEP must be delivered as part of a comprehensive sexual

healthcare package that is accessible regardless of location, income, age, literacy, culture or migrant status. While Aotearoa New Zealand's healthcare system has funded PrEP for high-risk people, there are still barriers: not all regions have easily accessible free sexual healthcare; temporary migrants are often excluded from publicly funded healthcare; and many PrEP-seeking MSM report discomfort requesting PrEP from a clinician.[16]

HIV risk categories and targeted availability of PrEP in Aotearoa New Zealand

The local epidemiology of HIV transmission in NZ has informed the pragmatic acknowledgement of the need for PrEP and therefore its likely benefit. In turn, the data provided by the Sydney-based Health in Men (HIM) study[17] have provided extremely useful evidence of subpopulations at greatest HIV risk, on the assumption that New Zealand and Australia have a broadly similar HIV epidemic profile. Subsequently, the 2017 ASHM PrEP guidelines[18] provided important additional contemporary data to formulate PHARMAC's original targeted PrEP eligibility criteria. NZ data, where available, have since been used to estimate the number of PrEP-eligible people in NZ.[19]

Table 3.1 summarises the main factors associated with an increased risk of HIV acquisition among gay and bisexually identified men in the Sydney-based HIM study.[17] Five factors were associated with HIV incidence of above 1.8 per 100 person-years; these factors formed the criteria for identifying people at high risk of HIV acquisition. Two more factors with an HIV incidence above 1.0 and below 1.8 per 100 person-years formed the criteria for identifying people at medium HIV acquisition risk. Although the HIM study collected data from 2001 to 2007 and HIV notification trends have changed since then, the same factors are likely to remain relevant to HIV transmission and its prevention today, and these factors were validated as eligibility criteria in an analysis of data from the Victorian PrEPX study[20] and continue to guide PrEP prescribing throughout Australia and NZ.

Risk factor	HIV incidence per 100 person years (95% CI)
All gay and bisexual men regardless of behavioural practices	0.78 (0.59–1.02)
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)
At least one episode of receptive, unprotected anal intercourse with any casual male partner with HIV infection or a male partner of unknown HIV status during the last 6 months	2.31 (1.48–3.63)
Rectal gonorrhoea diagnosis in last 6 months	7.01 (2.26–21.74)
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)
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)
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)
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)
In circumcised men (comparison group, low risk, PrEP not recommended)	0.65 (0.16–2.61)

Table 3.1 Factors associated with elevated risk of HIV acquisition among men who have sex with men in the Health in Men (HIM) study, Australia, 2001–2007[17]

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

CI: confidence interval;
CLAI: condomless anal intercourse;
HIV: human immunodeficiency virus;
PrEP: pre-exposure prophylaxis

Of note, due to the specifics of data collection for the HIM study, not all indicators were available to support each individual eligibility criterion for PrEP. Some indicators were collected in different forms or had a different denominator or reference period. Most importantly, the HIV viral load of HIV-positive regular partners is now known to have a significant impact on HIV transmission,[21-23] and data on the HIV viral load of the source partners were not collected in the HIM study. Similarly, infectious syphilis was uncommon in the HIM cohort and was not associated with HIV transmission. However, its incidence has increased greatly since 2007 in Australia and NZ. Syphilis is associated with an increased risk of HIV among MSM globally,[24,25] and is therefore included in the PrEP suitability assessment. Drug use is another important factor that influences sexual behaviour and HIV risk acquisition and that has emerged since the HIM study. Methamphetamine use has been associated with increased risk of HIV infection in high-income countries internationally.[26] In Australia associations have been observed between injecting drug use and sexual risk taking[27] with a higher incidence of drug use initiation occurring in younger versus older MSM.[28]

The reference period for PrEP eligibility assessment in these guidelines reflects behaviour over the previous 3 months whereas the HIM study addressed behaviour over the previous 6 months.[17]

When PrEP was first publicly funded in Aotearoa New Zealand, the access criteria limited it to people at highest risk of HIV. At that time PrEP was only available as a brand medication, considerably more expensive than the generic medication currently in use. The now lower cost may justify expanding the access criteria to moderate-risk people.

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4. Eligibility for PrEP

This chapter replaces *Suitability for PrEP* in the Australian guidelines. It provides New Zealand (NZ)-specific information about eligibility for PrEP for populations at risk of HIV.

While the Australian guidelines no longer classify a person's risk of HIV acquisition as high or low and no longer require that a person demonstrates HIV risk in the previous 3 months, these New Zealand guidelines still classify a person's risk and eligibility for PHARMAC-funded PrEP.

The PrEP eligibility criteria that are provided in these guidelines are not intended to limit or deny access to PrEP to any person who seeks it. Instead, they are intended to help identify and actively recommend PrEP to people who will benefit from it and to guide clinicians in their discussions about PrEP with patients who are uncertain about their HIV risk and need for PrEP use. There may be cases where a patient will benefit from PrEP but not meet the PHARMAC eligibility criteria – in these cases the patient would need to self-fund their medication.

The section regarding people who inject drugs remains largely unchanged from the Australian guidelines.

Pre-exposure prophylaxis (PrEP) is registered in New Zealand (NZ) with the NZ Medicines and Medical Devices Safety Authority, Medsafe, and a generic form is publicly funded through a sole supply agreement with the NZ Pharmaceutical Management Agency (PHARMAC). All general practitioners and other relevant prescribers can prescribe PrEP using the PHARMAC special authority. No specialist training is required to prescribe PrEP, however resources and training guidance are available for clinicians who are new to prescribing PrEP.

In NZ's universal public healthcare system, access to funded treatments is dictated by need. PrEP should be provided, as part of a comprehensive sexual healthcare package, to high-risk people who meet the eligibility criteria outlined in this chapter.

People presenting for PrEP are typically from populations at high risk of human immunodeficiency virus (HIV) infection and they should not be dissuaded from using PrEP if they do not meet the PHARMAC eligibility criteria. People requesting PrEP who do not meet the PHARMAC eligibility criteria should still be assessed to determine if they would benefit from PrEP and these people then have the option of self-funding or importing

the medicine from overseas. Please refer to chapter 12. How to access PrEP in New Zealand for further information on accessing non-funded PrEP. Doctors who are not comfortable prescribing PrEP should refer the patient immediately to a colleague, or another service that does provide PrEP.

It should also be highlighted that sexual history taking is a necessary and routine part of medical practice, and when this process identifies that a patient may be at risk of HIV, clinicians should proactively offer these patients PrEP. Furthermore clinicians are encouraged to raise PrEP as an HIV prevention strategy with patients whom they perceive to be at risk of HIV infection, even if the purpose of the patient's visit is not related to sexual health, sexually transmissible infections (STIs) or drug use.

These PrEP guidelines recommend daily PrEP for all people who meet the PHARMAC eligibility criteria and people who might be considered at moderate risk of HIV infection, as outlined below. In addition, these guidelines also recommend that event-driven PrEP should be considered as an alternative option to cis-gender men who have sex with men (MSM) in cases where daily PrEP is not acceptable, sex is infrequent or a person feels they can plan their sexual activity. Please refer to chapter 6. Providing PrEP for further information on initiating PrEP.

PrEP providers need to obtain a thorough sexual and drug-use history at baseline to determine a person's eligibility for PrEP and to review their ongoing need for PrEP at each 3-monthly clinical review.

The following eligibility criteria can be used to help structure a discussion with a patient about their sexual health and behaviour (Box 4.1). Guidance on how to initiate and guide a discussion about a person's sexual and drug using behaviour in primary practice is available.[1]

Clinicians who have limited experience with prescribing PrEP are encouraged to discuss with a PrEP-experienced clinician those patients whose PrEP eligibility is unclear.

Box 4.1. PrEP eligibility criteria for men (cis or trans)* and trans-women who have sex with men

High risk of HIV: eligible for funded PrEP

The clinician should prescribe PrEP if the patient describes a history of any of the following HIV acquisition risks in the previous 3 months and if the patient foresees that they are likely to have multiple events of condomless anal intercourse (CLAI) in the next 3 months

- At least one episode of receptive condomless anal intercourse with any casual+ male partner
- One or more episodes of engaging in sexualised drug use, sometimes referred to as chemsex. In the NZ context this scenario typically involves the use of crystal methamphetamine (called P in NZ)
- One or more episodes of rectal gonorrhoea, rectal chlamydia or infectious syphilis, including any STIs diagnosed at screening for PrEP
- At least one episode of CLAI (insertive or receptive) with a regular HIV-positive partner who is either not on treatment, or who is on treatment but has a detectable HIV viral load

Not eligible for funded PrEP: patient could consider self-funded PrEP

The clinician could prescribe PrEP, on the advice of a specialist, if the patient describes any of the following acquisition risks:

- They are likely to have CLAI in the next 3 months
- Plans to travel during which time they anticipate that they will be having condomless sex with casual partners
- More than one episode of anal intercourse where a condom slipped off or broke where the HIV serostatus of the partner was not known, or where the partner was HIV positive and not on treatment or had a detectable viral load on treatment
- They have recently left a monogamous relationship and will be having condomless sex with casual partners in the future
- Entering or leaving institutional or correctional facilities in the near future where they may have condomless sex, or injecting use with casual partners in the future
- Commencing or recommencing sex work
- Concerns of deteriorating mental health and a history of having previously increased their HIV-acquisition risk behaviour in this setting
- A history of intermittent binge drinking of alcohol or recreational drug use and a history of having increased their HIV-acquisition risk behaviour in this setting
- A history of recurrent genital ulceration or dermatoses (e.g. psoriasis), as this may increase the risk of HIV transmission.

