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Guidance for the prescription of human immunodeficiency virus pre-exposure prophylaxis in Singapore

Chiaw Yee Choy[1,2], MBBS, MRCP, Chen Seong Wong[1,2,3], MBBS, MRCP, P Arun Kumar[2], MPH, BSc(Hons), Benson Yeo[4], MBBS, FAMS, Sumita Banerjee[5], MSc, Yangfa Leow[6], RSW, Dariusz Piotr Olszyna[7], MD, PhD, Kok Kuan Tan[8], MBBS, Rayner Kay Jin Tan[9], PhD, Jonathan Ti[10], MB, BCh, Roy Chan[4,5,9,11], MBBS, MRCP, Daniel Le[7], Chronos Kwok[5], BBus, Sophia Archuleta[2,3,7], MD, ABIM

[1]Department of Infectious Diseases, Tan Tock Seng Hospital, [2]National Centre for Infectious Diseases, [3]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, [4]National Skin Centre, [5]Action for AIDS, [6]Oogachaga, [7]Division of Infectious Diseases, National University Hospital, [8]Dr Tan Medical Center, Novena Medical Centre, [9]Saw Swee Hock School of Public Health, National University of Singapore, [10]Dr Tan & Partners @ Robertson Walk, [11]Department of Sexually Transmitted Infections Control Clinic, Singapore

Correspondence: Dr Chen Seong Wong, Consultant, National Centre for Infectious Diseases, 16 Jalan Tan Tock Seng, Singapore 308442. Chen_Seong_Wong@ncid.sg

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WHAT IS NEW IN THE GUIDANCE?

Special Clinical Scenarios

- Under raised creatinine after starting PrEP: new data pertaining to the safety of TDF/FTC has been added. TAF/FTC has also been added as a potential regimen for cis-gender men who have sex with men and trans-gender women who have sex with men with eGFR between 30ml/min and 60ml/min.
- Under hepatitis B virus infection: TAF/FTC has also been added as a potential regimen for cis-gender men who have sex with men and trans-gender women who have sex with men with eGFR between 30ml/min and 60ml/min and have chronic HBV infection.
- A new section entitled "Interpretation of HIV antigen-antibody test" has been added to aid PrEP prescribers on what to do in the setting of an indeterminate HIV antigen-antibody test.

Table II: Contraindications to PrEP

- Under known impairment of renal function, further clarifications have been made that PrEP is contraindicated in individuals with estimated creatinine clearance <60 ml/min who are considering TDF/FTC and estimated creatinine clearance < 30ml/min for individuals eligible for TAF/FTC.

Table III: How should PrEP be taken?

- The appropriate use of TAF/FTC has been included in this table.

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

- Under serum creatinine: repeat creatinine is only required for all individuals 1-3 months after starting PrEP. However, subsequent creatinine monitoring is only required at least annually for those with kidney related co-morbidities and age 50 years and above.
- Under anti HCV monitoring: changes have been made to include people who use drugs.

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] 680 000 people still died of acquired immunodeficiency syndrome (AIDS)-related illness across the globe in 2020.[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] There has since been a decreasing trend in the number of new cases since 2018, with 261 new cases being reported among Singapore residents in 2020.[3-5] 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. In addition, from 2020, the arrival of the COVID-19 pandemic has resulted in the implementation of a series of safe-distancing measures, which may have played a part in reducing the transmission of HIV infection.[6]

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 2020 acquiring HIV infection via sexual intercourse.[3,5] 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).[7] 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 tenofovir alafenamide or TAF and FTC, co-formulated as a single pill known as Descovy™ 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),[8] the US Centers for Disease Control and Prevention (CDC),[9] British HIV Association (BHIVA),[10] the Australasian Society for HIV Medicine (ASHM),[11] European AIDS Clinical Society[12] and the Taiwan AIDS Society,[13] 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 or TAF/FTC for PrEP as directed
- Options for source of TDF/FTC or TAF/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.

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.[14] 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.[15]

In 2020, the DISCOVER trial found that TAF/FTC is non-inferior to TDF/FTC for the prevention of HIV infection in adult cis-gender men who have sex with men and transgender women who have sex with men.[16] Similar to TDF, TAF can treat HBV infection and cis-gender men who have sex with men and transgender women who have chronic HBV infection starting on PrEP should be on the daily PrEP regimen rather than on demand PrEP.[17]

If PrEP is no longer required for HIV prevention, a clinical decision will have to be made on whether TDF or TAF 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.[18,19] Nevertheless, given the potential risk involved, these individuals should be monitored closely by an experienced clinician after stopping PrEP.

