



衛生防護中心
Centre for Health Protection

**Interim statement on
HIV pre-exposure prophylaxis (PrEP)**

**Scientific Committee on AIDS and STI (SCAS)
Centre for Health Protection
Department of Health**



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Scientific Committee on AIDS and STI (SCAS)

has the following terms of reference :

- (a) to advise the Controller of the Centre for Health Protection (CHP) on the scientific basis for the prevention, care and control of HIV/AIDS and STI in Hong Kong;
- (b) to develop recommendations and guidance regarding HIV/AIDS and STI in Hong Kong; and
- (c) to keep under review local and international development of HIV/AIDS and STI.

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Interim statement on HIV pre-exposure prophylaxis (PrEP)

Background

In recent years, a number of randomised clinical trials have been completed overseas wherein antiretrovirals in various formats were evaluated for the prevention of HIV infection.^{1,2} Subjects ranged from men who have sex with men (MSM), heterosexual men and women, to people who inject drugs. Major antiretrovirals evaluated included coformulated tenofovir disoproxil fumarate / emtricitabine (TDF/FTC), oral tenofovir alone, tenofovir vaginal gel, and dapavirine vaginal ring. There are also ongoing studies of other antiretrovirals for prevention, including injectables and long acting agents. As preventive agents administered prior to exposure, they are collectively called pre-exposure prophylaxis (PrEP).

2. These trials of PrEP were conducted with HIV-negative subjects, and in the presence of a combination prevention package which typically comprised risk-reduction counselling, condom distribution, and regular screening for sexually transmitted infections (STI). These trials yielded results varying from being inefficacious to 86% of protection. Sub-analyses and open label extensions of some of these trials clarified factors of success and risks, and assessed behavioural change with more extended use.

¹ WHO (2015). Technical Update on pre-exposure prophylaxis
(Available at <http://www.who.int/hiv/pub/prep/prep-technical-update-2015/en/>. Accessed 2 Sep 2016)

² Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *AIDS* 2016;30:1973-83

Definition

3. As of today, oral TDF 300 mg / FTC 200 mg is the most extensively studied antiretroviral agent for PrEP. It is also the drug most often adopted in countries with PrEP programmes. In Hong Kong, patented TDF/FTC (Truvada®) is available, although its indication is limited to treatment of established HIV infection. Unless otherwise stated, PrEP in this statement will henceforth refer to the administration of oral TDF/FTC to HIV negative individuals for the sole purpose of preventing acquisition of HIV.

Translating research success into practice – anticipated benefits, risks and concerns

4. Success of PrEP in clinical trials has since reinvigorated research in prevention, and challenged care providers and policy makers alike to improve on existing HIV prevention methods. Its integration into standard medical practice is however not straightforward. Other than the obvious financial implication of such treatment, there are potential risks that have to be balanced against the anticipated benefit of HIV prevention.

5. PrEP works only if it is taken. In most of the clinical trials, the degree of success was highly dependent on the extent of adherence. In the iPrEX study, it was also shown by modeling that protection efficacy decreased from 96% at 4 doses per week to 76% at 2 doses per week.³ However, it cannot be overemphasised that there is no validated adherence threshold and full adherence should be the goal in clinical practice.

6. Adverse effects reported with PrEP are generally nonspecific and mild. However, creatinine was noted to be elevated and bone mineral density (BMD) decreased.⁴ In HIV infected patients, TDF/FTC is associated with

³ Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet* 2014;14:820-9

⁴ Mulligan K, Glidden DV, Anderson PL, et al. Effects of emtricitabine/tenofovir on bone mineral density in HIV-negative persons in a randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2015;61:572-80

lactic acidosis, liver steatosis and renal impairment including acute renal failure and Fanconi syndrome.⁵ The possibility therefore exists that clinically significant toxicity may occur after prolonged use, particularly in those who have preexisting impaired renal function or osteoporosis.

7. For those who are chronically infected with hepatitis B, potential hepatitis flare on drug discontinuation is also cause for concern. This is particularly detrimental to those with cirrhosis. In many studies of PrEP, subjects with chronic hepatitis B were excluded. Limited data of those who were put on PrEP suggested that it was safe,⁶ but more studies are certainly needed.

8. An increase in sexually transmitted infections (STI), indicative of risk compensation, has been observed among users of PrEP. In a meta-analysis of 18 cohort studies, occurrence of gonorrhoea, *Chlamydia trachomatis* infection and syphilis was found to be substantially increased (up to 45 times) for those MSM on PrEP.⁷ Its significance is three-fold. First, it portends that a rise in risk behaviour may occur with the use of PrEP. Second, untreated STI increases the infectiousness of HIV and therefore has to be expeditiously treated in order not to undermine the effectiveness of PrEP. Third, it highlights the status of PrEP as being an additional option in a full prevention package, rather than a stand-alone measure.