* **Cis:** gender identity or expression matches the sex assigned at birth
* **Trans:** gender expression or identity differs from sex assigned at birth
* **Casual partner:** a non-exclusive sexual partner

Only a small proportion of participants in PrEP studies have been transgender (trans) or gender-diverse people.[2-4] As a result, limited data are available for these populations. Incorrect assumptions can be made about trans people and their sexual practices, as they may practise vaginal or neovaginal and anal intercourse, both insertive and receptive. Trans and gender-diverse people who are at risk of acquiring HIV on the basis of their sexual history are eligible to access PrEP. It is essential for clinicians to take a sexual history using appropriate and sensitive language to assess risk.

Box 4.2. PrEP suitability criteria for heterosexual people

High risk of HIV: eligible for funded PrEP

The clinician should prescribe PrEP if the patient describes:

- at least one episode of condomless intercourse (insertive or receptive) with a regular HIV-positive partner who is either not on treatment, or who is on treatment but has a detectable HIV viral load

Not eligible for funded PrEP: patient could consider self-funded PrEP

The clinician could prescribe PrEP, on the advice of a specialist, if the patient describes any of the following acquisition risks:

- Receptive condomless intercourse with any casual MSM partner of unknown status (in last 3 months or expected in next 3 months)
- Future episodes of planned condomless insertive or receptive vaginal sex in an effort to conceive with an HIV-positive partner, regardless of the HIV-positive partner's viral load
- Plans to travel to countries with high HIV prevalence during which time they anticipate having condomless sex with casual partners
- Reports of recently having left a monogamous relationship and of having condomless sex with a casual HIV-positive partner with a detectable or unknown viral load, or a male or female partner of unknown HIV serostatus from a country with high HIV prevalence, or a male partner who is thought to have sex with men
- Reports of entering or leaving institutional or correctional facilities in the near future where they may have condomless sex, or injecting use with casual partners in the future
- Reports of commencing, or recommencing sex work
- Concerns of deteriorating mental health and a history of having increased their HIV acquisition risk behaviour in this setting
- A history of intermittent binge drinking of alcohol or recreational drug use and a history of having had increased their HIV acquisition risk behaviour in this setting.

PrEP eligibility criteria for people who inject drugs

In the first instance, people who inject drugs should be advised of and provided with options for using sterile needles, syringes and other injecting equipment, and offered opioid substitution therapy for those who use opioids. People who inject drugs can be referred to local needle and syringe programs, or the Australian Injecting and Illicit Drug Users League affiliates in their state or territory.

Because people who inject drugs are susceptible to a range of infections and injuries, PrEP and other HIV-prevention interventions should be integrated into prevention and clinical care services for hepatitis A, B and C infection and other infectious diseases, and overdose prevention. These interventions include screening for hepatitis A, B and C viruses and providing incentivised vaccination for hepatitis A and B where clinically indicated, as well as screening for injection-related injuries and infections including abscesses, septicaemia and endocarditis.[5]

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 people who inject drugs, and emphasises that access to harm-reduction services remains a critical component of HIV prevention in people who inject drugs.[6] This approach is particularly relevant in Australia and NZ where sterile needle and syringe coverage is high and HIV prevalence and incidence among people who inject drugs remains low and stable.[7,8]

A recent systematic review of HIV-treatment adherence among people who inject drugs in the USA and Canada, undertaken to inform potential PrEP adherence interventions for people who inject drugs, found that younger age, female sex, homelessness and incarceration were obstacles to HIV treatment adherence.[9] By comparison, self-sufficiency, use of opioid substitution therapy and high quality patient-provider relationships were facilitators for adherence.[9] Self-reports from HIV-negative people who inject drugs were that HIV–related stigma in social networks, negative experiences with healthcare providers, lack of money, homelessness and the criminal justice system were likely barriers to PrEP access.[10] These factors should be considered when providing support to people commencing PrEP when they are at risk of HIV through injecting drug use.

The ASHM PrEP Guidelines Panel will continue to monitor the outcomes of the few ongoing studies of HIV PrEP in people who inject drugs.

Box 4.3. PrEP eligibility criteria for people who inject drugs

High risk of HIV: eligible for funded PrEP
There are currently no criteria in which people who inject drugs are eligible for funded PrEP. It may be possible in some cases that people who inject drugs are eligible for funded PrEP through sexual behaviour.
Not eligible for funded PrEP: patient could consider self-funded PrEP
The clinician could prescribe PrEP, on the advice of a specialist, if the patient describes any of the following acquisition risks: • Shared injecting equipment with an HIV-positive person or with MSM of unknown HIV status (in last 3 months or expected in next 3 months).

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5. Clinical assessment before starting PrEP

In Aotearoa New Zealand the following investigations are required for initial Special Authority application:

- Human immunodeficiency virus (HIV)
- Syphilis
- Hepatitis B (if not immune)
- Full sexually transmissible infections (STIs) screening within the previous 2 weeks
- Renal function testing (creatinine, phosphate, and urine protein creatinine ratio) within the previous 3 months.

The practitioner must also ensure treatment is not contraindicated and assess drug-drug interaction.

Although not required by Special Authority criteria, the New Zealand (NZ) authors also recommend baseline bloop pressure reading, urinalysis, full blood count and liver function tests. Otherwise the criteria are as per the ASHM guidelines.

All patients whose sexual or drug injecting 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 for whom it could present specific health risks that would require close monitoring.

HIV testing

For patients' safety, those with acute or chronic 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 pre-exposure prophylaxis (PrEP) as the daily, or event-driven 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 and p24 antigen venous blood test should be used and should be performed within 14 days of the patient's being evaluated for PrEP. If there is no recent HIV test result, clinicians should prescribe PrEP on the same day as an HIV test and advise patients to start PrEP once informed the test is negative.

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] These tests include rapid home-based HIV testing kits which are available in NZ. 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 and 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 New Zealand HIV Testing Guidelines.[2] 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 local health pathways.

A course of non-occupational post-exposure prophylaxis (nPEP) may be required before transitioning to PrEP, in accordance with the PEP and nPEP guidelines[3] if a patient has had a recent high-risk exposure (within 72 hours). For more information refer to the PEP guidelines, local District Health Board pathways, or refer to a local infectious diseases or sexual health physician.

Patients who have had a recent high-risk exposure outside the 72-hour window for the commencement of nPEP should be assessed for 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.

Acute HIV infection should be suspected in people 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 men who have sex with men (MSM); recent injecting drug use with shared injecting 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 and signs occurred in 94% of participants with acute HIV infection, just before and around the time of peak HIV viraemia.[4] 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).

Initiation of TD*/FTC PrEP in people 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.[5-8]

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.[9] Such patients can only be started on PrEP if and when HIV infection is excluded.

	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.[4]

[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 people on PrEP developing TD* or FTC resistance is low.[10] 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.[10] Similar findings were reported in a more recent review of clinical trials and case reports of HIV resistance occurring in the PrEP setting.[11] 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.[12]

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.[13] Tenofovir use was not associated with increased risk of fractures, hypophosphataemia or severe proteinuria.[13] Rarely, proximal renal tubular dysfunction (including Fanconi syndrome) may occur with TD* use.[13-15]

Overall, tenofovir use in PrEP studies has not been associated with significant clinical renal problems.[16-18] 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 with PrEP cessation.[16] 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.[18] **There are no data for people using PrEP who have an eGFR below 60 mL/min/1.73m^2 therefore starting PrEP in people whose eGFR is well established to be below 60 mL/min/1.73m^2 is not recommended.** However, see comments below on managing people 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 tenofovir disoproxil fumarate (TDF)/FTC exposure suggesting that subclinical tubular injury occurs on PrEP.[19]

There are limited data regarding whether event-driven 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 9.4 months follow-up,[20] suggesting that event-driven PrEP may not influence renal function. In the Alternative Dosing to Augment PrEP Pill Taking (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 event-driven PrEP study arms ($p = 0.05$).[21]

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.[22] More broadly the DISCOVER study found that TAF/FTC was non-inferior to TDF/FTC in terms of preventing HIV infection,[22] however TAF/FTC has not been licensed yet in NZ for use as PrEP.

