BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2017

Guideline writing group

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Contents

1 Objectives

We aim to provide evidence-based guidance on best clinical practice in the provision, monitoring and support of pre-exposure prophylaxis (PrEP) for the prevention of HIV acquisition. The guidelines include:

(i) guidance on risk assessment prior to PrEP;

(ii) baseline assessment;

(iii) dosing schedules;

(iv) monitoring;

(v) supporting adherence;

(vi) buying generic PrEP; and

(vii) cost effectiveness.

The guidelines are aimed at clinical professionals directly involved in, and responsible for, HIV prevention, and at community advocates and organisations responsible for supporting HIV prevention strategies in those at risk of HIV acquisition.

A detailed review of the evidence base is included in Section 3. Sections 4 to 6 are intended to offer practical guidance in risk assessment, starting PrEP, ongoing management while on PrEP and stopping PrEP.

1.1 Inclusivity

We recognise the importance of these guidelines being inclusive and relevant to all, regardless of sexuality or gender identity or expression. For the sake of brevity in the main text of the guidelines, phrases such as 'men who have sex with men' refers to cis-gendered or non-binary or gender-queer men who have sex with men and 'heterosexual men and women' refers to cis-gendered or non-binary or gender-queer men and women who have heterosexual sex. Where sections are specifically relevant to trans people, we identify this using the terms trans people, trans men or trans women.

2 Methods

2.1 Search strategy

The multidisciplinary guideline writing group developed the guidelines based on the process outlined in the *BHIVA Guidelines Development Manual* [1]. All members of the group underwent GRADE training. We undertook a comprehensive literature review on PrEP and HIV prevention using the PICO question shown below. The recommendations are the result of a series of face-to-face and virtual meetings of the writing group and a meeting of community activists and organisations who commented on a draft of the guidelines in May 2017. The writing group also reviewed and incorporated input from the public consultation process.
PICO questions were set as:

- POPULATIONS: HIV negative
- INTERVENTION: PrEP
- COMPARISON: No specific comparators were applied to ensure all were picked up in the search
- OUTCOME: HIV infection, adverse event, risk behaviours or risk compensation (condom use, number of sexual partners, STIs), adherence

The literature review was from January 2004–May 2016. The Medline, Embase and Cochrane databases were searched. Only papers in English were included and animal studies were excluded. In addition, relevant evidence published between May 2016 and July 2017 has been included

2.2 GRADE system

A Grade 1 recommendation is a strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording 'We recommend'.

A Grade 2 recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording 'We suggest'.

The strength of a recommendation is determined not only by the quality of evidence for defined outcomes, but also the balance between desirable and undesirable effects of a treatment or intervention, differences in values and preferences, and where appropriate, resource use. Each recommendation concerns a defined target population and is actionable.

The quality of evidence is graded from A to D and is defined as follows:

- **Grade A** evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials (RCTs), or overwhelming evidence from another source (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect.
- **Grade B** evidence means moderate-quality evidence from randomised trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias.

- **Grade C** evidence is low-quality evidence from controlled trials with several serious limitations, or observational studies with limited evidence on effects and exclusion of most potential sources of bias.
- **Grade D** evidence is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate.

2.2.1 Good practice points

In addition to graded recommendations, the writing group has also included good practice points (GPP). GPP are recommendations based on the clinical judgement and experience of the working group and feedback from public consultation. GPPs emphasise an area of important clinical practice for which there is not, nor is there likely to be, any significant research evidence. They address an aspect of treatment and care that is regarded as such sound clinical practice that healthcare professionals are unlikely to question it, and where the alternative recommendation is deemed unacceptable. It must be emphasised that GPPs are not an alternative to evidence-based recommendations.

2.3 Stakeholder involvement, piloting and feedback

The guideline writing group included representation from Terrence Higgins Trust and NAZ. In order to widen the stakeholder involvement, a meeting of community activists and organisations was held in May 2017 when feedback was sought on the content of the draft guidelines and recommendations prior to wider public consultation. We acknowledge the following for their helpful contributions: Yusef Azad (NAT), Takudzwa Mukiwa (THT), Will Nutland (Prepster), Greg Owen (I Want PrEP Now), Michelle Ross (CliniQ), Sophie Strachan (Sophia Forum), Marc Thompson (Prepster/Black Out UK) and George Valiotis (HIV Scotland)

2.4 References

1. BHIVA. BHIVA Guidelines Development Manual. 2012. Available at: www.bhiva.org/GuidelineDevelopmentManual.aspx (accessed July 2017).

