GUIDELINES

Southern African guidelines for the safe use of pre-exposure prophylaxis in men who have sex with men who are at risk for HIV infection

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Background. The use of oral antiretrovirals to prevent HIV infection among HIV-negative men who have sex with men (MSM) has been shown to be safe and efficacious. A large, randomised, placebo-controlled trial showed a 44% reduction in the incidence of HIV infection among MSM receiving a daily oral fixed-dose combination of tenofovir disoproxil fumarate and emtricitabine (Truvada) in combination with an HIV prevention package. Improved protection was seen with higher levels of adherence.

Aim. The purpose of this guideline is to: (*i*) explain what pre-exposure prophylaxis (PrEP) is; (*ii*) outline current indications for its use; (*iii*) outline steps for appropriate client selection; and (*iv*) provide guidance for monitoring and maintaining clients on PrEP.

Method. PrEP is indicated for HIV-negative MSM who are assessed to be at high risk for HIV acquisition and who are willing and motivated to use PrEP as part of a package of HIV prevention services (including condoms, lubrication, sexually transmitted infection (STI) management and risk reduction counselling).

Recommendations. HIV testing, estimation of creatinine clearance and STI and hepatitis B screening are recommended as baseline investigations. Daily oral Truvada, along with adherence support, can then be prescribed for eligible MSM. PrEP should not be given to MSM with abnormal renal function, nor to clients who are unmotivated to use PrEP as part of an HIV prevention package; nor should it be commenced during an acute viral illness. Three-monthly follow-up visits to assess tolerance, renal function, adherence and ongoing eligibility is recommended. Six-monthly STI screens and annual creatinine levels to estimate creatinine clearance are recommended. Hepatitis B vaccination should be provided to susceptible clients. Gastro-intestinal symptoms and weight loss are common side-effects, mostly experienced for the first 4 - 8 weeks after initiating PrEP. There is a risk of the development of antiretroviral resistance among those with undiagnosed acute HIV infection during PrEP initiation and among those with sub-optimal adherence who become HIV infected while on PrEP. Risk compensation (increasing sexual behaviours that can result in exposure to HIV) while on PrEP may become a concern, and clinicians should continue to support MSM clients to continue to use condoms, condom-compatible lubrication and practice safer sex. Research is ongoing to assess optimum dosing regimens, potential long-term effects and alternative PrEP medications. Recommendations for the use of PrEP among other at-risk individuals, and the components of these recommendations, will be informed by future evidence.

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Men who have sex with men (MSM) is a term that describes men who have sex with men, regardless of social identity (gay, bisexual, heterosexual) or whether they also have sex with women.[1] MSM have been shown to be at disproportionately high risk of HIV acquisition and transmission.[2,3] Biological susceptibility (efficiency of rectal HIV transmission), behaviours (including unprotected anal intercourse and multiple partners) as well as structural and social factors (including homophobia and discrimination) have been associated with increased vulnerability to HIV.[3] Unprotected receptive anal intercourse is the main risk factor for sexual transmission of HIV among MSM.[4] The high concentration of rectal cells vulnerable to HIV-1 infection (macrophages, T-cells and dendritic cells) and the single-cell layer of rectal mucosa, results in a per-act risk for HIV transmission that is 10 - 20 times greater than unprotected vaginal intercourse.[4-6]

MSM and HIV in southern Africa

There is emerging and consistent evidence about the high HIV burden among MSM in southern Africa.[7] HIV prevalence among MSM sampled in cross-sectional surveys in South Africa has ranged from 10 - 50%.[8-11] However, owing to the lack of accurate population size estimates, it is hard to assess attributable risk.[12] A 2009 modelling study on the modes of

HIV transmission in South Africa estimated that 8% of all new HIV infections in South Africa occur among MSM.[13] High-risk sexual practices (including unprotected anal intercourse, multiple and concurrent partnerships, and sex work) and limited knowledge about HIV and substance use (alcohol, methamphetamines and heroin) have been associated with increased risk for HIV infection among MSM in South Africa.[2,9-11,14-16] Many MSM also have female sexual partners. Almost half (49%) of the participants in a Soweto-based MSM study reported recent female sexual partners.[10] Homophobia, stigma and discrimination (including criminalisation of same-sex behaviours in some southern African countries), health care worker ignorance (about MSM vulnerability to HIV and appropriate management of MSM clients) and the heterosexual focus of the HIV response have been contributing factors to the failure of southern African public health services to address the health needs of MSM.[2,12,17-24]

The purpose of the MSM pre-exposure prophylaxis guideline is to:

- explain what pre-exposure prophylaxis (PrEP) is
- outline current indications for its use
- outline steps for appropriate client selection
- provide guidance to monitor and maintain clients using PrEP.