For all patients considered for PrEP, their risk factors for chronic kidney disease 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. 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 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 as reported by the laboratories.

For people 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, creatinine 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 a person'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, in this setting, event-driven 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 and 6 monthly thereafter. Special Authority renewal requires renal function testing (creatinine, phosphate and urine PCR) within the previous 12 months. However, based on currently available evidence, more intensive monitoring may be warranted in the following people:

- 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 people may experience a decline in eGFR; the Australian Chronic Kidney Disease 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.[23]

Assessment and management of sexually transmissible infections at baseline

People 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 NZ Sexual Health Society STI management guidelines.[24] 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 1774 evaluable study participants tested positive for STIs at baseline.[25]

Patients starting on PrEP should be informed about:

- prevention of STI acquisition and transmission
- combining condom and PrEP use for the prevention of STIs
- 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

People being assessed for PrEP can also be at risk of acquiring hepatitis A, hepatitis B virus (HBV) infection[26] and hepatitis C virus (HCV) infection.[27] Hepatitis A, HBV and HCV infection status should be documented by screening serology when PrEP is initiated. HBV status needs to be assessed each time an application is made, unless the person is immune.

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.[28,29] People 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. Those with chronic hepatitis B infection should only be offered daily PrEP and not event-driven 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. People 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 people receiving TD*/FTC for PrEP in the IPREX study.[30] People 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.[31] A clinician may suspect that a person 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.[32]

There are no data available on whether event-driven 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.[22]

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. 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 people of childbearing potential

The risk of HIV transmission to women increases by over two-fold when they are pregnant.[33] As reviewed recently, current evidence suggests that PrEP can be used safely during pregnancy and breastfeeding.[34]

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[35,36] as has a lower length and head circumference at 1 year of age.[36]

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.[37] 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.[38] The World Health Organization has included PrEP as an HIV prevention strategy during pregnancy[39] and a number of other jurisdictions recommend PrEP for safe conception and for use during pregnancy and breastfeeding.[40]

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.[40] The lead

time for PrEP to reach highly effective levels in women is 7 days. 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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6. Providing PrEP

Goals of PrEP

The ultimate goal of human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) is to reduce the acquisition of HIV infection and its resultant morbidity, mortality and associated cost to people and society. Therefore, clinicians initiating 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 New Zealand (NZ) 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 event-driven 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 including the use of condoms.
- 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 New Zealand

Co-formulated tenofovir disoproxil* and emtricitabine (TD*/FTC) is registered by the NZ Medicines and Medical Devices Safety Authority, Medsafe, for daily use and is subsidised by the NZ Pharmaceutical Management Agency, PHARMAC.

Daily PrEP

Daily PrEP is the most commonly prescribed PrEP regimen in NZ. 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)[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 chapter 2. PrEP safety and efficacy.

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

Event-driven PrEP

Event-driven PrEP involves taking 2 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. This regimen is referred to as The 2 + 1 + 1 dosing of PrEP.[6] If sex continues for several days, people take one tablet of TD*/FTC daily until the last sex act, following which one dose 24 hours later and again at 48 hours are taken after the last episode of sex.

World Health Organization (WHO) recently released a technical brief recommending the use of event-driven PrEP for cis-gender men who have sex with men (MSM).[6] **The 2019 ASHM PrEP Guidelines Panel endorses WHO's recommendation that event-driven PrEP should be offered to cis-gender MSM.**

Event-driven 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 event-driven versus daily PrEP to adolescent MSM because there have been no trials of event-driven PrEP in adolescent MSM and because adherence rates to daily PrEP have been consistently low in studies of adolescent MSM.[7,8] **Of note, event-driven PrEP is contraindicated in people with chronic hepatitis B infection.**

Evidence in support of event-driven 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 event-driven 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 event-driven PrEP does not provide adequate tissue levels of PrEP to provide high levels of HIV protection; therefore event-driven PrEP should not be recommended for cis-gender women.

Data on how efficacious event-driven 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 event-driven PrEP comprising 2 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 2 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 (2 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 event-driven 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 event-driven PrEP was reported in 361 participants with a median follow-up of 18 months.[10] In a study of 1069 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 International AIDS Society (IAS) conference on HIV science showed that of 2143 participants, 47% took daily PrEP and 52% took event-driven PrEP.[11] The median number of partners in the 3 months before PrEP commencement was 15 (interquartile range (IQR): 7-25) in the daily group and 10 (IQR 5-15) in the event-driven 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 event-driven participants, respectively ($p = 0.04$). Follow-up in the daily and event-driven 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 event-driven groups, respectively.[11]

The efficacy of event-driven PrEP in people who use it infrequently

To address the question of whether event-driven 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 (IQR 9–21). The post-hoc study looked at the follow-up time between 2 consecutive visits during which participants in the placebo and active study arms used less than 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 5 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 event-driven 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 event-driven PrEP. These updated data show that the median number of partners in the previous 3 months for participants using event-driven 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 event-driven participants of 0 (95% CI: 0-0.4).[11]

Toxicity and event-driven PrEP

There are few data available to determine whether event-driven 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 9.4 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 event-driven PrEP study arms (p = 0.05).[15]

Preference for event-driven versus daily PrEP

In the ongoing French Prévenir study, in which MSM are offered the choice of daily or event-driven 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 event-driven.[16] In a report from the PRELUDE study from New South Wales, Australia, 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 event-driven PrEP study 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 event-driven 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, people who inject drugs and for people with chronic hepatitis B.[6]

Only cis-gender MSM have a choice between daily and event-driven 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.

Event-driven PrEP would be suitable for those MSM whose preference is for the event-driven 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 event-driven 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 event-driven PrEP, including those who use event-driven 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 and when sex can be delayed for 2 hours. Daily PrEP is the only suitable regimen for cisgender 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 chapter 10. Improving 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 4 tablets per week when taking a daily regimen) and the patient's safety, the clinician should stop 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. Reasonable attempts should be made to avoid multiple patient visits when initiating PrEP. A prescription can be provided on the same day as the baseline HIV test is ordered as long as the patient is advised not to fill the script until confirmed HIV negative and the Special Authority is approved. Another option is to send the script to the patient or pharmacy once the Special Authority is approved.

PrEP prescriptions should cover no more than 90 days of TD*/FTC supply at a time. People who use event-driven 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 schedule at baseline and follow-up

The recommended schedule of testing and follow-up of people on PrEP is outlined in Table 7.1 in chapter 7. Clinical follow-up and monitoring of patients on PrEP.

Indicated medication

The medications proven safe and effective and currently approved by Medsafe 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 people who inject drugs 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 2 tablets the next day.

The event-driven PrEP regimen, which is recommended for cis-gender MSM only, involves the person taking a loading dose of PrEP where 2 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 event-driven PrEP for an isolated act of sex was recently endorsed by WHO.[6]

People who have more than one episode of at-risk sex over a period of days should keep taking a single PrEP tablet every day that they are having sex until the last day that at-risk sex occurs, then they should take a single daily PrEP tablet for 2 days after the last at-risk 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 or hepatotoxicity. 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 chapter 5. 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 and 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,[27,28,29] they can take this PrEP loading dose whether they intend to commence daily, or event-driven PrEP.[6]

The ASHM PrEP Guidelines Panel agrees with this recommendation on PrEP dosing initiation for MSM whether they are commencing daily or event-driven PrEP.

PrEP and travel

PrEP can play an important role in preventing HIV infection in people travelling outside of NZ, along with other measures to reduce HIV and STIs.[29] If an MSM patient wants to take daily PrEP while on an overseas trip, he can commence 2 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 event-driven 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.[30]

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 event-driven 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 event-driven PrEP can safely cease PrEP by taking a dose of PrEP 24 and 48 hours after their last at-risk sexual exposure.[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 event-driven PrEP

Event-driven 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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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.