Raised creatinine after starting PrEP

TDF has been associated with increased renal toxicity and osteoporosis when used as regular treatment for people living with HIV,[20,21] 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.[22] 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.[23] In addition, a meta-analysis of global programme data found that <1% who were screened before starting oral PrEP had abnormal creatinine clearance levels and less than 3% of oral PrEP users experienced a decline in creatinine clearance to <60 mL/min. Older individuals, especially those over 50 years, with baseline creatinine clearance of <90 mL/min and with kidney-related comorbidities such as diabetes or hypertension, had a higher probability of declining to abnormal levels of

creatinine clearance.[8] Less than 1% of oral PrEP users younger than 30 years experience abnormal creatinine clearance.[8] In view of the above data, the population of individuals who require creatinine monitoring and the frequency of creatinine monitoring has been changed to better adapt the above findings (refer to table IV and V).

However, there is no data concerning the use of PrEP for individuals with eGFR < 60ml/min. Hence, the use of TDF should still be stopped in individuals whose eGFR falls to <60ml/min. For cis-gender men who have sex with men and trans-gender women who have sex with men with eGFR between 30ml/min and 60ml/min, there is now an option to use TAF/FTC instead.[24] As there is limited data on the use of TAF in patients with eGFR < 30mL/min, most international guidelines have advised avoiding the use of TAF in these patients.

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.[25] 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.

Interpretation of HIV antigen-antibody testing results

All individuals should have 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 a HIV antigen-antibody test returns as indeterminate, this could suggest very early HIV infection (i.e. acute HIV infection or HIV seroconversion) or a false positive result.[26] In these instances, a HIV RNA viral load may be considered and/or a repeat HIV antigen-antibody test. PrEP should NOT be started in these instances and physicians can consider making a referral to an infectious disease specialist for further evaluation.

Individuals with high-risk exposure who are non-adherent to the PrEP regimen are still at risk contracting HIV infection. However, HIV-1 seroconversion may be delayed while patient is partially compliant to PrEP.[27] Hence, an indeterminate HIV antigen-antibody test in these individuals should raise suspicions for possible HIV infection. These individuals should also stop PrEP to prevent development of potential resistance and referred to an infectious disease specialist from further evaluation.

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 (please refer to Special Clinical Scenarios section – Interpretation of HIV antigen-antibody testing results) - Known impairment of renal function (estimated creatinine clearance < 60 ml/min for individuals considering TDF/FTC and estimated creatinine clearance < 30ml/min for individuals eligible for TAF/FTC) - 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	- All individuals: daily dosing of co-formulated TDF/FTC - Cis-gender men who have sex with men and trans-gender women who have sex with men: these individuals can also use daily dosing of co-formulated TAF/FTC Note: - Needs to be taken for 7 days before high levels of protection are achieved for both vaginal and rectal exposure to HIV. - Alternative regimens such as taking PrEP four times a week is **not** recommended - TAF/FTC can be only be used in cis-gender men who have sex with men and trans-gender women who have sex with men as daily PrEP regimen.
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. Note: - TAF/FTC **cannot** be used in on-demand PrEP regimen

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	Lab based HIV 4th General EIA test is preferred
	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
Offer STI screening and treatment	Syphilis screening	
	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	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	3rd/4th generation HIV test (either routine HIV EIA OR rapid POCT finger-prick blood test) 3 monthly	
	Serum Creatinine All individuals should get a repeat creatinine 1-3 months after starting PrEP. In individuals younger than 50 years old without any co-morbidities, nil further creatinine monitoring is required if the repeat creatinine test is normal. Individuals with kidney related co-morbidities or age 50 years and above should have a repeat serum creatinine check at least once every 12 months.	For individuals with co-morbidities or 50 years and above with routine creatinine monitoring done in other settings, PrEP providers can consider using these results in their clinic review instead of obtaining a separate serum creatinine if appropriate.

	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	Especially for PrEP services provided to men who have sex with men and people who use drugs.
	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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