9. Other than suboptimal adherence, inappropriate prescription of PrEP for those who are already HIV infected is another cause of ‘breakthrough’ infection. In this case, undue delay in initiating PrEP after a negative HIV antibody test is the usual culprit.

⁵ Truvada® [package insert]. Hong Kong: Gilead Sciences;2014

⁶ Solomon MM, Schechter M, Liu AY, et al. The safety of tenofovir-emtricitabine for HIV pre-exposure prophylaxis (PrEP) in individuals with active hepatitis B. *J Acquir Immune Defic Syndr* 2016;71:281-6

⁷ Kojima N, Dabey DJ, Klausner JD. Pre-exposure prophylaxis for human immunodeficiency virus and sexually transmitted infection acquisition among men who have sex with men. *AIDS* 2016;30:2251-2

10. Not only is TDF/FTC alone inadequate treatment of established HIV infection, it results in archived drug resistance which limits future antiretroviral option. It is therefore important that clients be put on PrEP only in the presence of a very recent negative HIV test and in the absence of seroconversion symptoms. The client should continue to be monitored for HIV acquisition.

Potential role of PrEP in Hong Kong

11. Given the aforementioned limitations, it follows that PrEP should be targeted to selected populations at high risk of HIV infection. World Health Organization (WHO) makes the general recommendation that PrEP be offered as an additional prevention choice for people at substantial risk* of HIV infection.⁸

12. In Hong Kong, MSM as a broad population group currently carries the highest HIV incidence at an estimated 1.1%. Epidemiological data suggested that unprotected receptive anal sex, use of recreational drugs, and newly acquired syphilis in the previous six months are all risk factors for HIV transmission among MSM, implying the existence of substantial risk. Of note, a serodiscordant relationship does not necessarily imply high risk by itself. A landmark study has shown a 93% reduction in transmission when the infected index patient was put on treatment. Furthermore, no linked transmission occurred if viral load was suppressed.⁹

⁸ WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach (2nd edition) 2016. (Available at http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf. Accessed on 2nd Sep 2016)

⁹ Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med 2016;375:830-9

*WHO currently defines substantial risk as one reaching 3 per 100 person-years.

Interim principles of practice for PrEP

I. PrEP for individual protection should be considered only where there is a high and ongoing risk of HIV infection

13. The level of risk should be determined on a case-by-case basis and in the context of local epidemiology. In Hong Kong, MSM with a history of unprotected receptive anal sex, use of recreational drugs, especially methamphetamine, or acquisition of syphilis in the previous six months are considered to be at elevated risks.

14. The sexual practices should be carefully assessed to ascertain a high and ongoing risk. Reasons for high risk behaviour should be explored and counselling given where appropriate. The prospective client should understand the risks and limitations of PrEP as well as the extent of efficacy. This process of assessment should be repeated in subsequent visits.

15. It is imperative that pre-existing HIV infection be excluded before PrEP. Therefore, a recent (within 7 days) negative HIV test that uses the 4th generation ELISA Ag-Ab format should be available before initiation. The client should also be free of symptoms suggestive of HIV seroconversion. Where there is doubt, PrEP should be withheld until acute HIV infection can be definitively excluded with repeat tests. Until then, the client should be counselled to cease all HIV risk practices.

II. If prescribed, PrEP should be given daily and adherence carefully monitored

16. The vast majority of PrEP studies employed a once daily regimen. Although an intermittent regimen has been studied and reported to be efficacious (for example, one study required TDF/FTC to be taken at least 2 hours before sexual activity and continued for 48 hours afterward),¹⁰ it is still unclear how this relative complexity may affect adherence and if its efficacy

¹⁰ Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med* 2015;373:2237-46

can be generalised to community settings. Until more studies are available, a daily regimen is preferred.

17. Adherence, being the single most important factor of PrEP success, should be monitored by either pill count or at least client report. The client should be educated on its importance and advised to commit to it. Possible obstacles to adherence should be proactively addressed and side effects of PrEP quickly managed. A prescription of PrEP more than 3 months is generally not recommended. The drug should be discontinued when it is obvious that the client cannot adequately adhere to it. Clients on PrEP should be seen no less frequently than one month after initiation and every three months thereafter.