Pre-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) is the taking of a pharmaceutical agent prior to an exposure to prevent an outcome (e.g. infection by a microbe). PrEP for HIV utilises antiretroviral medications to prevent HIV infection. Research into the use of existing and novel PrEP agents, topical (microbicide) and oral (tablet) formulations is ongoing. In the Global iPrEx trial, PrEP was shown to decrease HIV incidence among at-risk MSM (see text box).[25] The results of this randomised placebo-controlled trial offer a new opportunity for HIV prevention. Truvada, the oral antiretroviral agent used in the iPrEx trial, is available for off-label use for PrEP in South Africa.

Development of PrEP

Truvada (tenofovir disoproxil fumarate (TDF) in combination with emtricitabine (FTC)) was chosen for the evaluation of pre-exposure prophylaxis because of its high level of activity in inhibiting HIV replication; its acceptable safety profile; its high barrier to generating resistant virus; and its low levels of side-effects.[26] The protective activity of TDF and FTC has been shown in animal models, with best efficacy when both agents were used together.[27,28] Several trials of daily oral TDF or TDF/FTC among heterosexual men and women have recently been completed. Additional trials with heterosexual women and injecting drug users are ongoing (http://www.avac.org/ht/a/GetDocumentAction/i/3113). The findings of the PrEP trials among heterosexual men and women have yielded differing efficacy results, with some showing efficacy among heterosexual sero-discordant couples receiving either TDF or TDF/FTC (Partners-PrEP) and among young men and women (TDF2) receiving TDF/FTC. One PrEP trial assessing the efficacy of daily oral TDF/FTC among women (FEM PrEP) was stopped for reasons of futility (the inability to determine efficacy), and the oral and topical tenofovir arms in the VOICE trial with women were stopped for futility while assesment of efficacy of daily oral TDF/FTC in the VOICE trial is continuing.[29-31] Research is under way to assess reasons for these differing results.

The global iPrEx trial

The global iPrEx trial was a double-blinded, randmised placebo-controlled trial to assess the safety and efficacy of daily oral Truvada for the prevention of HIV among MSM and transgender women. The subjects were 2 499 HIV-seronegative MSM or transgender women who have sex with men enrolled from 11 sites in 6 countries. The Cape Town site was initiated later than other sites, and only 88 MSM from South Africa were enrolled (3.5% of total cohort) before the study was fully enrolled. All subjects received monthly HIV testing, risk-reduction counselling, condoms and management of STIs. The study subjects were followed for 3 324 person-years (median 1.2 years, maximum 2.8 years)(until 1 May 2010). Of the subjects, 10 were infected with HIV at enrollment (in their 'window' period), and 100 became infected during follow-up (36 in the Truvada group and 64 in the placebo group). In the modified intent-to-treat analysis (excluding those who were infected at enrolment and those with no follow-up HIV test results), an overall 44% reduction in the incidence of HIV infection (95% confidence interval 15 - 63%; p=0.005) among those randomised to Truvada use was seen. An as-treated analysis showed that participants who reported taking the study drug at least 50% of the time, experienced 50% fewer infections. Participants who reported taking 90% or more of their daily doses, experienced an efficacy of 73%.[25]

Drug levels were assessed in a case-control analysis of a subset of trial participants. Each MSM who acquired HIV infection during the trial was matched with two MSM who remained uninfected. No drug was detected in participants in the placebo arm. Among participants in the Truvada arm, drug was detected in 22 of 43 participants without HIV infection (51%) and in 3 of 34 HIV-infected participants (9%) (p<0.001).[25]

Nausea and unintentional weight loss were reported more frequently during the first 4 weeks in the group receiving Truvada than in the placebo group (p<0.001). The two groups had similar rates of serious adverse events (p=0.57).[25]

Motivation for a MSM PrEP guideline

The iPrEx trial results contributed to the development of interim guidance on the use of PrEP among MSM by the United States Centers for Disease Control and Prevention.[32] Based on the results of the iPrEx and Partners PrEP trials, a submission to the United States' Food and Drug Administration is under consideration for expanding the indications for the use of Truvada to include the prevention of sexual acquisition of HIV among MSM and heterosexual adults. Truvada is not currently licensed for use as PrEP in South Africa. Southern African guidelines will assist practitioners who may be considering, or are already, prescribing PrEP to at-risk MSM clients. This guideline is based on current evidence, and future data will inform its revision and the potential extension of indications to other population groups.