3 Evidence for safety and efficacy in key populations

3.1 Evidence for safety and efficacy in men who have sex with men (MSM)

3.1.1 Efficacy

Efficacy: summary

- **PrEP consisting of oral tenofovir-emtricitabine (TDF-FTC) taken daily or on-demand prior to potential risk exposure is highly efficacious in preventing HIV infection in MSM.**
- **One Phase 3 randomised double-blind placebo controlled trial (iPrex) and one Phase 3 open-label RCT (PROUD) reported the efficacy of daily oral PrEP with TDF-FTC in preventing HIV infection in MSM at 44% and 86%, respectively.**
- **One Phase 3 randomised double-blind placebo controlled trial (IPERGAY) reported the efficacy of on-demand PrEP with TDF-FTC in preventing HIV infection in MSM at 86%.**
- **There is less evidence to support TDF alone as PrEP in MSM. One Phase 2 trial (the CDC MSM Safety Trial) has demonstrated the safety of TDF alone as PrEP.**
- **Open-label extension studies have demonstrated effectiveness of PrEP in MSM**
    - **iPrex Open-label Extension (iPrex-OLE) reported no HIV seroconversions when drug levels were compatible with taking four or more pills per week.**
    - **IPERGAY Open-label Extension (IPERGAY-OLE) demonstrated a 97% reduction in HIV transmission risk compared to the placebo arm of the IPERGAY randomised phase.**

3.1.1.1 Phase 3 clinical studies

3.1.1.1.1 iPrEx

The iPrEx study [1] was a Phase 3, randomised, double-blind, placebo-controlled, multi-centre trial conducted among 2499 MSM and transgender male-to-female adults (*n*=339) in Peru, Ecuador, Brazil, Thailand, South Africa and the United States. Participants were randomly assigned to either a daily dose of TDF-FTC (1251 participants) or placebo (1248 participants). Primary outcome was HIV infection with a total of 3324 person-years of follow-up. Over the course of the study, 100 participants became infected with HIV; 36 in the TDF-FTC group and 64 in the placebo group, representing a 44% (95% confidence interval [CI] 15–63) reduction in HIV incidence using a modified intention-to-treat (ITT) analysis, excluding those confirmed HIV positive at randomisation. Efficacy was higher in the per-protocol analysis; at visits where adherence was >50% by self-report and pill count/dispensing, efficacy was 50% (95% CI 18–70).

3.1.1.1.2 PROUD

The PROUD study was a Phase 3, randomised, open-label, multi-centre trial conducted among 544 MSM at 13 sexual health clinics in England [2]. Participants were randomly assigned to a daily dose of TDF-FTC immediately (275 participants), or after a deferral period of 12 months (269 participants). Primary outcomes were time to accrual of 500 participants and retention at 12 and 24 months; HIV infection was a secondary outcome. At interim review, the DSMB recommended that all study participants should be offered study drug. A total of 23 participants became infected with HIV over the course of the study; three in the daily TDF-FTC group and 20 in the deferred (no-PrEP) group, representing a rate difference in HIV infection of 7.8 per 100 person-years (90% CI 4.3–11.3) in the modified ITT analysis removing the three additional infections at randomisation. The relative risk reduction was 86% (90% CI 64–96%) and the number needed to treat over 1 year to prevent one HIV infection was 13 (90% CI 9–23).