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 people who are prescribed prep, including event-driven prep

Test	Baseline (Week 0)	About day 30 after initiating PrEP (recommended if recent HIV risk before starting PrEP)	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** Retest HIV if any doubt about window period for baseline HIV test. Can be done by giving client a lab form to do this and does not require a visit	**Y**	**Y**	**N**
Full blood count	**Y**	**N**	**N**	**N**	**N**
Phosphate	**Y**	**N**	**N**	**N**	**Y** Every 12 months
Urine analysis	**Y**	**N**	**N**	**N**	**N**
Assess side-effects	**N**	**Y**	**Y**	**Y**	**N**
Hepatitis A serology Vaccinate if non-immune	**Y**	**N**	**N**	**N**	**N**
Hepatitis B serology Vaccinate if non-immune	**Y**	**N**	**Y** (if not immune)	**Y** (if not immune)	**Y** If patient required hep B vaccine at baseline, confirm immune response to vaccination 1 month after last vaccine dose
Hepatitis C serology	**Y**	**N**	**N**	**N**	**Y** Every 12 months, or more frequently if ongoing risk e.g. non-sterile injecting drug use and MSM with sexual practices that predispose to anal trauma
Liver function tests	**Y**	**N**	**N**	**N**	**Y** Every 6 months
STI (i.e. syphilis, gonorrhoea, chlamydia) as per www.nzshs.org/guidelines	**Y**	**N**	**Y**	**Y**	**N**
eGFR at 3 months and then every 6 months	**Y**	**N**	**Y**	**N**	**Y** At least every 6 months or according to risk of chronic kidney disease
Urine protein:creatinine ratio (PCR) baseline	**Y**	**N**	**Y**	**N**	**Y** At least every 6 months
Pregnancy test (for people who may become pregnant)	**Y**	**Y**	**Y**	**Y**	**N**

Y: yes
N: no
eGFR: estimated glomerular filtration rate
STI: sexually transmissible infection
MSM: men who have sex with men

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 urine PCR tests for chlamydia (first-pass urine, pharyngeal swab, vaginal and anal swab) and *Neisseria gonorrhoea* (pharyngeal swab, vaginal and anal swab) and a blood test for syphilis serology[1]
- Assess side-effects, PrEP adherence and ongoing PrEP suitability
- Apply for renewal of Special Authority ensuring the special authority covers the script is written for and provide script
- Respond to questions and provide any new information about PrEP use
- Provide support for medication adherence and risk-reduction behaviours
- Patient has tested for hepatitis B in the last 2 weeks (unless Hepatitis B immune)

In addition:

- Repeat pregnancy testing for people of childbearing age
- Test for hepatitis C virus (HCV) in people who inject drugs 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 predispose to anal trauma).

At least every 6 months:

- Monitor estimated glomerular. filtration rate (eGFR), creatinine and urine PCR
- If the patient has risk factors for renal impairment (e.g. hypertension, diabetes), renal function may require more frequent monitoring and may need to include additional tests (e.g. urine PCR)
- 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
- liver function test every 6 months.

At least every 12 months:

- Test for hepatitis C
- Test creatinine, phosphate and urine PCR (mandatory for Special Authority).

Patients who access PrEP through personal importation should allow a lead time of 2–6 weeks for the drug to arrive in NZ 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 home testing HIV diagnostic kits, 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 chapter 10. Improving medication adherence). Patients should be familiar from their baseline visit with the requirement for quarterly clinical visits to obtain ongoing PrEP prescriptions.

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 infectious diseases or sexual health physician. 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 initial emphasis should be on supporting the person 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 injecting equipment with an HIV-positive partner). Also, infection with tenofovir disoproxil* (TD*)- or emtricitabine (FTC) - resistant HIV is possible, however, it is very uncommon while on PrEP, with only a few cases reported internationally.[2] 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 Table 5.1 in chapter 5. Clinical assessment before starting PrEP 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).[3-5] 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 event-driven 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 chapter 9. 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 in chapter 5. Clinical assessment before starting PrEP). 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 one 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 event-driven 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[6] 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 NZ Sexual Health Society (NZSHS) Sexual Health Check Guidelines.[1] Partner notification should be undertaken using the most appropriate available resources.

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

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 hepatitis B and 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 one 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 one 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.[7] If people living with chronic HBV infection stop taking these medications, severe hepatic flares can occur.[7] 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 chapter 8. Special clinical considerations.

Hepatitis C virus monitoring

All people who inject drugs including MSM, and those who are trans and gender diverse and heterosexual

should be monitored for hepatitis C virus (HCV), as should MSM and trans and gender diverse people who engage in sexual contact that may predispose to anal trauma. The incidence of HCV has currently been low at approximately 1% per annum in PrEP studies of MSM,[8,9] and higher in HIV-positive MSM.[10,11] 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.[12]

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 one month, when 39% of participants reported symptoms, compared with 22% at baseline. Gastrointestinal symptoms occurred in a median of 28% of participants across study sites (range 11–70%) and non-gastrointestinal symptoms occurred in a median of 24% of participants (range 3–59%). The odds of gastrointestinal symptoms were higher in those with evidence of high adherence to PrEP. By 3 months, symptoms had returned to pre-PrEP levels.[13]

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%).[14,15] However, in NZ there are no clinical laboratories that quantify TD*/FTC concentrations in plasma, cells or urine for therapeutic drug monitoring in the setting of PrEP16 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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8. Special clinical considerations

This chapter replaces *Special Clinical Considerations* in the original guidelines. It provides information about relevant patient groups in New Zealand (NZ).

Māori

Little is known about pre-exposure prophylaxis (PrEP) among Māori men who have sex with men (MSM). An Auckland demonstration project of early PrEP adopters found that at enrolment, Māori reported similar rates of condomless receptive anal intercourse and rectal sexually transmissible infections (STIs) as that of Europeans.[1] Preliminary data of 12-month follow-up suggested proportionately lower study retention and medication adherence among non-European MSM.[2] These results are consistent with US findings where Black MSM had poorer engagement with PrEP services.[3] A study of unrecognised human immunodeficiency virus (HIV) in 2011 found Māori MSM had the same HIV prevalence as non-Māori MSM, although proportionately less of that was diagnosed.[4] HIV diagnosis may therefore occur later, supported by surveillance data showing Māori MSM being more likely than European MSM to present with advanced HIV disease (CD4 < 200 cells/μL).[5] Community studies also suggest Māori MSM are less likely to have ever tested for HIV,[6] may engage in more condomless casual sex,[7] and report illicit drug use,[8] which if involving methamphetamine is an indication for PrEP. An evaluation of the Ending HIV campaign found Māori MSM less likely than non-Māori MSM to self-report PrEP use in the previous 6-months.[9] Overall, these data imply that PrEP is needed by Māori MSM but they will face proportionately greater barriers accessing PrEP when delivered through existing health services.

The Aotearoa Statement on closing the gap on STIs and bloodborne viruses (BBVs) among indigenous peoples of Australasia (www.nzshs.org/events/the-aotearoa-statement) is an important framework to use to plan responses to Māori sexual health needs. This statement recommends that interventions will be most effective when led by or co-designed with Māori. Furthermore, all tangata whenua (people of the land) are entitled to equitable access to the health care that meets their needs. To optimise HIV prevention and PrEP use, clinicians caring for Māori MSM need to actively check their cultural competence and provide cultural safety for their patients. This prerequisite starts with understanding any unconscious biases and acknowledging that different health outcomes for Māori cannot be explained by genetics or behaviour but are in fact the result of structural barriers and socio-cultural factors.[10] This understanding should inform a clinician's approach to providing care for Māori MSM.

Developing Māori Health Equity Capability among Health Professionals from 'competence' to 'safety'
Professor Papaarangi Reid, Dr Rhys Jones and Associate Professor Elana Curtis

Dealing with Diversity, The Profession and in Practice
Professor Papaarangi Reid

Clinicians should initiate a conversation with Māori MSM if they suspect the patient will benefit from PrEP (e.g. if they have had a recent diagnosis of syphilis or a rectal STI). Clinicians should not hesitate, where convenient for the patient, to refer to a public sexual health clinic that offers free services and comprehensive care.

Clinicians should be sensitive when taking a sexual behaviour history bearing in mind that Māori MSM, like other MSM, may not feel comfortable discussing sexual history. If Māori MSM request PrEP without disclosing full sexual history, clinicians should acknowledge that the conversation might be uncomfortable for the patient and manage the situation rather than simply declining PrEP. Laboratory evaluations should not delay the provision of a script for PrEP; scripts can be provided on the first visit with laboratory results followed up separately. To maximise retention, services should be designed to be easily accessible and minimise the need for multiple visits.

There are large ethnic disparities in chronic hepatitis B virus (HBV) infection. Recent data suggest that 6% of Māori, 7% of Pacifica and 8-9% of people with Chinese or South Asian ethnicity have chronic HBV compared to less than 1% of European or Indian ethnicity.[11] Given the higher rates of chronic HBV infection among Māori, clinicians caring for Māori MSM must carefully follow these ASHM PrEP guidelines and screen for HBV and, as required, provide HBV vaccinations. Note that people with chronic HBV should only be offered daily PrEP to maintain sustained virological suppression of HBV.

People ineligible for publicly funded PrEP, including newly arrived migrant MSM

Little is known about PrEP use among newly arrived migrant MSM. In 2019, the number of MSM reported to have HIV infection in NZ has continued to decline since the peak in 2016. A much higher proportion of the MSM with HIV infection reported in 2019 had been previously diagnosed overseas (39%). This increase has mostly been an increase in the number of Asian and Latin American men.[12]
People who come to NZ to study or work (with a work visa of less than 2 years duration) are in most cases ineligible for publicly funded healthcare.[13] International students are often required to have overseas student health insurance, however the coverage for sexual health needs is typically limited. Additionally, some students are reluctant to use their private health cover for sexual health testing, prevention and treatment because of concerns about privacy or a prospective immigration process.