Initiation of PrEP

Steps for the screening, initiation and maintenance of PrEP for MSM are shown in Fig. 1.

1. Identification of potential PrEP users

Providers should educate and counsel MSM clients about PrEP and conduct an individualised risk-benefit assessment to assess eligibility.

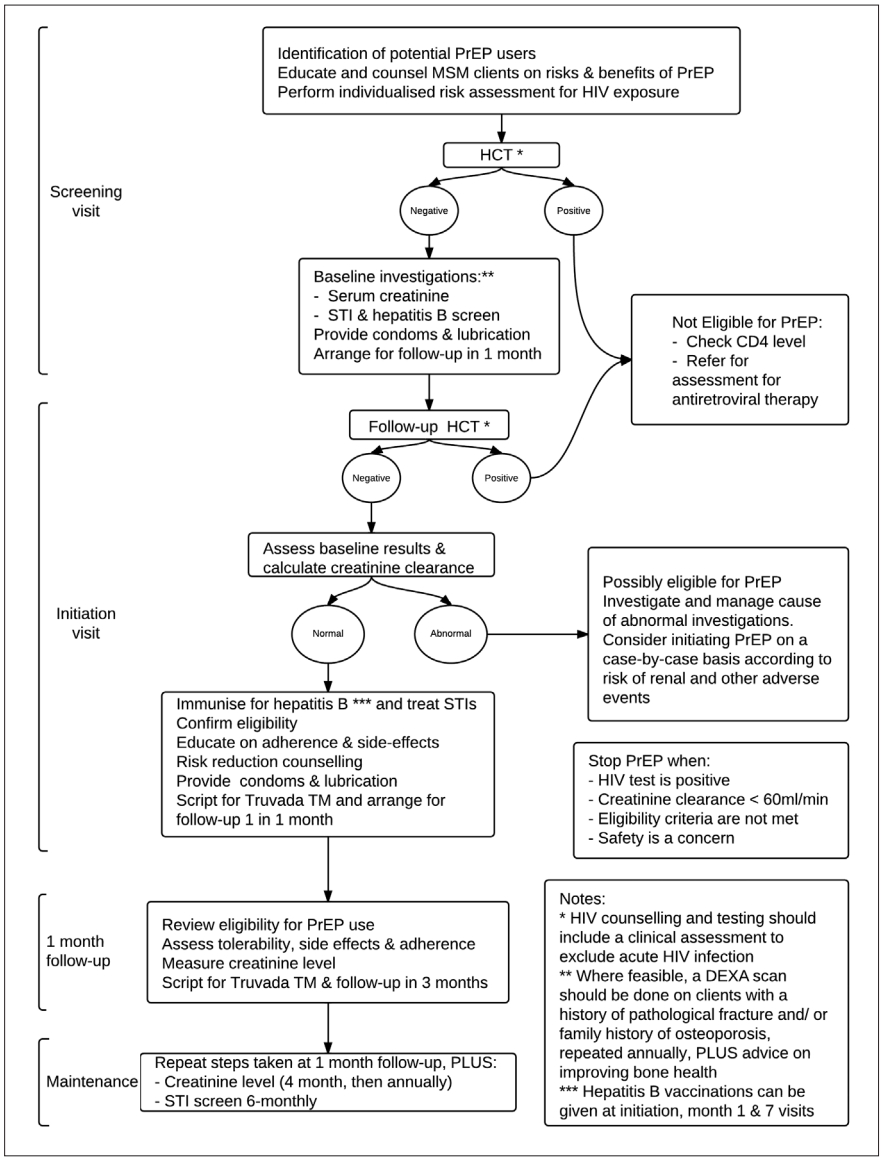

Fig. 1. Flowchart for the screening, initiation and maintenance of PrEP among MSM.