3.1.1.1.3 IPERGAY

The IPERGAY study was a Phase 3 double-blind, randomised, multi-centre trial conducted among 414 MSM in France and Canada [3]. Participants were randomly assigned to either receiving an on-demand regimen of TDF-FTC (206 participants) or placebo (206 participants). The on-demand regimen involved taking a double dose of TDF-FTC 2–24 hours before sex, and a daily dose during periods of sexual risk and for 48 hours (two doses) after ceasing sexual risk. Participants were followed up every 8 weeks for HIV testing and risk-reduction advice, and every 6 months for sexually transmitted infection (STI) testing for a total of 431 person-years of follow-up. Primary endpoint was HIV infection. At interim review, the placebo group was discontinued and all study participants were offered study drug. Over the course of the study, 16 people became infected with HIV: two in the TDF-FTC group and 14 in the placebo group, representing a relative risk reduction of 86% (95% CI 40–98%) in the ITT analysis.

3.1.1.2 Phase 2 clinical studies

One Phase 2 safety trial, the CDC MSM Safety Trial [4] compared tenofovir (TDF) to placebo in a randomised, double-blind, placebo-controlled, wait-listed design among 400 HIV-negative MSM. Participants were randomly assigned in a 1:1:1:1 design to receive TDF or placebo immediately or after 9 months. Main endpoints were safety and behavioural outcomes. There were no infections among those taking active drug. Seven participants seroconverted: four in the placebo arm and three among delayed-arm participants who were not on the study drug. An eighth participant was HIV positive at enrolment.

3.1.1.3 Randomised pilot studies

Two further smaller studies include a pilot feasibility and acceptability study, Project PrEPare, which recruited 58 young MSM aged 18–22 in the United States. Participants were randomly allocated to receive a behavioural intervention alone, the behavioural intervention and PrEP (TDF-FTC) or the behavioural intervention and placebo. There were no seroconversions among the 58 participants [5].

The IAVI Kenya Study was a small safety and adherence study conducted among Kenyan MSM and female commercial sex workers (CSW). Sixty-seven MSM and five female CSW were randomised to daily TDF-FTC or placebo, or intermittent (Monday, Friday and within 2 hours after sex) TDF-FTC or placebo in a 2:1:2:1 ratio. There was one seroconversion in the placebo arm [6].

3.1.1.4 Open-label studies

The iPrEx Open-label Extension (iPrEx-OLE) [7] enrolled 1603 HIV-negative men and trans women who have sex with men who were previously part of PrEP studies (iPrEx, ATN082/Project PrEPare and CDC MSM Safety Trial).Participants were offered daily TDF-FTC and were followed up for 72 weeks after enrolment. Uptake was high at 76%, and this was higher among those reporting condomless receptive anal intercourse and those who were herpes simplex-2 virus (HSV-2) seropositive, suggesting use during periods of risk. HIV incidence was 1·8 infections per 100 person-years, compared with 2·6 infections per 100 person-years in those who concurrently did not choose PrEP (hazard ratio [HR]: 0.51, 95% CI 0.26–1.01, adjusted for sexual behaviours) [7]. Examination of drug levels by dried blood spot testing was extrapolated to pill taking and compared to HIV incidence each quarter. No seroconversions were seen when drug levels were compatible with taking four or more pills per week.

The IPERGAY Open-label Extension (IPERGAY-OLE) enrolled 362 individuals to take on-demand TDF-FTC and followed them for a median of 11.7 months and of whom 299 (83%) completed follow-up with a single HIV infection (0.19 per 100 person-years, 95% CI 0.01–1.08) [8].

3.1.1.5 Observational data

A community-based clinic in San Francisco screened 1249 MSM (and three trans men) and offered PrEP with TDF-FTC with 95.5% uptake. Condomless sex was reported by 93% at enrolment. After a maximum of 16 months' follow-up there were no new HIV infections in the men enrolled in the programme [9].

At the time of writing there have been three case reports of HIV transmissions in MSM taking PrEP despite apparent confirmed adherence. Two individuals were infected with resistant virus and, in one case, transmission occurred with wild-type virus sensitive to both tenofovir and emtricitabine [10].

