

Interim statement on HIV pre-exposure prophylaxis (PrEP)

(By Scientific Committee on AIDS and STI (SCAS) in December 2016)

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CME / CNE / PEM point accreditation (*please refer to the attached test paper for the number of credit points awarded*)

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).

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 ineffectual 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.

Definition

As of today, oral TDF/FTC 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

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.

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.

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 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.

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.

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.

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.

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

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

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

* 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

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.

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.

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

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

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

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.

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.

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.

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

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

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.

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.

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 into the overall management plan.

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.

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

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.

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.

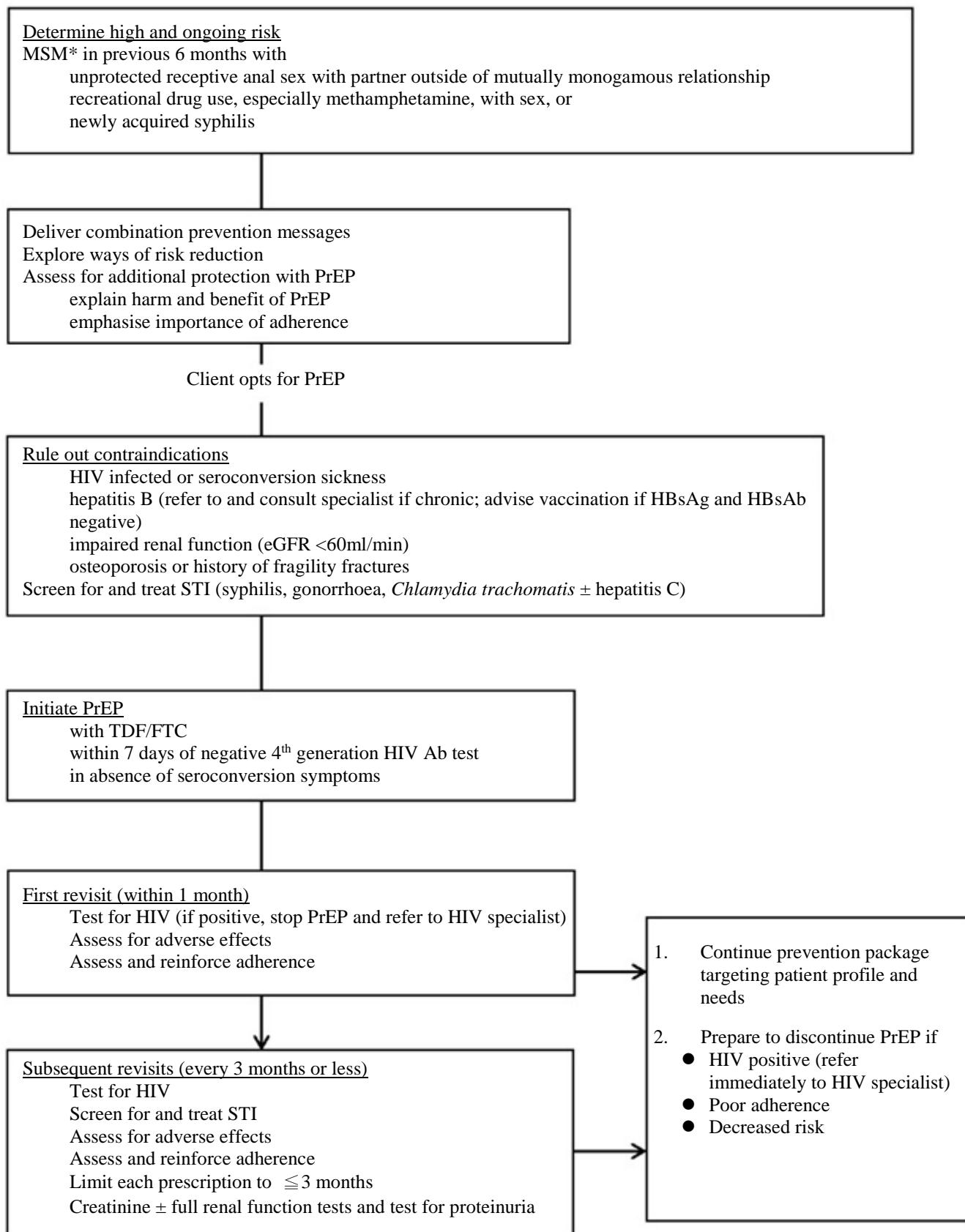
Towards this end, further studies are needed of acceptability and demand of PrEP among high risk groups, their willingness to pay and, above all, effective ways to reach the targeted population. Similarly, data from local studies and experience of implementation should be collected, especially in relation 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

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**.