Eligibility criteria for PrEP use include:

- men who have sex with men (MSM) (including those who also have sex with women) who are identified by the provider and client as being at high risk for HIV exposure (see text box on Indications for the use of PrEP)
- no contra-indications to Truvada (FTC/TDF)
- HIV-negative by routine rapid antibody test
- absence of symptoms of acute HIV infection (recent acute viral illness) and, if symptoms reported, HIV-negative by 4th-generation HIV test or other HIV antigen test if available (this reduces, but doesn't eliminate, the window period)
- motivated to follow PrEP prescribing guidelines
- willing and able to adhere to daily oral dosing†
- willing and able to attend 3-monthly PrEP maintenance visits, inclusive of HIV counselling and testing, clinical review and safety monitoring procedures
- client understanding that the protection provided by PrEP is not complete, and of the need for PrEP to be used as part of a package of HIV prevention services (inclusive of condoms, lubrication, risk reduction counselling and STI management)

2. Baseline investigations

After documenting eligibility and motivation for PrEP use, mandatory baseline investigations should be completed (Table 1). If resources permit, a DEXA scan to measure bone mineral density among individuals who report a history of pathologic fracture or a family history of osteoporosis should be considered. Unavailability or inability to cover the costs of a DEXA scan should not preclude PrEP use. Condoms and condom-compatible lubrication should be provided, and arrangements for follow-up made.

Indications for the use of PrEP

PrEP may be suitable for MSM who:

- engage in anal sex and are HIV uninfected
- are at high risk for HIV acquisition
  - MSM with multiple partners
  - MSM engaging in transactional sex, including sex workers
  - MSM who use or abuse drugs
  - MSM who drink alcohol heavily
  - More than 1 episode of a STI in the last year
  - Couples‡
    - HIV-negative partner in a discordant relationship, especially if the positive partner is not on antiretroviral therapy (ART)
    - Both partners HIV negative in a non-monogamous concordant relationship
  - MSM who are unable or unwilling to achieve consistent use of male condoms
- are motivated, able and willing to adhere to daily oral dosing.

Contraindications for PrEP:

HIV-1 infected or evidence of possible acute HIV infection

- allergy to tenofovir disoproxil fumarate and/or emtricitabine
- poor renal function (estimated creatinine clearance <60ml/min)
- unwilling or unable to return for 3-monthly HIV testing, counselling and safety monitoring visits.

3. Implementing PrEP

At the follow-up visit, repeat the rapid HIV test and do a review for acute viral symptoms. Review results from baseline investigations and confirm that estimated creatinine clearance >60 ml/min. Commence hepatitis B vaccination if susceptible and provide STI treatment as required (Table 2). Educate

†Therapeutic drug monitoring is currently not routine, although methods that require less invasive procedures, such as measuring drug levels in hair, are being validated.
‡Couples in this instance refers to men who have had sex with each other more than once.

Table 1. Mandatory baseline investigations for PrEP initiation among MSM

HIV infection	Rapid HIV antibody test
Renal function	Estimated creatinine clearance (ml/min) (formula for males) $\frac{(140 - \text{age in years}) \times \text{weight (kg)}}{0.82 \times \text{plasma creatinine (µmol/l)}}$
Hepatitis B screen	Surface antigen (HBsAg) Antibody to surface antigen (HBsAb)
STI screen	Symptomatic screen Examination if indicated Urine dipstix for urethritis Serological screening for syphilis (rapid or laboratory)

the client about potential PrEP side-effects and their management, as well as signs and symptoms of acute HIV infection (and need to return for 'urgent' HIV testing). Initiate a medication adherence plan and provide a 1-month Truvada prescription (1 tablet orally, daily) together with a 1-month follow-up date (Table 3).

Risk-reduction counselling

Risk-reduction counselling is a behavioural intervention that attempts to decrease an individual's chances of acquiring HIV and other STIs,[33] and should be implemented together with adherence counselling at follow-up visits for clients using PrEP. The main objective of risk-reduction counselling is for clients to set a realistic goal for behaviour change that could reduce their risk of contracting HIV. This is most effective when it is non-prejudicial and client-centred. Risk reduction counselling can be provided by any trained healthcare provider and should address the following points:

1. Explore the context of the user's specific sexual practices, and assist client to recognise which of their behaviours are associated with higher risks for HIV infection. Clinicians should also be aware that clients may not always perceive their own risk, or be in denial about it.
2. Identify the sexual health protection needs of the user and reflect on what their main concerns appear to be.
3. Strategise with the user on how they can manage these concerns or needs.
4. Agree on which strategies the user is willing to explore and guide the user to decide on how to implement the strategy.

Adherence support

Adherence to daily PrEP medication, as shown in the iPrEx study and other PrEP trials, is a challenge. Adherence counselling should be implemented at each visit where PrEP prescriptions or distributions are made. In iPrEx, MSM who took PrEP more consistently and had evidence of drug detection in their blood, had higher levels of protection than those who did not.[25]

Clients will need to be made aware of the fact that drugs only work if present at adequate levels in tissues and, preferably, drug levels should be adequate before and after exposure to HIV has occurred.