3.1 Evidence for safety and efficacy in men who have sex with men (MSM): recommendations

1. **We recommend that PrEP with on-demand or daily oral TDF-FTC should be offered to HIV-negative MSM who are identified as being at elevated risk of HIV acquisition through condomless anal sex in the previous 3–6 months and ongoing condomless anal sex. (1A)**
2. **We recommend that PrEP with on-demand or daily oral TDF-FTC should be offered to HIV-negative MSM having condomless anal sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)**
3. **We suggest that tenofovir alone should not currently be offered as PrEP to MSM. This recommendation is based on lack of evidence, rather than evidence of lack of effect. (2C)**

Good practice point

- **Consider PrEP on a case-by-case basis in MSM with current factors other than condomless anal sex in previous 3–6 months that may put them at increased risk of HIV acquisition. See Section 4.**

3.1.2 Adherence in MSM populations

Adherence in MSM populations: summary

- **PrEP efficacy is highly dependent on adherence.**
- **In iPrEX among those who had detectable TDF-FTC levels the reduction of HIV incidence was 92% compared to those who had no drug detected.**
- **In iPrEx-OLE, no seroconversions were seen when drug levels were compatible with taking four or more pills per week.**
- **In PROUD sufficient study drug was prescribed for 88% of the total follow-up time and tenofovir was detected in all samples taken from a convenience sample of 52 participants who reported taking study drug.**
- **In IPERGAY 86% of a subset of 113 participants in the active treatment group who had drug levels measured had protective drug levels of tenofovir.**

Efficacy of PrEP is highly dependent on adherence with a meta-analysis of PrEP studies [11] demonstrating that adherence is a significant moderator of PrEP effectiveness. The higher the levels of adherence to oral PrEP in the study population, as measured by detectable drug, the greater the efficacy.

In the iPrEX study, adherence was monitored using pill count and self-reported adherence. Pharmacokinetic plasma and intracellular drug-level sampling was conducted in a pre-specified subgroup analysis where subjects with HIV infection were matched with two controls selected from seronegative subjects. In those who had detectable drug levels of TDF-FTC, the reduction in HIV incidence was 92% (95% CI 40–99%) compared to those who had no drug detected [1], suggesting that a high level of adherence is associated with a high level of efficacy.

In the PROUD study, adherence was monitored using prescription data, self-reported adherence and drug levels in a convenience sample of study participants. Overall, sufficient study drug was prescribed for 88% of the total follow-up time and tenofovir was detected in all samples taken from 52 participants who reported taking study drug within the preceding 3 days [2].

In the IPERGAY study, adherence was monitored using pill counts, self-reported adherence and drug levels in a subset of 113 participants. Of participants in the active treatment group who had drug levels measured, protective drug levels of tenofovir were detected in 86%. However, computer-assisted interview (CASI) data collected in 319 participants in the randomised phase suggested that only 43% of people took study drug correctly during last sexual intercourse, 29% took a suboptimal dose and 28% did not take the study drug at all [3]. In the open-label phase, adherence in 362 men completing 1617 CASI returns reported 50% of men taking study drug correctly during last sexual encounter, 24% taking a suboptimal dose and 26% taking no study drug at all [8].

Comparison of adherence to different regimens of TDF-FTC PrEP has been investigated in MSM in the HPTN 067 (ADAPT) study. The study recruited MSM and trans women in Harlem (New York, USA) and Thailand and heterosexual women in South Africa. Following a 4-week phase of daily dosing, participants were randomly assigned 1:1:1 to one of three regimens: daily dosing ('daily'), one tablet twice a week and one tablet post sex ('time driven') or one tablet 24–48 hours before sex and one tablet within 2 hours after sex ('event based'). Results from 178 Thai MSM showed that coverage (defined as taking more than one pill in the 4 days before sex and more than one pill in the 24 hours afterwards) was significantly higher in the daily (85% of events covered) and time-driven (84%) arms than in the event-driven arm (74%). Two seroconversions occurred in the 4 week pre-randomisation phase [12]. In 179 MSM in Harlem, figures were 66%, 47% and 52%, respectively, with one seroconversion in the pre-randomisation phase and one in the randomised phase [13]. Adherence was higher in the daily-dose arms: in Thailand, 85% of daily doses, 79% of twice-weekly doses, and 65% of event-driven doses were taken as prescribed. In Harlem, the respective figures were 65%, 46% and 41%. Although these represent two diverse populations of MSM in different settings, the study demonstrated similar coverage of sex acts for daily and non-daily regimens with both groups demonstrating lower adherence and coverage rates for the event-driven approach.