Clinicians should refer people who are ineligible for publicly funded health care, or who are unable or unwilling to use private healthcare cover, to public sexual health clinics that offer free HIV and STI testing and provide PrEP prescriptions. These PrEP prescriptions can be filled by paying the full, unsubsidised amount for a private script, or by personal importation of PrEP through online pharmacies.

More information can be found in chapter 12. How to access PrEP in New Zealand.

Transgender women

Transgender women have a high prevalence of HIV infection[14] and experience high HIV incidence rates compared to non-transgender men and women.[15] Furthermore, transgender women have represented less than 1% of study participants in PrEP trials[16] and this paucity of data may help explain the overall low uptake of PrEP by transgender women.[17]

The Iniciativa Profilaxis Pre-Exposición (iPrEX) clinical trial enrolled the highest number of transgender women to date and found that compared to MSM, transgender women were more likely to report transactional sex, condomless anal intercourse and more recent sexual partners.[18] In iPrEX, no HIV infections were observed in transgender women whose blood levels were compatible with taking 4 or more doses of PrEP weekly. However, using stratified analyses, PrEP did not provide a benefit for transgender women in the iPrEX study (hazard ratio 1.1, 95% confidence interval (CI): 0.5 to 2.7) compared to the overall 44% reduced HIV incidence in the active study arm.[18]

A recent retrospective analysis of the iPrEX study sought to determine whether the differential efficacy of PrEP in MSM versus transgender women was a result of different baseline clinical and behavioural factors that could make PrEP less efficacious in transgender women.[16] The authors found that baseline characteristics between MSM and transgender women explained almost 100% of the difference in PrEP's efficacy during the iPrEX study.[17] However, the authors were not able to comment on whether the use of gender-affirming hormone therapy[19] (may have contributed to PrEP's being less effective in the transgender women study participants.[17]

Oestrogen, which is used as part of gender-affirming hormone therapy, increases the activity of 5'-nucleotidase enzymes and can decrease the active metabolites of tenofovir and emtricitabine, or increase the nucleotides that compete against the active metabolites of tenofovir and emtricitabine within cells. Therefore, oestrogen could plausibly reduce cellular levels of tenofovir and emtricitabine in transgender women, making PrEP less efficacious. There have been some small studies in transgender women taking gender-affirming hormone therapyand PrEP. One study of 20 Thai transgender women commencing gender-affirming hormone therapyand PrEP showed a 12% reduction in plasma tenofovir levels in the presence of gender-affirming hormone therapy,[20] although PrEP did not reduce oestrogen levels.

In another study, 31% lower levels of plasma tenofovir were observed in 8 transgender women taking gender-affirming hormone therapy compared to eight cis-gender men; plasma emtricitabine was also significantly lower in the transgender study participants.[19] A further study compared the rectal tissue levels of the active metabolites of tenofovir and emtricitabine in 4 HIV-positive transgender women taking gender-affirming hormone therapy versus 4 HIV-positive post-menopausal cis-gender women. This study reported that there was a significantly lower ratio of the active metabolite of tenofovir diphosphate to its competing nucleotide dATP in the rectal tissue of the transgender versus cis-gender participants.[21] However, this study did not find a decrease in the ratio of the active metabolite emtricitabine triphosphate to its competing nucleotide, dCTP. Further larger pharmacological studies are needed urgently to determine whether gender-affirming hormone therapy reduces the levels of tenofovir disoproxil* and emtricitabine (TD*/FTC), or vice versa in transgender women.

The consensus of the authors writing this New Zealand commentary is that PrEP can be used when clinically appropriate for transgender women on gender-affirming hormone therapy.

As noted, in a post-hoc analysis of transgender women in the iPrEX study, no HIV infections were observed in transgender women whose blood levels were compatible with taking 4 or more doses of PrEP weekly.[18] Therefore, supporting transgender women to optimise their PrEP adherence is important until larger studies have determined whether gender-affirming hormone therapy reduces levels of TD*/FTC in transgender

women taking gender-affirming hormone therapy. To help support transgender women to optimise their PrEP use and adherence, it is recommended that health practitioners provide gender-affirming care.[22] Such clinical care includes appropriate use of preferred pronouns and names, safe access to bathrooms of choice and appropriate treatment and referral for hormone therapy and surgery.[22]

Transgender men

There are very few data regarding PrEP knowledge, acceptability and use in transgender men. Nor are there data regarding whether gender-affirming hormone therapy influences PrEP drug levels or vice versa in transgender men. A 2016 review of HIV and STI research undertaken in transgender men was unable to find any data on the use of PrEP in transgender men.[23] In a 2017 study of 181 transgender youth from the USA, of 42 people identifying as transgender men (23.2%), only 16 had ever used HIV prevention services and none had ever used PrEP.[24] Transgender men were significantly less likely to have ever used PrEP than transgender women.[24] To optimise HIV prevention and PrEP use, clinicians caring for transgender men need to actively raise PrEP as an HIV prevention option for them and take a sensitive and detailed sexual behaviour. Gender-affirming care should be provided to transgender men by health practitioners.

Social stigmatisation and discrimination, including within the healthcare system, is a barrier to accessing health services and contributes to adverse outcomes. Transgender people have the right to respectful health care.[25]

Clinicians should take steps to create a welcoming environment for their trans and gender-diverse patients. This approach includes considering the clinical environment, using the right language, asking the right questions and sensitively recording medical notes. Some helpful resources for clinicians are:

- Trans Hub
  www.transhub.org.au/clinicians
- Gender Minorities Aoteroa
  https://genderminorities.com/database/medical-surgical/providers/ and
  https://genderminorities.com/wp-content/uploads/2016/06/a-third-opinion-pamphlet.pdf
- Rainbow Mental Health
  http://rainbowmentalhealth.nz/
- Trans and gender diverse language guide
  https://www.acon.org.au/wp-content/uploads/2019/07/TGD_Language-Guide.pdf

People taking PrEP during conception, pregnancy and breastfeeding whose partners are not virologically suppressed

Conception in serodiscordant couples

People without HIV infection who have sexual partners with documented HIV infection are at 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 with their patients the available information about the potential risks and benefits of PrEP in these circumstances.[26] For people wanting to conceive where their HIV-positive male partner is stably virologically suppressed on combination antiretroviral therapy (cART), PrEP can still be offered to the patient if they express concerns about the risk of acquiring HIV in this setting. In this case the patient would need to self-fund PrEP.

Pregnancy

The risk of acquiring HIV increases by approximately two-fold during pregnancy.[27] In addition, if HIV infection is acquired during pregnancy there is a higher risk of HIV transmission to the infant than if the pregnancy occurred during chronic HIV infection because the HIV viral load is much higher during acute HIV infection.

The current evidence suggests that PrEP can be used safely during pregnancy and breastfeeding.[28]

The use of TD*-containing regimens by HIV-positive cis-women throughout pregnancy has not been associated with adverse pregnancy outcomes, but lowered bone mineral density (BMD) has been observed in newborns exposed to TD* in utero[29] as has a lower length and head circumference at one year of age.[30]

In the Partners PrEP study, which compared the efficacy of combination tenofovir disoproxil fumarate and emtricitabine (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 cis-women who received TDF or TDF/FTC versus placebo PrEP.[31] However, the authors noted that the confidence intervals for these findings were wide and therefore definitive statements about the safety of TDF/FTC as PrEP during pregnancy for cis-women could not be made based on this study's findings. A subsequent study from this group examined the pregnancy outcomes of 30 cis-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 2 groups.[32]

The World Health Organization (WHO) has included PrEP as an HIV-prevention strategy during pregnancy[33] and a number of other jurisdictions recommend PrEP for safe conception and for use during pregnancy and breastfeeding.[34]

Some people with HIV-positive partners may prefer to continue PrEP while pregnant, due to the increased risk of acquisition of HIV if their partners are not virologically supressed during pregnancy.[34]

Providers should discuss with their patients available information on potential adverse pregnancy outcomes when beginning or continuing PrEP during pregnancy so that they can make an informed decision. It should be noted that TD* is classified as category B3 by the Australian Therapeutic Goods Administration (TGA),[35] meaning that, to date, tenofovir has been taken by only a limited number of pregnant cis-women and cis-women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. However, studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The consensus of the authors writing this New Zealand commentary is that PrEP may be continued during pregnancy in people at risk for HIV acquisition.

Breastfeeding

Although experience with PrEP during breastfeeding is lacking, there is substantial experience with the use of TD*/FTC during the breastfeeding period by HIV-positive cis-women taking TD*/FTC-based antiretroviral therapy. TD* and FTC are secreted in breast milk, although at much lower concentrations (0.03% and 2%, respectively) than the levels achieved with the doses recommended for the treatment of infants with HIV infection.[36] In the PrEP setting, a study evaluating antiretroviral excretion in breast milk and infant absorption suggests PrEP can be safely used during breastfeeding with minimal infant drug exposure.[37]

If a woman acquires HIV infection while she is 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 can be continued during breastfeeding in people at risk of HIV acquisition.