The use of cell phone reminders, pill boxes, and linking pill taking with a daily routine activity are currently being evaluated for their impact on improving PrEP adherence. Clinicians and clients could use any of these or other strategies to assist in maximising adherence (see text box on Tips to Support Adherence). Any trained healthcare worker can implement adherence counselling. A client-centred approach is recommended. Drug level testing for tenofovir levels in plasma is available, but is expensive. Drug level testing may be useful to assess adherence in the future.

Tips to support adherence

Include patient-focused adherence counselling at each contact. Provide a clear explanation of the benefits of adherence. In a neutral manner, ask if the client has any challenges that may make adherence difficult. Also explore possible facilitators to pill taking. Include identified facilitators when developing strategies to improve adherence.[34]

Options to improve daily pill taking:

- use reminders (cell phone, alarm clock, diary, partner reminder)
- link with daily activity (breakfast, brushing teeth)
- use of a pill box.

Strategies to reduce likelihood of antiretroviral resistance

Feasibly exclude acute HIV infection before initiating PrEP by:

- conducting antibody HIV testing before commencing or represcribing PrEP
- among persons with a negative antibody HIV test, conduct a clinical screen to detect signs and symptoms of acute HIV infection – history of fever, sore throat, rash, joint pain, cough in the past month and a targeted examination (temperature, ENT and skin exam)(see Acute HIV infection text box)
- If symptoms or signs of acute HIV infection found:
  - at screening: postpone PrEP until symptoms subside and rapid antibody test remains negative
  - at screening: do not initiate PrEP until confirmatory HIV antigen/antibody testing complete*
  - at follow-up: may elect to continue PrEP while awaiting results of confirmatory HIV antigen/antibody testing or may decide to withhold PrEP until confirmatory tests available
- support client to maximise adherence and include adherence counselling at each visit
- stop PrEP should requirements for PrEP eligibility not be fulfilled.

*Use 4th-generation HIV rapid (antigen+antibody) tests where available to confirm HIV infection status.

Table 2. Syndromic treatment of STIs among MSM

Urethritis	Cefixime 400 mg PO stat, **plus** doxycycline 100 mg PO 12-hourly for 7 days. If symptoms persist after 7 days and repeat exposure and poor adherence are excluded, give metronidazole 2g PO stat. If still symptomatic after a further 7 days, refer.
Genital ulcers	Benzathine penicillin 2.4 million units IM stat for primary syphilis (repeat benzathine penicillin x 2, at weekly intervals for late syphilis), **plus** erythromycin 500 mg PO 6-hourly for 7 days **and** acyclovir 400 mg PO 8-hourly for 7 days
Rectal discharge/proctitis	Cefixime 400 mg PO stat (or ceftriaxone 250mg IMI stat) **plus** doxycycline 100 mg 12-hourly for 7 days (also screen for syphilis and consider acyclovir if any suggestion of ulcerative anal disease).

Table 3. Summary of PrEP visits and procedures

Visit	Recommended procedures
Screening visit	Educate about the risks and benefits of PrEP Assess eligibility and motivation Conduct HIV counselling and testing, serum creatinine level and STI and hepatitis screen Arrange follow-up
PrEP initiation visit	Conduct HIV counselling and testing Confirm eligibility (including investigation results and a calculation of creatinine clearance) Commence hepatitis B immunisation (if indicated) Provide STI treatment (if indicated) Educate client about PrEP side effects and their management Educate client about signs and symptoms of acute HIV infection Discuss behaviours that promote bone health, such as weight-bearing exercise, maintaining adequate calcium and vitamin D intake, and avoiding alcohol, tobacco and recreational drugs Initiate a medication adherence plan Provide condoms and lubricant Provide 1-month Truvada prescription and 1-month follow-up date
1-month follow-up	Same as PrEP initiation visit, plus: assess tolerability, side-effects and adherence measure serum creatinine and calculate creatinine clearance provide 3-month Truvada prescription and follow-up date
4-month follow-up and maintenance	Repeat procedures done at 1-month follow-up Measure serum creatinine and calculate creatinine clearance at 4-month follow-up, and annually thereafter Conduct 6-monthly STI screen for urethritis, genital ulcers and proctitis, including urine dipstix and rapid syphilis test Complete hepatitis B immunisation