Higher coverage of events in the Thai MSM was associated with older age and higher level of education. Use of stimulant drugs and higher sexual frequency was associated with lower coverage [14].

3.1.3 Safety

Safety: summary

- **RCTs have shown good safety data (including renal safety data) for daily and on-demand oral TDF-FTC as PrEP in MSM.**
- **Where renal function has been affected, TDF-FTC was associated with mild, non-progressive and reversible reductions in creatinine clearance (CrCl).**
- **Being aged >40 years or having a CrCl <90 mL/min at baseline prior to starting PrEP were independently associated with a (small) risk of CrCl falling to ≤60 mL/min.**
- **Where bone mineral density has been studied, small net decreases have been noted in those taking TDF-FTC. There are no long-term data on bone health or evidence of increased fracture risk.**

3.1.3.1 Adverse events and grade 3–4 safety data

To date, studies of TDF-FTC PrEP suggest short-term safety. A meta-analysis of PrEP studies [11] demonstrated no difference in the proportions of adverse events comparing PrEP to placebo across 10 placebo-controlled RCTs (odds ratio [OR]: 1.01, 95% CI 0.99–1.03, *P*=0.27) with no differences seen in subgroup analysis that included mode of acquisition, adherence, sex, drug regimen, dosing or age. No differences were seen in grade 3 or 4 adverse events comparing PrEP and placebo groups across 11 placebo-controlled RCTs (risk ratio [RR]: 1.02, 95% CI 0.92–1.13, *P*=0.76). Results were not presented by subgroup.

In the iPrEx study, there was no difference in reported adverse events between the two study arms: 867/1251 (67%) of participants in the TDF-FTC arm reported any adverse event, compared to 877/1248 (70%) in the control arm. Both arms reported similar rates of grade 3 and 4 adverse events: 151/1251 (12%) of TDF-FTC participants compared to 164/1248 (13%) of control-arm participants [1]. There was no difference in permanent or temporary discontinuation of study drug between the two arms: 25/1251 (2%) permanent discontinuation in the intervention arm compared to 27/1248 (2%) in the placebo arm and a total of 79/1251 (6%) permanent or temporary discontinuations in the intervention arm compared to 72/1248 (6%) in the placebo arm. However, nausea was more common among those taking TDF-FTC compared to placebo in the first month (95% vs 5%). Depression-related adverse events were the most common severe or life-threatening adverse events reported in iPrEx, but were not associated with being randomly assigned to TDF-FTC (OR 0.66, 95% CI 0.35–1.25) [15].

In the PROUD study, 21/275 participants (8%) interrupted or missed study drug doses because of adverse events, the commonest of which were headache and nausea [2]. In IPERGAY, drug-related gastrointestinal adverse events were reported more commonly in the TDF-FTC group compared to the placebo group (14% vs 5%, *P*=0.002), but there was no difference in the frequency of grade 3 or 4 adverse events [3].

3.1.3.2 Renal function

PrEP trials have shown modest, but statistically significant declines in renal function with administration of daily TDF-FTC, but the incidence of serious renal events was very low and mostly reversible.

In PROUD, three participants interrupted drug due to elevated creatinine concentrations (two were classed as mild elevation, defined as 1.1–1.3 times the upper limit of normal [ULN], and one as moderate, 1.4–1.8 ULN), although the most likely explanation in one man was recreational drug use and the other two men were older with comorbidities [2]. In the IPERGAY study, 18% of active drug participants experienced elevated creatinine levels compared to 10% of placebo group (*P*=0.03). All but one was mild and transient, and none led to discontinuation of study drug [3].

In the iPrEx study, use of TDF-FTC was associated with a mild non-progressive decrease in estimated creatinine clearance (CrCl) of 2.4% from baseline, which was reversible [13]. Creatinine elevations of greater than 1.1 ULN were similar between active and placebo arms, occurring in 32 (2.6%) in the active arm and 24 (2.2%) in the placebo arm (RR: 1.35, 95%CI 0.80–2.3). Most excess creatinine elevations in the active arm of the study (median follow-up 72 weeks) occurred at 12–24 weeks and all occurred at less than 48 weeks. Proteinuria by dipstick was detected regularly (613/ 5081 [12%] dipsticks performed), but there was no between-group difference in the proportion of participants ever positive for proteinuria (20% placebo vs 21% TDF-FTC; *P* = 0.62). In addition, the positive predictive value of proteinuria in predicting a confirmed creatinine elevation was poor at 0.7% [13].