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

Patients with chronic active HBV infection

Both TD* and FTC are active against HIV and hepatitis B virus (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 NZ. Therefore, ongoing treatment with TD*/FTC may be especially indicated in people with active HBV infection who are also at risk of HIV acquisition.

Of note there are 2 case reports of patients who were receiving TD* for treatment of hepatitis B and who acquired HIV infection.[38] Plasma levels of tenofovir and prescription refills suggested that the patients' medication adherence was good. These guidelines recommend that people 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 people 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 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 before PrEP is prescribed, and at regular intervals (e.g. every 3–6 months) while taking PrEP.[39] 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 re-activation of HBV infection with the attendant risk of hepatic injury, and to minimise the possible risk of developing TD*-resistant HBV infection.[40] For these reasons, event-driven PrEP is contraindicated in patients with chronic hepatitis B infection.

If PrEP is no longer needed to prevent HIV infection in a patient with chronic hepatitis B, a separate determination should be made about whether the patient requires ongoing treatment for HBV infection. Acute flares resulting from the re-activation of HBV infection have been seen in those with and without HIV infection 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

Patients without HIV infection and with established chronic renal failure, e.g. with estimated glomerular filtration rate (eGFR) that is stably less than 60 mL/min/1.73 m^2 should not be prescribed PrEP. The only PrEP regimen proven effective to date and approved by the TGA is TD*/FTC, which is not indicated for those with chronic renal failure.[41] However, if a patient with chronic renal failure is at substantial risk of HIV, their condition should be discussed with specialists in the management of HIV and renal disease.

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 injecting 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 data discussed below on the safety and efficacy of daily PrEP taken by persons under 18 years of age, including the possibility of bone mineral density loss, and other toxicities among youth who are still growing. Data are also available about the safety of TD*/FTC when used in treatment regimens for young people with HIV infection.[42] The clinician and the patient may conclude that the short-term, proximal risk of acquiring HIV infection greatly outweighs any short-term, or as yet undetermined, long-term risk of PrEP toxicity. Clinicians are encouraged to seek expert advice in complex situations.

Adherence to PrEP in adolescents may be suboptimal: a PrEP demonstration program involving daily PrEP use for 18–22-year-old HIV-negative MSM reported that tenofovir diphosphate intracellular levels, a marker of cumulative TD* adherence, were consistent with good adherence peaking at 56% at month, but declining thereafter.[43] In another open-label 48-week study of 78 adolescent MSM commencing PrEP, Project PrEPare, highly protective levels of PrEP were observed in 54% of adolescents at week 4 but declined thereafter.[44]

Following this finding that PrEP levels declined markedly in these adolescent participants after the week 4 visit, the authors recommended that adolescents should be offered more frequent clinical monitoring to enhance their PrEP adherence. **The ASHM PrEP Guidelines Panel endorses this approach and encourages clinicians to work with adolescents taking PrEP to design an augmented clinical review schedule.**

In the Project PrEPare study, there was no observed elevation in serum creatinine levels and significant increases were observed in bone mineral density for the spine, hip and total body between baseline and week 48. However, there was a slight but statistically significant decline in the total body Z-score during this time, suggesting that bone growth may have been suboptimal in the study participants.[44] Although not observed in this study, higher levels of PrEP adherence as measured by red blood cells levels of tenofovir diphosphate have been associated with lower hip bone mineral density in adolescents.[45] Further research is needed to determine whether there is a long-term increased risk of bone fractures in young MSM who have had PrEP.

Globally until recently, regulatory approval of Truvada [tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC)] PrEP was limited to adults over 18 years of age. However, on 15 May 2018, the US Food and Drug

Administration (FDA), based on data from the Project PrEPare study discussed above, expanded its approval of Truvada as PrEP against HIV to include adolescents at risk weighing at least 35 kg.
PrEP use for prevention of HIV in adolescents has not been approved by the NZ Medicines and Medical Devices Safety Authority, Medsafe.[46] However, clinicians are able to prescribe PrEP off-label for adolescents. In this setting, a decision to prescribe PrEP for a person under 18 years of age should be made at the discretion of the prescriber and on the advice of a specialist. The prescriber is responsible for obtaining and documenting informed consent from their patient. Informed consent should take into account the risks and benefits of that treatment versus other available treatments or no treatment at all based on the individual circumstances.

Adolescents may obtain publicly funded PrEP with an off-label prescription, provided they meet the NZ Pharmaceutical Management Agency, PHARMAC, criteria.

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9. HIV non-occupational post-exposure prophylaxis and pre-exposure prophylaxis

In New Zealand (NZ), the decision to commence nPEP should be made according to the local health pathway for nPEP or on the advice of a local infectious diseases or sexual health specialist

People not receiving human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) who seek care within 72 hours after an isolated sexual or injection-related HIV exposure should be evaluated for the need for non-occupational post-exposure prophylaxis (nPEP). nPEP may also be considered where a person receiving PrEP reports being poorly adherent and seeks care within 72 hours after an HIV exposure.

The clinician should take a sexual history to differentiate isolated exposures from ongoing exposure. If the HIV exposure is isolated (e.g. an isolated condom failure, sexual assault), nPEP should be prescribed, but ongoing antiretroviral medication is not indicated after completion of the 28-day nPEP course.

If the person needs a 3-drug nPEP regimen, the nPEP should be prescribed initially and then the person should be supported to transition to PrEP. The decision to transition to PrEP is dependant upon:

- eligibility for PrEP (including a confirmatory negative human immunodeficiency virus (HIV) test result)
- the person's willingness to continue taking daily tenofovir disoproxil* and emtricitabine (TD*/FTC)
- the person's willingness to attend quarterly clinic visits while on PrEP.

For a person already using PrEP, a course of nPEP may be required if the PrEP user had a recent high-risk exposure (within 72 hours) and did not take PrEP during the period that the high-risk exposure occurred. The decision to recommence PrEP following a course of nPEP is dependent upon the person's ongoing eligibility for PrEP (including a negative HIV test result) and their willingness to continue taking daily TD*/ FTC.

If exposures are not isolated but ongoing, clinicians should consider offering PrEP immediately.

10. Improving medication adherence

Medication adherence is critical to achieving the maximum prevention benefit of pre-exposure prophylaxis (PrEP) and reducing the risk of selecting for a drug-resistant virus in the event of human immunodeficiency virus (HIV) acquisition.[1,2] In randomised, blinded, placebo-controlled trials of PrEP, adherence varied[1] and was lower among cis-gender women in some studies,[3,4] in transgender women[5] and young PrEP users.[6-8] PrEP adherence has generally been higher in more recent trials, open-label extensions and demonstration projects, particularly among men who have sex with men (MSM). These better adherence rates have been due to increasing knowledge about PrEP's efficacy and differing motivations for taking PrEP.[1,9-12]

Common reasons for non-adherence include a perceived low risk of acquiring HIV,[3,4,13] start-up symptoms[3,14-16] and concerns regarding long-term side-effects,[13,17] factors of daily life such as medication management,[18,19] perceived and enacted stigma due to being eligible for PrEP[19-22] and lack of social support from partners, family and friends.[19] Common challenges to PrEP adherence, particularly for MSM, are party drug and alcohol use.[18] Party drug use (at the event level) is known to increase the likelihood of missing a dose on the same as well as the next day, thus potentially affecting the efficacy of event-driven PrEP.[23] People with mental health disorders are also more likely to self-discontinue the use of PrEP.[24] Studies of adolescent MSM using PrEP have shown that approximately 55% of participants have evidence of high adherence at week 4, but adherence declines markedly after the first month.[7,8]

Patient education and adherence counselling focused on medication self-management are needed to support ongoing daily PrEP use (Box 10.1).

Box 10.1 Key components of medication-adherence counselling

Establish trust and bidirectional communication

Provide simple explanations and education on the following issues:

- Relationship of adherence to the efficacy of PrEP
- Medication dosage and schedule
- Management of common side-effects
- 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 (e.g. beepers, alarms widely available over the counter) to minimise forgotten doses
- Identify and address potential 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 factors
- Assess side-effects and provide advice on how to manage them.

Various approaches can be used to effectively support medication adherence.[25] These include:

- educating patients (including population groups other than MSM particularly women who may be considering PrEP) about the medications
- helping patients anticipate and manage side-effects
- helping patients establish dosing routines that fit with their work and social schedules
- providing reminder systems and tools such as pill boxes and electronic reminders
- addressing substance abuse or mental-health needs that may impede adherence
- arranging more frequent clinic visits for adolescents to enhance their adherence
- facilitating social and peer support, especially for women.

