Title: Guidance for the Prescription of HIV Pre-Exposure Prophylaxis (PrEP) in Singapore

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Abstract (102 words)

Pre-exposure prophylaxis (PrEP) is a supplementary preventive measure against HIV. In recent years, trials involving PrEP have suggested that it may also be considered in specific groups as an additional strategy to prevent HIV infection. Recognising that physicians in Singapore may wish to prescribe PrEP for their patients, in May 2019, a PrEP Workgroup, convened by the National HIV Programme (NHVIP), met to develop guidance for physicians on how to do so. It is hoped that the development and dissemination of this guidance will be helpful for physicians who are keen to use PrEP as an additional tool to prevent HIV infection.

Keywords: PrEP, HIV, Pre-exposure prophylaxis

Introduction

Every year, approximately 1.7 million people are diagnosed with human immunodeficiency virus (HIV) infection (1). While the availability of highly active combination antiretroviral therapy (cART) has drastically improved the quality of life and life expectancy of people living with HIV(2), 690 000 people still died of acquired immunodeficiency syndrome (AIDS)-related illness across the globe in 2019 (1).

The number of new cases of HIV infection reported each year in Singapore remained fairly constant between 2008 and 2017, and ranged from 400-500 new cases annually (3). In 2018 and 2019, 313 and 323 cases of newly-diagnosed HIV respectively were notified to the National HIV Registry, which is nearly 30% fewer than the previous year (3, 4). This decrease is likely to be due to multiple factors, including ongoing campaigns focusing on conventional behavioural prevention strategies such as condom use, as well as biomedical strategies such as widespread use of highly effective cART for HIV-infected individuals for prevention of transmission.

HIV is primarily transmitted via sexual intercourse, exposure to infected blood or perinatal transmission. In Singapore, sexual intercourse is the main mode of transmission, with 95% of the cases diagnosed in 2018 acquiring HIV infection via sexual intercourse (3). HIV prevention strategies therefore include a combination of methods, including the national framework of "ABCD", which stands for: A (Abstinence), B (Be Faithful), C (Correct and Consistent condom use) and D (early Detection and treatment for viral suppression) (5). The most effective way to prevent HIV infection is to remain faithful to one's spouse/ partner and to avoid casual sex, and sex with sex workers. Persons engaging in high-risk sexual behaviour, such as having multiple sexual partners or engaging in casual or commercial sex, are strongly advised to use condoms to reduce their risk of HIV infection and other sexually transmitted infections (STI). Condoms should be used consistently and correctly during every sexual encounter.

Pre-exposure prophylaxis (PrEP) is a supplementary preventive measure against HIV. In recent years, trials involving PrEP have suggested that it may also be considered in specific groups as an additional strategy to prevent HIV infection. PrEP involves the use of anti-retroviral drugs (the combination of tenofovir disoproxil fumarate or TDF and emtricitabine or FTC, co-formulated as a single pill known as Truvada™ or bioequivalent generics) by HIV-negative individuals at high risk of acquiring HIV infection to prevent transmission and its use has been increasing worldwide.

Recognising that physicians in Singapore may wish to prescribe PrEP for their patients, in May 2019, a PrEP Workgroup, convened by the National HIV Programme (NHVIP), met to develop guidance for physicians on how to do so. The Workgroup consisted of clinicians and researchers with expertise in HIV, as well as representatives of community-based organisations involved in Singapore's HIV response and adopted a consensus decision making process. The Workgroup's guidance is an updated adaptation of current major international guidelines on PrEP from the World Health Organisation (WHO) (6), the US Centers for Disease Control and Prevention (CDC) (7), British HIV Association (BHIVA) (8), the Australasian Society for HIV Medicine (ASHM) (9), European AIDS Clinical Society (10) and the Taiwan AIDS Society (11), as well as a previous local guideline created by the PrEP taskforce in April 2018. The guidance aims to: assist clinicians in their evaluation of patients who are seeking PrEP; and assist clinicians in commencing and monitoring their patients on PrEP. It is hoped that the development and dissemination of this guidance will be helpful for physicians who are keen to use PrEP as an additional tool to prevent HIV infection.