In iPrEx-OLE the probability of CrCl falling to ≤60 mL/min at least once over the first year on PrEP was low, but was more likely when participants started PrEP at older ages (>40 years) or with a starting CrCl ≤90 mL/min [14]. For participants under 40 years of age, the mean decline in CrCl over the duration of the study (median 72 weeks) was modest (−2.6%) and no patients experienced a CrCl drop to ≤60 mL/min even in those with full adherence to daily dosing indicating that annual monitoring of renal function in this group should be sufficient. However, being aged >40 years or with a lower baseline creatinine clearance (≤90 mL/min) at initiation of PrEP were independently associated with a risk of CrCl falling ≤60 mL/min, especially with daily dosing. This suggests that more frequent renal monitoring on PrEP may be required in older PrEP users (>40 years) and in those with marginal renal function at baseline, even if there are no other concomitant risk factors for renal disease.

3.1.3.3 Bone mineral density

In an iPrEx sub-study of 500 participants who underwent 6-monthly DEXA scans to assess bone mineral density (BMD), a small net decrease in BMD of 0.7–1% was seen among those randomly assigned to TDF-FTC (*n*=247) compared to placebo (*n*=256) after 24 weeks in both spine and total hip measures [16]. There are no long-term data on bone health for people on TDF-FTC PrEP. In the CDC MSM study, in multivariate analysis, back pain was associated with use of TDF and also a small decrease in BMD among a subset of 184 men in the San Francisco site. However, TDF use was not associated with bone fractures [17].

3.1.3.4 Drug resistance

In the iPrEx trial, FTC-related drug resistance developed in two participants who had unrecognised acute HIV infection at baseline [18]. These individuals had a negative antibody test before starting PrEP, but later tested positive. In the PROUD study, two of the three participants with a positive HIV test at enrolment or the 4-week visit had FTC-related drug resistance; no resistance was detected in participants who acquired HIV post-randomisation [2]. In IPERGAY, none of the incident HIV infections post-randomisation demonstrated resistance mutations to study drug [3].

In a meta-analysis, Fonner *et al.* reviewed results from six trials that reported cases of FTC or TDF drug resistance using standardised genotypic laboratory assays [11]. Although the only study of MSM included in this analysis was iPrEx, the risk factors associated with development of drug resistance will be similar in MSM and people who have heterosexual sex. The risk of developing an FTC-related mutation among those acutely infected with HIV at enrolment was significantly higher in the group randomly allocated to receive TDF-FTC compared to placebo (risk ratio=3.72, 95% CI 1.23–11.23, *P*=0.02). The risk of a TDF-related mutation was not statistically different between PrEP and placebo regardless of PrEP regimen among those acutely infected at enrolment. Additionally, six (2%) TDF- or FTC-resistant infections occurred among 544 post-randomisation HIV infections; five in PrEP groups and one in a placebo group. Numbers were too small to calculate a pooled relative risk.

3.1.4 Risk behaviour/STIs in MSM

Risk behaviour/STIs in MSM: summary

- **Findings from placebo-controlled trials of PrEP do not permit conclusions to be drawn regarding the effect of PrEP on sexual behaviour.**
- **PROUD demonstrated no difference between the immediate and deferred arms in total number of sexual partners or the incidence of STIs, which were high in both groups prior to enrolment and during the trial. A greater proportion of the immediate group reported receptive anal sex without a condom with 10 or more partners in the 3 months prior to the 1-year questionnaire compared to the deferred group.**
- **In the open-label phase of IPERGAY (IPERGAY-OLE) there was a highly significant reduction in reported condom use over time.**
- **A large observational cohort in San Francisco reported that condom use reduced in a substantial minority of MSM on PrEP.**

Risk behaviour has been measured using outcomes including STI diagnoses, condom use and sexual partner numbers. The most clinically relevant outcome is STI diagnoses, not least because the other two indicators are self-reported and, as such, subject to reporting bias.