When initiating a PrEP regimen, clinicians need to educate patients about medication schedules (for daily or event-driven PrEP, that is, the use of PrEP before and after potential HIV exposures), how to commence taking PrEP and how to cease taking PrEP and what to do if they experience problems such as side-effects or missed doses. See chapter 6. Providing PrEP regarding specific recommendations about dealing with missed doses.

Medication adherence should be discussed at each visit when the PrEP script is provided to identify barriers to optimal PrEP adherence and develop appropriate management plans.

Emerging evidence that different dosing strategies can be effective provides an opportunity to offer flexibility, choice and convenience to patients who are benefiting from PrEP. Event-driven PrEP is now an option for cis-gender MSM in these revised ASHM PrEP guidelines and was recently endorsed in guidance from the World Health Organization[26] (see chapter 6. Providing PrEP). Event-driven PrEP could be considered for this group when taking daily medication is not acceptable, sex is infrequent or a person feels like they can plan their sexual activity. If patients choose to take event-driven PrEP, their behaviour and PrEP pill use patterns should be discussed at each visit, to help determine if they should perhaps switch to daily PrEP.

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.

In the context of discussing PrEP adherence, patients should be reminded about the need to be tested for HIV and sexually transmissible infections (STIs) every 3 months or earlier if required, due to perceived risks or symptoms.

The importance of using condoms to prevent STIs, or to help prevent HIV if PrEP adherence has been sub-optimal should be discussed with patients. To improve adherence and effectiveness of PrEP, patients should also be informed about how to stop taking PrEP and re-start it, so that they are prepared for these changes. See chapter 6. Providing PrEP regarding specific recommendations on starting and ceasing PrEP.

Clinicians may wish to explore and address other potential barriers to optimise PrEP use such as misconceptions about PrEP, behavioural factors (e.g. substance use), depression, partner violence and unstable housing. To improve adherence to their PrEP medication, some patients may need referral to mental health or social services, or peer-based support services provided by various organisations (e.g. services provided by New Zealand AIDS Foundation, Body Positive, Positive Women Inc, New Zealand Prostitutes Collective).

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11. Behavioural strategies to reduce risk

In the era of human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) and treatment as prevention, behavioural methods of risk reduction – including condom use, clean injecting equipment, HIV serosorting, strategic positioning, and negotiated safe practices with sexual partners– retain their importance in preventing HIV transmission (Box 11.1). However, some vulnerable people, particularly some cis-gender and transgender women, may be unable to effectively negotiate use of these prevention strategies, especially condoms, with their regular or casual partners. The initiation of PrEP is straightforward, but on occasion it may be appropriate to refer some particularly vulnerable people with complex needs to health professionals with expertise in HIV prevention and sexual health.

PrEP's efficacy relates directly to the patient's adherence to PrEP medication not to whether the patient is using condoms in tandem with PrEP.[1,2] People using PrEP should be supported with ongoing information about the role that condoms and other practices play in preventing HIV when PrEP adherence is sub-optimal as well as the role that condoms play in sexually transmissible infection (STI) prevention.

Box 11.1 Discussion points on behavioural reduction of HIV and STI risk.

Provide feedback on HIV risk factors identified during sexual and substance use history taking:
- Elicit barriers to, and facilitators of, consistent condom use and other safer sex and substance use practices
- Elicit barriers to, and facilitators of, reducing injecting drug use
- Discuss with patients the barriers to, and facilitators of, evidence-based drug treatment where indicated and requested.

Support risk-reduction efforts:
- Help patients identify one or two 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-judgmental manner:
- Acknowledge the effort required for behavioural change
- Reinforce success.

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

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12. How to access PrEP New Zealand

There are 3 ways to access HIV pre-exposure prophylaxis (PrEP) in New Zealand (NZ):

1. Publicly funded PrEP

For people eligible for publicly funded health care, PrEP will be funded provided that they meet the NZ Pharmaceutical Management Agency, PHARMAC, funding criteria for emtricitabine with tenofovir disoproxil. Any relevant prescriber can write a script for PrEP which can be taken to any pharmacy for dispensing. If PrEP is accessed in this way, a $5 co-payment at the pharmacy is made.

2. Private script for supply from pharmacy

Any doctor can write a private script for PrEP. The brand stocked in NZ is currently produced by Teva Pharma (New Zealand) Limited. Patients can have this script dispensed at a community pharmacy. The cost for a private script is higher than for publicly funded PrEP; depending on pharmacy mark-up, each bottle of 30 pills will cost approximately NZD$90-110. This option is generally used by people who are not eligible for publicly funded PrEP and who do not feel comfortable using personal importation.

3. Through personal importation

If a person is not eligible for publicly funded PrEP or finds the cost of purchasing PrEP locally too high, then another option is to purchase a generic version of the drug online from a reliable overseas supplier. A script from a clinician is still required before ordering online. There are multiple overseas suppliers who will supply PrEP for import into NZ at a range of costs. The Ending HIV website has more information on personal importation.

Tips for clinicians:

- Personal importation is legal, but not routine. It is recommended that patients are asked to sign a consent form acknowledging that they understand and accept the risks of importing generic PrEP from overseas. New Zealand's Medical Protection society has developed a patient consent form specifically for importing PrEP. You can contact them on 0800 225 5677 to obtain a copy of the form.
- Add "I am aware that this is to be imported from overseas" to the script to help prevent the shipment being delayed at the border.

13. Models of PrEP delivery in clinical practice

Since 2017, many sexual health specialists, general practitioners (GPs) and nurses in New Zealand (NZ) have been involved in making pre-exposure prophylaxis (PrEP) available through PrEP implementation studies and personal importation of medicine from overseas. Since 1 March 2018, combination tenofovir disoproxil* and emtricitabine (TD*/FTC) for HIV PrEP has been publicly funded by the NZ Pharmaceutical Management Agency, PHARMAC, and can now be initiated by any relevant prescriber including GPs and nurse practitioners.

Making PrEP easily accessible across the board to all New Zealanders requires clinicians to be aware of, and be competent and comfortable with, prescribing PrEP. The role of medical providers in primary care is instrumental to optimising PrEP access and use.

Below is a list of PrEP resources designed for clinicians to upskill their knowledge and skills in the provision of PrEP:

- Webinar on HIV PrEP for primary care: https://www.goodfellowunit.org/events/hiv-prep-update-primary-care
- Best Practice Advocacy Centre (BPAC) HIV-PrEP how-to guide: https://bpac.org.nz/2019/prep.aspx (some changes have occurred since publication)
- ASHM's Online Learning Module: HIV PrEP prescribing in general practice
- Ending HIV PrEP information for patients: https://www.endinghiv.org.nz/protect-test/protect/prep/
- NZ AIDS Foundation (NZAF) PrEP information for clinicians: https://www.nzaf.org.nz/prep-information-for-clinicians/

The prescription and provision of PrEP clinical and laboratory monitoring are straightforward for GPs and other clinicians. However some providers who are less experienced in serving populations at high risk of acquiring human immunodeficiency virus (HIV) and sexually transmissible infections (STIs) (e.g. men who have sex with men, transgender and gender-diverse people, Māori, people involved in sex work, people who have sex overseas in places of high HIV prevalence, people whose partners are at high risk for HIV and STIs, and people who inject drugs) may wish to consider establishing relationships with specialist colleagues experienced in HIV and sexual health medicine. HIV clinics and sexual health clinics can provide information and support if required and may be able to do so over the phone, using emails or via innovative communication technologies such as telehealth.

When starting PrEP services, providers should also establish:

- appropriate referral pathways to ensure that specific needs of PrEP users are adequately provided (e.g. regular HIV and STI testing, the management of chronic hepatitis B infection, treatment of hepatitis C and possible abnormal liver and kidney function – see chapter 5. Clinical assessment before starting PrEP for more details.

- communication with local pharmacies to ensure uninterrupted refills of PrEP scripts. Some community pharmacies do not keep the medication in reserve and would have to order it in. Same day order and delivery might not always be possible. Other pharmacies with higher client load requiring HIV medications will have PrEP medication in reserve. Many pharmacies also offer a delivery service. It is important for PrEP users to get their scripts renewed and filled before they completely run out of medication.

An important approach to successful PrEP implementation is to engage representatives from HIV community-based organisations working with relevant populations in the delivery of PrEP. Community-based organisations such as the NZAIDS Foundation and Body Positive can assist with PrEP promotion and education and, depending on their capacity, may also be able to assist with behavioural screening and adherence support. Similarly, support can be useful from community-based organisations working with culturally diverse communities to ensure equality of access to PrEP.