Recommendations for the Use of PrEP in Singapore

Providers need to obtain and document the following important aspects of history-taking and discussion during their initial consultation with patients:

- Thorough sexual history including timing of last unprotected sex acts
- HIV and STI screens in the last year, and date of the last HIV test
- History of bone or renal disease
- Importance of 3-monthly HIV/STI screens
- Importance of taking TDF/FTC for PrEP as directed
- Options for source of TDF/FTC for PrEP
- Risk reduction including information and support for recreational drug use as appropriate

Prior to starting PrEP, all clients will need a baseline 4th generation HIV test to exclude HIV infection. The initiation of PrEP in the context of undiagnosed HIV infection puts an individual at risk of developing antiretroviral resistance. If they test positive for HIV, PrEP should not be started and they should be linked to care for HIV treatment instead. PrEP should also be stopped immediately if clients show early signs of HIV seroconversion while on PrEP.

Special Clinical Scenarios

There are certain clinical scenarios which physicians need to take note of when prescribing PrEP:

a. *Hepatitis B virus (HBV) infection*

TDF and FTC are both active against HIV and HBV infections. All individuals who test positive for the hepatitis B surface antigen (HBsAg) will need a baseline HBV DNA quantitative assay to determine the level of replication prior to starting PrEP(12). HBV DNA levels should be monitored 6-12 monthly in these cases.

As TDF and FTC can treat HBV infection, these individuals should be started on daily PrEP rather than on demand PrEP. It is important to emphasize adherence to the regimen to prevent reactivation of HBV infection with potential acute liver injury and to reduce the risk of developing TDF resistant HBV infection (13).

If PrEP is no longer required for HIV prevention, a clinical decision will have to be made on whether TDF is needed for treatment of HBV infection. While acute flares from reactivation of HBV infection have been seen in HIV-infected individuals who stop TDF and other medications used to treat HBV infection, similar flares have not been documented in individuals on PrEP (14, 15). Nevertheless, given the potential risk involved, these individuals should be monitored closely by an experienced clinician after stopping PrEP.

b. *Raised creatinine after starting PrEP*

TDF has been associated with increased renal toxicity and osteoporosis when used as regular treatment for people living in HIV(16, 17), but the same effect has not been seen in patients on PrEP. A metanalysis of 13 randomised trials comparing the use of TDF/FTC or TDF alone as PrEP versus placebo found no significant differences in risk of grade 3/4 clinical adverse events, bone or renal adverse outcomes (18). In cases where there was substantive decline (i.e. more than 25% of baseline) in the estimated glomerular filtration rate (eGFR),

cessation of PrEP resulted in normalization of the eGFR in almost all patients (19). However, there is no data concerning the use of PrEP for individuals with eGFR < 60ml/min. Hence, the use of PrEP should be stopped in individuals whose eGFR falls to <60ml/min.

c. *High Risk Exposures within 72 hours*

It is important to ensure that individuals are HIV negative prior to starting PrEP. In individuals who have high risk exposure within the last 72 hours, it may be appropriate to consider the use of post exposure prophylaxis (PEP) prior to the use of PrEP. As it takes up to 72 hours for HIV to be detected in regional lymph nodes and up to 5 days to be detected in blood, the use of PEP can help to prevent the acquisition of HIV infection following exposure by inhibiting viral replication (20). PEP is likely to be ineffective if started beyond 72 hours. In such cases, HIV testing should be repeated 4 weeks later to definitively exclude HIV infection. However, if the individual is keen to start PrEP immediately, HIV RNA viral load testing should be done to exclude acute HIV infection.