Managing abnormal screening results

Clients with abnormal renal function (estimated creatinine clearance <60 ml/min) should not be placed on PrEP. An abnormal estimated creatinine clearance result could be rechecked after 2 weeks and, if renal function returns to normal and other PrEP criteria are met, PrEP may be initiated. MSM who are susceptible to hepatitis B should be immunised.* Clients with a history of pathological bone fracture, a family history of osteoporosis, or decreased bone mineral density on DEXA scanning, should be educated on ways to improve bone health, such as weight-bearing exercise, maintaining adequate calcium and vitamin D intake, and avoiding alcohol, tobacco and recreational drugs.[35] MSM who are ineligible for PrEP require support to assess other prevention options (see HIV Prevention for MSM text box). Treat STIs syndromically as per national guidelines (Table 2).[36] MSM who test HIV positive should be clinically staged, have a CD4 count taken and be managed in line with HIV treatment guidelines (http://www.sahivsoc.org/practise-guidelines/national-dept-of-health-guidelines).

Safety monitoring and maintenance

MSM using PrEP require an initial 1-month follow-up to assess ongoing eligibility, tolerance, safety and adherence. Hepatitis B vaccination and STI treatment (as appropriate), condoms and condom-compatible lubricant, risk reduction counselling, adherence support, a 3-month prescription for Truvada and a follow-up date should be provided. Thereafter, 3-monthly visits are recommended (Table 3). Details on recommended monitoring of bone mineral density is provided under **Other notes for PrEP prescribers** below.

Managing abnormal follow-up visit results

PrEP should be stopped if estimated creatinine clearance <60 ml/min. Repeat creatinine clearance should be rechecked after 2 weeks; if renal function returns to normal and other PrEP criteria are met, PrEP may be restarted.

*Hepatitis B immunisations could be provided at PrEP initiation and at 1-month and 7-month follow-up visits. This schedule differs from standard vaccination at months 0, 1 and 6, but would minimise additional visits.

STIs should be treated syndromically (Table 2).

By mutual agreement, PrEP should be stopped if: HIV test is positive; the client no longer meets eligibility criteria; the client and provider feel that adherence to PrEP is too onerous; or it is perceived by the clinician that the risks of PrEP outweigh potential benefits.

MSM who are ineligible for PrEP require support to access other prevention options (see **HIV prevention for MSM** text box below).

Risks and side-effects

Antiretroviral resistance

The only HIV resistance documented to date among PrEP users has been among clients who started using PrEP when they were already HIV-infected (during acute HIV infection). Predictably, FTC resistance mutations were the first to occur.[25] To prevent the risks of ARV resistance, clinicians must focus on not providing PrEP during acute HIV infection.

HIV testing should be done 3-monthly, and should be accompanied by a symptom screen and a targeted examination to exclude acute HIV infection (see text box on **Acute HIV infection**). HIV testing should also be repeated whenever symptoms of a viral illness are present. Clinicians should advise clients on the need for an HIV test before resuming PrEP if it was stopped, particularly if they have potentially been exposed to HIV during this period.

Side-effects

Most available Truvada safety data are derived from studies of HIV positive individuals receiving ART.[26] Safety data of Truvada use in HIV-negative individuals are emerging from PrEP trials and are reassuring.[25]

Gastro-intestinal side-effects

The side-effects related to Truvada use in PrEP trials (nausea, weight loss) were mostly self-limiting start-up symptoms (first month), but these may adversely affect PrEP adherence. Supportive counseling and symptomatic treatment (anti-emetics) of these symptoms are often sufficient. Rates of other GIT symptoms (bloating, abdominal tenderness, flatulence) among PrEP trial participants who took Truvada were not significantly different from those who took placebo.[25]

Acute HIV infection

Severity of the syndrome ranges from mild non-specific 'viral' or 'flu-like' symptoms to a severe infectious mononucleosis like illness with immune dysregulation and transient profound CD4 depletion.[37,38]

Symptom	Sign
Malaise	Fever, sweating
Anorexia	Generalised lymphadenopathy
Myalgias	Hepatospenomegaly
Headache	Non-exudative pharyngitis
Sore throat	Aphthous ulceration
Sore glands	Truncal rash (maculopapular or urticarial)
	Viral meningitis
	Guillian-Barre syndrome
	Pneumocystis pneumonia
	Cryptococcal meningitis
	Oesophageal candidiasis

Potential predictable side-effects

Major side-effects: renal toxicity and metabolic complications (decreased bone mineral density)