When embarking on PrEP prescribing, providers should also consider the capacity of their practices to accommodate new patients and maintain follow-up every 3 months while taking PrEP. Several approaches may be helpful in dealing with these changes to practice:

- Careful planning of clinic appointments to allow sufficient space for PrEP initiation and regular follow-up visits
- Where resources allow, automating most steps in the patient pathway, to reduce the patient registration-to-PrEP prescription time
- Task shifting including having clinical nurse specialists, or trained nurses with clinician supervision in charge of PrEP-related services where possible
- Developing systems and procedures for recording and monitoring PrEP use.

Clinical practices that are planning to build up their PrEP patient population can consider developing a customised communications plan for PrEP demand creation, including media channels and communication strategies which will be used to drive local PrEP awareness and use, with input from relevant local community-based organisations and sexual health services.

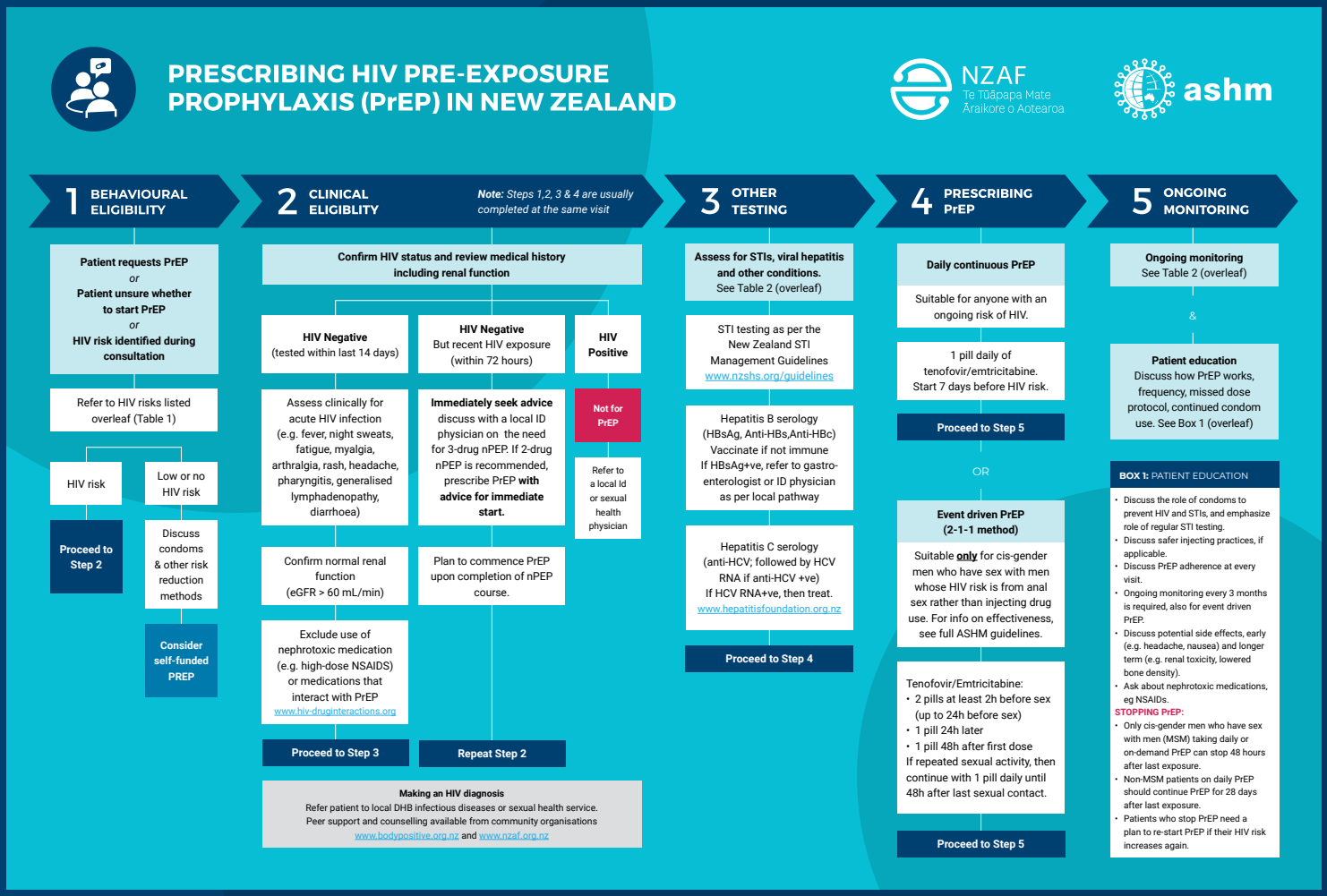
Lastly, if for relevant reasons a medical practitioner or clinic setting is not prescribing PrEP, provision should be made for people seeking PrEP or who are identified as likely to benefit from PrEP, to be efficiently directed to a local PrEP provider.

Appendix 1

PrEP Tool

For more information about PrEP: www.ashm.org.au/HIV/PrEP

Electronic version downloadable from: www.ashm.org.au/resources



Appendix 1

PrEP Tool

For more information about PrEP: www.ashm.org.au/HIV/PrEP

Electronic version downloadable from: www.ashm.org.au/resources

TABLE 1: HIV RISK

Men who have sex with men (MSM)	Trans & gender diverse people	Heterosexual people	People who inject drugs
High risk of HIV and eligible for funded PrEP 1. Likely to have multiple events of CLAI in the next 3 months; And having any one of the following: • At least one episode of receptive CLAI with one or more casual male partners in the last 3 months; • Rectal gonorrhoea, rectal chlamydia or infectious syphilis diagnosis during the last 3 months; • Methamphetamine use in the last 3 months OR 2. CLI with a regular HIV+ partner who is not on treatment and/or has a detectable viral load.		**High risk of HIV and eligible for funded PrEP** CLI with a regular HIV+ partner who is not on treatment and/or has a detectable viral load.	
Not eligible for funded PrEP; could consider self-funded PrEP Insertive CLAI with any casual male partner (in last 3 months or expected in next 3 months) Travelling to a high-HIV prevalence country and anticipates risk		**Not eligible for funded PrEP; could consider self-funded PrEP** Receptive CLI with any casual MSM partner (in last 3 months or expected in next 3 months) Travelling to a high-HIV prevalence country and anticipates risk	**Not eligible for funded PrEP; could consider self-funded PrEP** Shared injecting equipment with an HIV+ individual or with MSM of unknown HIV status (in last 3 months or expected in next 3 months)

CLI: Condomless intercourse; **MSM:** Men who have sex with men; **cis men:** assigned male at birth; **CLAI:** condomless anal intercourse

Notes on prescribing PrEP:

- Prescribe: Tenofovir 300mg + Emtricitabine 200mg (coformulated); 1 tablet daily for 90 days.
- Patient to be advised to commence PrEP within 14 days of negative HIV test. If there is no recent HIV test result, PrEP can be prescribed on the same day as an HIV test and patient advised to only start PrEP once informed the test is negative
- Apply for special authority, search for HIV prophylaxis on: https://www.pharmac.govt.nz
- Patients not eligible for PHARMAC funded PrEP can self-fund from a NZ pharmacy or can self import PrEP under the self importation scheme: www.endinghiv.org.nz/stay-safe/prep

TABLE 2: 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 Retest HIV if any doubt about window period for baseline HIV test. Can be done by giving client a lab form to do this and does not require a visit	Y	Y	N
Full blood count	Y	N	N	N	N
Phosphate	Y	N	N	N	Y Every 12 months
Urine analysis	Y	N	N	N	N
Assess side-effects	N	Y	Y	Y	N
Hepatitis A serology. Vaccinate if non-immune.	Y	N	N	N	N
Hepatitis B serology. Vaccinate if non-immune.	Y	N	Y (if not immune)	Y (if not immune)	Y If patient required hep B vaccine at baseline, confirm immune response to vaccination 1 month after last vaccine dose
Hepatitis C serology	Y	N	N	N	Y Every 12 months, or more frequently if ongoing risk e.g. non-sterile injecting drug use and MSM with sexual practices that predispose to anal trauma
Liver function tests	Y	N	N	N	Y Every 6 months
STI (i.e. syphilis, gonorrhoea, chlamydia) as per www.nzshs.org/guidelines	Y	N	Y	Y	N
eGFR at 3 months and then every 6 months	Y	N	Y	N	Y At least every 6 months or according to risk of chronic kidney disease
Urine protein:creatinine ratio (PCR) baseline	Y	N	Y	N	Y At least every 6 months
Pregnancy test (for people who may become pregnant)	Y	Y	Y	Y	N

Y: yes; **N:** no; **eGFR:** estimated glomerular filtration rate; **STI:** sexually transmissible infection; **MSM:** men who have sex with men

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

Appendix 2

Cockcroft–Gault formula
Basic formula [1]
eCrClCG=[[(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×eCrClCG (mL/min)÷BSA of the patient (m^2)
BSA (DuBois and DuBois formula [4])=(height (m) 0.725×weight (kg) 0.425)÷139.2

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Āraikore o Aotearoa