Table I: Who may be suitable for PrEP

Who may be suitable for PrEP?	Additional Considerations
Sexual partner of someone with HIV who is not on suppressive antiretroviral therapy	HIV viral suppression defined as plasma viral load <200 copies/mL for ≥ 6 months
Vaginal or anal intercourse without the consistent use of condoms with more than one partner in the last six months	If the high-risk exposure is after 72 hours but within 28 days of window period, HIV testing should be repeated after 4 weeks prior to starting PrEP. Alternatively, HIV RNA viral load can be done if patient is keen to start PrEP immediately.

Sexually transmitted infection in the last six months (laboratory confirmed, self-reported or received treatment)	Particularly syphilis
Received HIV post-exposure prophylaxis in the last six months	
Reported concerns about consistent use of condoms in the future	E.g. has difficulties using condoms
Engage in sexual activities under the influence of alcohol or other drugs	Or indicate that they may have such behaviour
Requesting for PrEP- case by case basis	E.g. left a monogamous partnership and will likely be having condomless sex in future

Table II: Contraindications to use of PrEP

Contraindications to use of PrEP
Known HIV infection
Clinical syndrome suggestive of acute HIV infection/HIV seroconversion
Known impairment of renal function (estimated creatinine clearance <60 ml/min)
Allergy or other known contraindication to any of the drugs in the PrEP regimen

Table III: How should PrEP be taken?

Methods	Suitable populations	Administration
Daily PrEP	All who have indications for PrEP	Daily dosing of co-formulated TDF/FTC

		<u>Starting PrEP:</u> Needs to be taken for 7 days before high levels of protection are achieved for both vaginal and rectal exposure to HIV.
On-Demand PrEP	Select populations only On-demand PrEP has only been investigated and is recommended in cis-gender men who have sex with men	A double dose (two tablets) of co-formulated TDF/FTC to be taken 2-24 hours before potential sexual exposure, to be followed by single doses 24 and 48 hours after the initial dose. When potential exposure is sustained for more than a 24-hour period, 1 tablet per day should be taken until the last exposure followed by the 2 post exposure tablets.

Table IV: What should be done at first consultation?

What should be done at first consultation?	Example	Additional Considerations
Ensure that patient is HIV-negative	Using a 4th generation HIV test (either routine HIV EIA (enzyme-linked immunoassay) **within the past 4 weeks** OR rapid point-of-care finger-	

	prick blood test **on the day of consultation** if no concern of recent exposure	
	If recent high-risk exposure (within the past 72 hours) consider PEP and re-test after 28 days	Consider Post Exposure Prophylaxis
	If high-risk exposure after 72 hours but within past 28 days, repeat HIV testing after 4 weeks	
	IF patient keen to initiate PrEP immediately consider HIV RNA (viral load) testing	
Baseline renal function testing	Serum creatinine	Estimated creatinine clearance can be calculated using the modified Cockcroft-Gault equation
	Urinalysis for proteinuria	Only for patients with pre-existing risk for renal impairment, e.g. diabetes, hypertension
Hepatitis B screening	Hepatitis B surface antigen (HBsAg) and antibody (anti-HBs)	Vaccination against hepatitis B should be offered to non-immune individuals. If patients test positive for hepatitis B, they should be considered for treatment and not be offered on-demand PrEP.
Offer Hepatitis C screening	Hepatitis C antibody (anti-HCV)	Referral for hepatitis C treatment if positive
	Syphilis screening	

Offer STI screening and treatment	Other bacterial STIs (gonorrhoea, chlamydia, etc)	At relevant and appropriate sites based on sexual history or consider three in one testing as per site availability (urethral, rectal, pharyngeal, etc)
Offer pregnancy screening	Urinary beta-HCG	Contraception should be discussed and provided for women who are on PrEP and who do not wish to become pregnant
Prescribe PrEP	Prescription should not exceed 3 months or 90 days with no automatic refills	A printed and endorsed prescription should be provided
Other services	Joint development of plan for effective PrEP use (including deciding on daily versus on-demand PrEP)	
	Vaccination against hepatitis A, B and human papillomavirus as indicated	
Counselling	Efficacy of PrEP	Key Message: PrEP is highly effective if taken as prescribed as part of an overall HIV prevention strategy (including the use of condoms)
	Adherence counselling	Key Message: It is important to take PrEP every day (for daily PrEP) and according to the schedule (for on-demand PrEP) for it to be effective.
	Engagement in care	Key Message: It is important to return for visits to get tested for HIV and assess for side effects to medication as