Minor side-effects: gastrointestinal symptoms (diarrhoea, nausea, vomiting and flatulence), unintentional weight loss and a small risk of lactic acidosis and hepatic steatosis or steatohepatitis

Less predictable side-effects: may include hypersensitivity reactions and flares of hepatitis B in clients who are chronic carriers who receive and then stop tenofovir, lamivudine or emtricitabine

Renal toxicity

Modest, transient increases in serum creatinine have been noted in completed PrEP studies, but these did not persist after stopping PrEP nor recur on rechallenge. Proteinuria, decreasing glomerular filtration rate (GFR) and Fanconi's syndrome* have been described in the setting of ART, and decreased GFR has been described in the setting of PrEP but has either been statistically or clinically insignificant.[25]

Renal function needs to be measured prior to commencement and monitored in clients using PrEP by measuring serum creatinine and calculating the estimated creatinine clearance. These parameters should be measured at baseline, at month 1, month 4 and then annually thereafter. Hypertensives, diabetics, and those with existing glomerulonephropathies (if the benefit of PrEP is still deemed to outweigh clinical risk) should have monthly renal function checks. Truvada-based PrEP should be avoided in patients who require the use of other nephrotoxic drugs such as aminoglycosides for the treatment of drug-resistant tuberculosis (TB). Clients with creatinine clearance <60 ml/min should **not** be placed on PrEP and, if found during maintenance, PrEP should be discontinued.

Decreased bone mineral density

Decreases in bone mineral density associated with TDF and FTC/TDF have been observed in completed PrEP trials. Decreases were less than those observed in HIV-infected individuals treated with the same drugs, and appeared to stabilise over time.[39,40] No difference in fracture rates were seen. Recreational drugs (amphetamines and inhalant use) were associated with reductions in bone mineral density in HIV-negative MSM taking TDF while enrolled in a PrEP study.[39]

Hepatitis B management

Tenofovir and emtricitabine both have hepatitis B antiviral activity. The risk exists that exposure to these antivirals may treat unidentified chronic hepatitis B infection with a consequent viral flare (rebound) upon drug withdrawal that can result in a severe liver injury.[41] It is recommended that screening for hepatitis B surface antigen and antibodies occurs prior to PrEP commencement. It is recommended that, if hepatitis B surface antigen (HBsAg) is positive, the client be referred for assessment prior to commencement of – in particular – short-term PrEP (Table 4). A possible approach to those with chronic hepatitis B infection may be to prescribe long-term tenofovir/emtricitabine. Liver function tests should be checked after stopping PrEP in those with chronic hepatitis B infection. Clients who are negative for both HBsAg and hepatitis B surface antibody (HBsAb) should commence a hepatitis B vaccine schedule. Clients with a history of injecting drug use should be

*Fanconi's syndrome consists of renal tubular acidosis, hypophosphataemia, hypouricaemia together with urinary losses of glucose, amino acids and protein sometimes coupled with a reduced glomerular filtration rate.

Table 4. Hepatitis B immune status and eligbility for PrEP

Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (HBsAb)	Action
negative (-)	negative (-)	Start PrEP, vaccinate concurrently
negative (-)	positive (+)	Start PrEP, no vaccine needed
positive (+)	N/A	Refer for evaluation

screened for hepatitis C and, if positive, referred for further care.

Risk compensation

This is the theoretical risk that individuals commencing PrEP will neglect other safer-sex measures, and put themselves at increased risk of HIV exposure. To date, no PrEP trials have borne out evidence in support of this risk. Providers should gauge this during risk reduction and adherence counselling opportunities.

HIV prevention package for MSM

The prevention of HIV acquisition requires a comprehensive approach, inclusive of a combination of biomedical and behavioural/psychosocial interventions tailored to individual needs. Where feasible, condoms and condom-compatible lubrication are key components of all HIV prevention packages, supported by STI detection and treatment, appropriate use of ART (post-exposure prophylaxis), and counselling around the identification of high-risk practices and ways to circumvent or reduce risk.

Stopping PrEP

PrEP should be stopped: whenever an HIV test is positive; at client request; for safety concerns (particularly if creatinine clearance <60 ml/min); and if the risks of PrEP outweigh the potential benefits. Linkage to appropriate HIV services should be arranged, and use of other HIV prevention strategies used, as needed.

The duration of PrEP use may vary and individuals are likely to start and stop PrEP depending on their risk assessment at different periods in their lives – including changes in relationship status, behaviours and ability to adhere to a PrEP maintenance programme. Clients should be advised that an HIV test should be done before PrEP is recommenced. Clinicians may want to discuss the options of when to discontinue PrEP with their clients.