In the placebo-controlled trials, one purpose of the placebo is to control for behaviour, and it is not possible to comment on the impact of PrEP on behaviour, as participants do not know if they are on active drug. However, it is possible to evaluate the impact of the risk-reduction support provided to all participants, and there were demonstrable benefits in iPrEx, the CDC MSM Safety Trial, but not the IAVI Kenya study.

In the iPrEx study, both PrEP and placebo groups reported increased condom use over the course of the study and reported condom use did not differ between the arms (*P*=0.36) [1]. The number of reported receptive sexual intercourse partners in both arms also declined over the course of the study with no significant difference in the number of partners reported in each group at each time point (*P*=0.97) [1]. The reduction in risk behaviours may reflect the fact that the majority of iPrEx participants came from populations with little access to risk-reduction support.

In IPERGAY, there were no significant differences between TDF-FTC and placebo groups in the proportion of condomless receptive anal sex (*P*=0.40) and incident STIs (*P*=0.10). There was a slight but significant decrease in the number of sexual partners in the previous 2 months in the placebo group compared to the TDF-FTC group (7.5 vs 8, *P*=0.001)[3,19].

In the CDC MSM Safety Trial (also placebo-controlled), mean number of sexual partners in the previous 3 months and the proportion reporting condomless anal sex declined over 24 months of follow-up.

The IAVI Kenya study, which included MSM, was the only trial to report an increase in study partners from baseline to follow-up, but partners may have been underreported at baseline [6].

In the open-label PROUD study, in which participants knew they were taking PrEP and that it was at least partially effective, there was no difference between the immediate and deferred (no-PrEP) groups in the total number of sexual partners (*P*=0.57) in the 3 months prior to the 1-year questionnaire, but a greater proportion of the immediate group reported receptive anal sex without a condom with 10 or more partners compared to the deferred group (21% vs 12%, *P*=0.03). There was no difference in the frequency of bacterial STIs during the randomised phase (*P*=0.74) [2].

In the iPrEx-OLE study, both groups reported decreases in reported condomless receptive anal intercourse from 34% (377/1115) to 25% (232/926 *P*=0.006) among those accepting PrEP and from 27% (101/369) to 20% (61/304; *P*=0.03) in the group who declined PrEP. Conversely, in IPERGAY-OLE there was a much higher baseline rate and a significant increase in reported condomless sex at last receptive anal intercourse from 77% at baseline to 86% at 18 months (*P*=0.003 for trend) [8]. Examination of three different trajectories of condom use (low, medium and high) and four of PrEP use over time in IPERGAY-OLE shows that in the majority of men, declines in condom use were compensated by increased on-demand PrEP use, but in a minority of men this is not the case. Compensation by using on-demand PrEP was lower in younger men for all three condom trajectories [20].

In a large observational cohort study of MSM PrEP in a community-based clinic in San Francisco, self-reported condom use for different sub cohorts of men taking PrEP for periods of 1–16 months was unchanged in 38–61%, increased in 5–12% and reduced in 16–48% [9].

3.1.5.1 STIs

Both the PROUD and IPERGAY studies documented high levels of bacterial STIs in MSM throughout the course of follow-up. Within IPERGAY, participants were screened at enrolment and every 6 months during follow-up for chlamydia and gonorrhoea (with triple site nucleic acid amplification tests) and syphilis [10]. Of participants receiving TDF-FTC, 41% acquired a new STI during follow-up, compared to 33% in the placebo arm; most STIs were rectal and 10% acquired a new syphilis infection [3]. Similar results were observed within the PROUD study where 3–6-monthly STI screening was offered and the proportions with a bacterial STI were 50% and 57% of men diagnosed with an STI, respectively, in the deferred an immediate treatment arms of the study (*P*=0.74). Similarly to IPERGAY, 10% of individuals in PROUD acquired a new syphilis infection [2]. In IPREX OLE the incidence of syphilis was similar in both groups, although numerically higher among PrEP users (7.2/100 person-years compared to 5.4/100 person-years in non-PrEP users, HR 1.35, 95% CI 0.83–2.19).