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.

Appendix. Suggested clinical approach to using PrEP



*MSM, men who have sex with men

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Test paper

Interim statement on HIV pre-exposure prophylaxis (PrEP)

(By Scientific Committee on AIDS and STI (SCAS) in December 2016)

Expiration Date: 21 April 2018

CME point # / CNE point: 1 / PEM point: 1 (Healthcare related which contributes to the enhancement of professionalism of midwives/nurses)

- Please indicate one answer to each question.
- Answer these on the answer sheet and make submission by fax to Special Preventive Programme, Department of Health.

Please contact respective authorities directly for CME/CPD accreditation if it is not on listed below.

Accreditors	CME Point
Department of Health (for practising doctors who are not taking CME programme for specialists)	1
Anaesthesiologists	1
Community Medicine	1
Dental Surgeons	1
Emergency Medicine	1
Family Physicians	1
Obstetricians and Gynaecologists	1
Ophthalmologists	1
Orthopaedic Surgeons	1
Otorhinolaryngologists	pending
Paediatricians	pending
Pathologists	1
Physicians	0
Psychiatrists	1
Radiologists	1
Surgeons	1

1. Which of the following statements is true about clinical studies of PrEP
 - (a). Truvada (TDF/FTC) is the only drug shown to be effective as PrEP
 - (b). All randomised clinical trials so far have shown success
 - (c). PrEP has been shown to work for men who have sex with men but not people who inject drugs
 - (d). Combination prevention of HIV is delivered to both treatment and control groups
 - (e). PrEP confers more protection if given for a longer time
2. Which of the following has not shown effectiveness as pre-exposure prophylaxis against HIV
 - (a). Tenofovir alone
 - (b). Tenofovir vaginal gel
 - (c). Dapavirine vaginal ring
 - (d). Nonoxytol-9 spermicide
 - (e). All of the above have shown effectiveness
3. Which of the following is considered the most important factor contributing to the success or failure of PrEP
 - (a). Use of Truvada (TDF/FTC) versus tenofovir alone
 - (b). Adherence
 - (c). Behavioural compensation
 - (d). Underlying hepatitis B infection
 - (e). Underlying hepatitis C infection

4. Which of the following is NOT an adverse effect of Truvada (TDF/FTC)
 - (a). Fanconi syndrome and nephrotoxicity
 - (b). Decreased bone mineral density
 - (c). Flare of hepatitis B associated with discontinuation
 - (d). Dilated cardiomyopathy
 - (e). Lactic acidosis
5. The significance of risk behaviour compensation while on PrEP includes the following
 - (a). It may undermine the effectiveness of PrEP
 - (b). Sexually transmitted infections increase the infectiousness of acquired HIV
 - (c). Other prevention strategies continue to be necessary even if given PrEP
 - (d). Screening of sexually transmitted infections is necessary while on PrEP
 - (e). All of the above
6. The following absolutely contraindicates the use of Truvada (TDF/FTC) for PrEP
 - (a). eGFR >60 ml/min
 - (b). chronic hepatitis B infection
 - (c). HIV infection
 - (d). concomitant use of methamphetamine
 - (e). chronic hepatitis C infection
7. Which of the following is indicated in a follow up visit for PrEP using Truvada (TDF/FTC)
 - (a). Test for HIV
 - (b). Screen for and treat STI
 - (c). Assess and reinforce adherence
 - (d). Assess creatinine
 - (e). All of the above
8. The following are indications that PrEP with Truvada (TDF/FTC) should be stopped or changed, except
 - (a). Consistent and frequent use of amphetamine has prevented adherence to PrEP
 - (b). New occurrence of *Chlamydia* proctitis while on PrEP
 - (c). New occurrence of a positive HIV antibody test
 - (d). osteoporosis
 - (e). subject expects to be sexually inactive in coming months
9. All of the following is true regarding prescription of Truvada (TDF/FTC) as PrEP in Hong Kong, except
 - (a). Truvada (TDF/FTC) is a prescription drug and should only be prescribed by a registered medical practitioner in a health care setting
 - (b). Truvada (TDF/FTC) is not approved for PrEP in Hong Kong
 - (c). It should be prescribed only after a recent (<7 days) negative HIV test
 - (d). Each prescription of PrEP should be no less than 3 months to enhance adherence
 - (e). Daily rather than on-demand PrEP is preferred
10. Studies of PrEP are encouraged in Hong Kong for which of the following reasons
 - (a). To study ways to reach target population
 - (b). To study willingness to pay for PrEP
 - (c). To accumulate implementation experience
 - (d). To gauge extent of risk compensation
 - (e). All of the above