Other notes for PrEP prescribers

PrEP will not suit all users. PrEP should be considered for MSM clients who are most likely to benefit from this specific prevention strategy as part of a package of HIV prevention services.

PrEP usage requires commitment. Usage will require commitment from both the provider and the user to ensure success. A paradox is that MSM clients who are most likely to benefit from PrEP because they are at the highest risk of exposure to HIV may find adherence to a programme particularly challenging. Providers may need to be innovative in providing support to these users.

HIV prevention for MSM

- accessibility of condoms and compatible water-based lubricant should be addressed
- no single HIV-risk reduction intervention is likely to suit all MSM
- combinations of prevention options, tailored to address specific risks, should be offered ('menu of prevention choices'), inclusive of biomedical and psychosocial/behaviour change interventions
- prevention options are likely to increase as new evidence becomes available.

Biomedical	Psychosocial
Male condoms and compatible lubrication	Regular HIV counselling and screening
Early access to ART	Reducing number of sex partners
Post-exposure prophylaxis (PEP)	Reducing alcohol and substance abuse
Pre-exposure prophylaxis (PrEP)	Addressing mental health needs
STI screening and treatment	Couples counselling and programming
Needle syringe exchange and opioid substitution therapy for MSM who inject drugs	Harm reduction counselling and support for drug using MSM

Drug-drug interactions

Tenofovir should not be co-administered with adefovir. Other drugs listed below can be co-administered but may require close monitoring, alteration of dosage or timing of administration.

Common drugs which may interact with emtricitabine (FTC) or tenofovir (TDF)

Drug name	FTC	TDF
Adefovir		X – do not co-administer
Cimetidine		X
Digoxin	X	X
Furosemide	X	X
Metformin	X	X
Naproxen	X	X
Ofloxacin	X	X
Streptomycin	X	X
Sulfadoxine/pyrimethamine	X	X

Source: University of Liverpool. Interactions with NRTIs, October 2011 (http://www.hiv-druginteractions.org/data/PrintableCharts/NRTI_col.pdf).

Table 5. Monitoring bone mineral density (DEXA scan) among MSM using PrEP

HIV acquisition risk	Osteopaenia risk	Resources	Intervention
High	High	High	PrEP + DEXA scan (baseline and 12-monthly)
Moderate	High	High	PrEP + DEXA scan (baseline and 12-monthly)
High	High	Low	PrEP + advise and observe
Moderate	Low	Low	PrEP + advise and observe
High	Low	High	PrEP + DEXA scan (baseline, repeat if indicated)
High	Low	Low	PrEP + observe

Monitoring of bone mineral density. Based on current evidence and expert opinion, and where feasible, baseline DEXA scans should be done in clients with a family history of osteoporosis and/or a pathological fracture. Importantly, the unavailability of DEXA should not preclude PrEP use. Annual follow-up DEXA scanning is suggested (Table 5). Ongoing research on the role of DEXA scanning will inform future recommendations.

PrEP: What we don't yet know

- What is the long-term efficacy of PrEP for MSM?
- What is the effect of PrEP on sexual behaviour and HIV risk?
- What are the long-term effects of tenofovir/emtricitabine on renal function, bone mineral density, chronic viral hepatitis B and other effects in HIV-negative MSM?
- Will resistance be a common event among those infected while using PrEP?
- What is the ideal PrEP regimen and dosing interval?
- What are the predictors of adherence for MSM who use PrEP?
- Which MSM are most likely to benefit from PrEP?
- What will be the role of PrEP among sero-discordant MSM couples?
- What will be the long-term effect on treatment programmes that share ART medications with PrEP programs?

The future of PrEP

Many questions surrounding the safe and effective use of PrEP exist; ongoing research aims to address these knowledge gaps (**PrEP: What we don't yet know** text box above).

The iPrEx open-label extension study, and other similar studies, are trying to increase our understanding around long-term PrEP usage (http://iPrExole.com/) specifically for MSM. Health facilities and health workers may be able to help answer these questions by keeping careful records of side-effects, patient adherence reports and HIV and hepatitis infections in their clients taking PrEP. Adverse events can be reported to the National Adverse Drug Event Monitoring Centre which is housed in the Division of Pharmacology at the University of Cape Town. The reporting guideline is available at: http://www.mccza.com/genericDocuments/2.11_ADR_reporting_Jun11_v2.doc.

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