III. If prescribed, PrEP should be given as part of a comprehensive prevention package

18. PrEP is an additional option; it never supplants a comprehensive prevention package for those at risk. This has been previously addressed by this Committee.¹¹ One should also be aware that after initiation of PrEP, an undetermined lead time to full prevention efficacy exists.

19. A nonjudgemental approach to elicit behavioural risks and their reasons, followed by advice towards effective prevention may suffice for many clients without the need of PrEP. Even for those on PrEP, risk reduction counselling should be part and parcel of each client visit to determine if PrEP continues to be useful.

20. The use of recreational drugs, especially methamphetamine, has to be addressed by a harm reduction approach in which recourse should be made to community and professional services. While cessation of drug use should not be made a condition of prescribing PrEP, the clinician should carefully evaluate if PrEP can be properly adhered to by these clients.

¹¹ Scientific Committee on AIDS and STI, CHP, DH (2016). Recommended practice and principles of HIV clinical care in Hong Kong. (Available at http://www.chp.gov.hk/files/pdf/principles_and_practice_of_hiv_care_160816_v2.pdf. Accessed 2nd Sep 2016)

21. Likewise, screening and treatment of STI should be done regularly. Commonly co-transmitted with HIV are syphilis, gonorrhoea and *Chlamydia trachomatis* which should be routinely screened for and treated. Screening for sexually acquired hepatitis C may be considered. These STIs are indicators of risk behaviour as well as treatable infections. Knowledge of hepatitis B status is important for the reason that its treatment overlaps with that for HIV. Those clients who are susceptible to hepatitis B should be advised to receive vaccination.

IV. Client safety has to be protected

22. Truvada® is a prescription drug currently approved in Hong Kong only for treatment of adult HIV infection. It shall only be prescribed by registered medical practitioners in a medical care setting. Furthermore, its use as PrEP is off-label, a fact that should be made known to the prospective client. Both harm and benefit should be fully explained for informed decision. Prescribing physicians should monitor for all adverse drug reactions and are encouraged to report them to the Department of Health.¹²

23. Based on experience with HIV infected patients, TDF/FTC should not be given to subjects with estimated GFR <60 ml/min. GFR should be monitored by following the level of creatinine. Clients with factors of renal impairment such as old age, hypertension and diabetes will require full renal function tests and test for proteinuria.

24. Dual-energy x-ray absorptiometry (DXA) scan is not necessary for monitoring. However, for older patients with risk factors of osteoporosis, DXA scan may be considered. If a client were already known to have osteoporosis or a history of fragility fractures, PrEP should not be given.

25. Chronic hepatitis B infection is a relative contraindication of PrEP. Consultation with experts in this field should be sought for these patients for treatment and monitoring of hepatitis B, and the possible integration of PrEP

¹² Drug Office, Department of Health.
https://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/adr_reporting

into the overall management plan.

26. For various reasons, PrEP can fail. Clients should be educated on signs and symptoms of seroconversion. Routine and symptom-directed HIV testing should be performed. All who acquire HIV should be immediately referred to HIV specialists for evaluation and effective antiretroviral treatment.

27. The demand for safety should rightfully be high for an additional tool of HIV prevention such as PrEP. Client-delivered therapy for partner is not appropriate. Whenever in doubt, PrEP should not be prescribed until after consultation with HIV specialists.

V. Knowledge gap exists and should be addressed

28. Against the backdrop of a rising HIV epidemic, the arrival of a new tool of prevention is welcome news. Studies of PrEP have been extensive, covering clinical trials and increasingly implementation data. Many of them yielded positive results. It follows that selected clients who have high and ongoing risk could benefit from the addition of PrEP to his prevention package.

29. Before an effective public health approach for PrEP can be devised, however, the balance between cost and benefit, among others, has to be addressed. Theoretically, a favourable balance is more likely if PrEP successfully targets people at high risk and achieves high prevention effectiveness.

30. Towards this end, further studies are needed of acceptability and demand of PrEP among high risk groups, their willingness to pay and, above all, effective ways to reach the targeted population. Similarly, data from local studies and experience of implementation should be collected, especially in relation to the setting of delivery, adherence, safety, level of risk compensation and overall prevention effectiveness. As such experience accumulates, estimation of demand can be made and the appropriate model of PrEP delivery determined.