		well as to obtain new prescription so that PrEP is not interrupted.
	Sexual health counselling	Key Message: PrEP does not prevent other STIs, and regular testing and treatment for other STIs is needed to maintain sexual health. PrEP also does not prevent pregnancy and contraception should be used to prevent pregnancy if needed.

Table V: What should be done after PrEP is started?

What should be done after PrEP is started?	Tests/agenda to be done	Additional Considerations
Consider reviewing the patient at 4 weeks for the following, either in clinic or using telemedicine	Consider repeat HIV testing at 4 weeks via use of 4th generation HIV test (either routine HIV EIA or rapid point-of-care (POCT) finger-prick blood test	Especially if there are concerns about adherence to PrEP in the first 4 weeks or if there was a high-risk exposure 3 days or more prior to PrEP initiation
		Check for adherence to PrEP
		Confirm that daily OR on-demand regimens are being taken appropriately
		Check for side-effects

Review 3-6 monthly thereafter	$3^{rd}/4^{th}$ generation HIV test (either routine HIV EIA OR rapid POCT finger-prick blood test) 3 monthly	
	Serum Creatinine 12 monthly if <40 years old and/or eGFR ≥ 90ml/min 6 monthly if ≥40 years old and/or eGFR < 90ml/min	
	STI screening and treatment	Syphilis, gonorrhoea and chlamydia screening 3 – 6 monthly Frequency of screening depends on patient-reported sexual risk behaviour
	Anti-HCV 12 monthly Consider 3 monthly with very high-risk behaviour	For MSM and transgender women
	Urinary beta-HCG 3 monthly	
Prescribe PrEP	Prescription should not exceed 3 months or 90 days with no automatic refill	For patients obtaining medications from external sources, a printed and endorsed prescription should be provided

Other services	Vaccination against hepatitis A, B and human papillomavirus if not previously offered	
	Contraception for women on PrEP who do not wish to become pregnant	
Counselling	Adherence counselling	Reinforce Key Messages as outlined in Table 4
	Engagement in care	
	Sexual health counselling	
Assess if PrEP is still needed	The need for continued PrEP should be determined based on assessment of the patient's risk of HIV infection 12 monthly	Patients should continue taking daily PrEP for 28 days after the last sexual exposure putting them at risk of HIV infection before discontinuing PrEP. Only cis-gender MSM can safely stop PrEP after taking a dose 24 and 48 hours after last at-risk exposure.
Linkage to care for patients who seroconvert	All patients who test positive for HIV should be referred for treatment at a HIV care centre on an urgent basis	HIV-infected patients can be started on HIV treatment without interruption

Table VI: What should be done if PrEP is discontinued?

What should be done if PrEP is discontinued?	Tests/agenda to be done	Additional Considerations

Assess HIV status	HIV testing	
Hepatitis B testing and treatment considerations	Consider repeat HbsAg testing on planning to discontinue PrEP unless there is documented immunity	Patients who are HbsAg-positive and stop PrEP should have their liver function and hepatitis B viral load monitored after cessation of PrEP as there is a risk of reactivation of infection
Counselling	Advice on re-initiation of PrEP	Patients should be counselled that they should consider reinitiation of PrEP if the risk of HIV infection should become present again, e.g. - Entering a period of engaging in unprotected sex - Leaving a long-term relationship - Starting a serodiscordant relationship with a partner who is yet to be virally suppressed or with a partner of unknown HIV status - Other risk factors for HIV acquisition

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