Conclusions

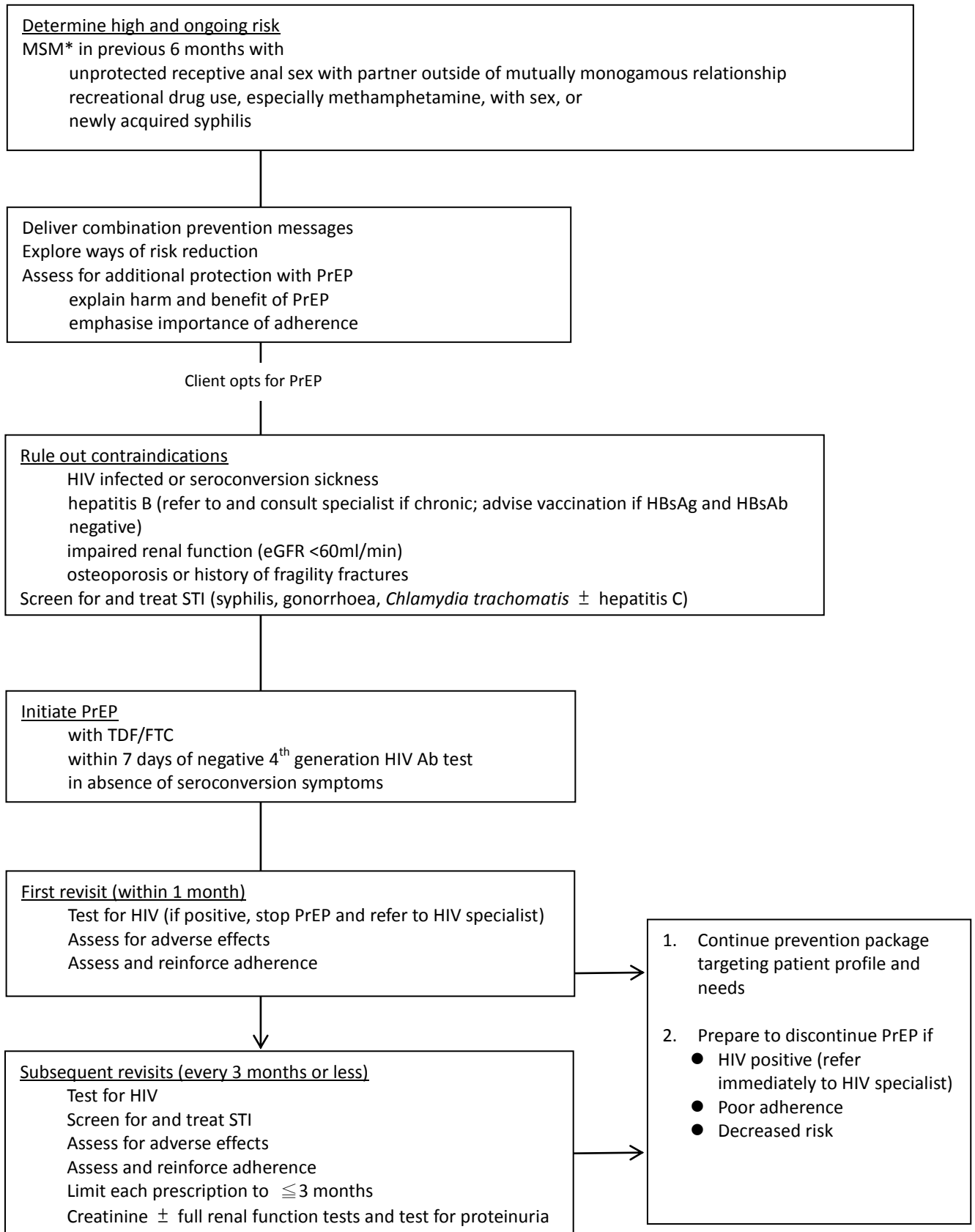
31. This Committee is highly encouraged by the progress made in HIV prevention. The addition of PrEP to the overall prevention effort has the potential to impact the epidemic itself. This statement affirms the role of PrEP for individual protection and is intended to provide guidance for safe and effective prescription of PrEP. A suggested clinical approach based on these recommendations is included in **Appendix**.

32. It is important to keep track of the continuing development of PrEP both locally and internationally. In particular, the overall epidemiological trend with its ever changing pattern of risk factors has to be monitored. Experience of implementation, especially in identifying and engaging people at high risk, is useful reference. On a global scale, the science of PrEP beyond TDF/FTC is progressing rapidly. New formats and agents of PrEP are expected in the near future. By addressing many of the concerns of using TDF/FTC, they may alter the landscape of considerations about PrEP and the very approach to using it.

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Appendix. Suggested clinical approach to using PrEP



*MSM, men who have sex with men