In IPERGAY, incidence rate of first STI was 35.2 per 100 person-years in the double-blind phase, and 40.6 per 100 person-years in the open-label phase [3].

Incident hepatitis C has also been reported in clinical trials and PrEP access projects. In Amsterdam, HIV-negative MSM who enrolled in the Amsterdam PrEP demonstration project had considerably higher hepatitis C virus (HCV) prevalence at 4.8% than HIV negative MSM in the general Amsterdam STI clinic survey at 0.3–1.2% [21]. Genetic analyses suggested that circulating HCV strains in HIV-negative men on PrEP were similar to those in local HIV/HCV co-infected MSM. In the PROUD study 5/160 (3.1%) participants who had tested on one or more occasions for HCV had incident HCV infection (3.1%). There were three incident HCV infections in the immediate arm and two in the deferred arm [2]. In IPERGAY, overall, there were five incident HCV infections [3].

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3.2 Evidence for safety and efficacy in heterosexual populations

3.2.1 Efficacy

Efficacy: summary

- **There are no clinical trials of PrEP for heterosexual individuals in high-income countries; while the biological efficacy is likely to be identical, the extent to which data from other settings are generalisable to the UK remains uncertain.**
- **Four RCTs undertaken in sub-Saharan Africa (SSA) have evaluated the efficacy of daily oral PrEP for preventing HIV infection in heterosexual men and women at risk.**
- **One RCT provides strong evidence of PrEP having high efficacy in preventing HIV acquisition by heterosexual men and women at risk, and one RCT provides weak evidence of high efficacy**
- **Two other RCTs were limited by inadequate adherence to study drug and do not provide reliable evidence about efficacy.**
- **No studies have evaluated the efficacy of an on-demand oral PrEP regimen in heterosexual men and women**
- **There is evidence that tenofovir-based PrEP offers some protection against HSV-2.**
- **Contraception is an important consideration. Depot medroxyprogesterone acetate (DMPA) use is associated with an increased risk of HIV acquisition, and there is evidence that this is counteracted by PrEP.**

3.2.1.1 Overview

Two RCTs have demonstrated the efficacy of daily oral PrEP in preventing HIV acquisition amongst heterosexual individuals. One Phase 3 RCT, Partners PrEP [1], assessed the efficacy of daily oral TDF versus TDF-FTC versus placebo in serodifferent heterosexual couples in East Africa and one Phase 3 RCT, TDF-2 [2], evaluated TDF-FTC versus placebo in sexually active heterosexual adults at high risk of HIV acquisition in Botswana. No studies have evaluated the efficacy of an on-demand PrEP regimen in heterosexuals and to date there are no RCTs undertaken in heterosexual men and women in high-income countries. Although there is no reason to think the biological efficacy would be different, given the lack of RCTs in heterosexuals in high-income countries, it remains difficult to generalise the finding of high PrEP efficacy from these two trials in sub-Saharan Africa (SSA) to the UK because HIV incidence is much lower, and no well-defined group of heterosexuals with high HIV incidence can be identified in national surveillance data. Furthermore, there are likely to be differences in cultural beliefs and sociodemographic circumstances that influence adherence and efficacy and further complicate any extrapolation of the data.

Two RCTs (FEM-PrEP [3] and VOICE [4]), both in heterosexual women in SSA, reported low efficacy rates of daily oral PrEP. In both cases, the studies were well conducted and the null results, and inconsistency of the results when compared to TDF-2 and Partners PrEP, are primarily attributed to low adherence (measured using drug levels) to the study drug in the intervention arm.

3.2.1.2 Phase 3 clinical studies

3.2.1.2.1 Partners PrEP

Partners PREP was a double-blind, placebo controlled Phase 3 RCT following 4747 heterosexual couples, comparing single and dual agent PrEP (TDF vs TDF-FTC) with placebo conducted from 2008 to 2010 [1]. Participants were sexually active serodifferent heterosexual couples in Uganda and Kenya. HIV-negative participants were aged between 18 and 65 years old, sexually active with an HIV-positive partner (≥6 episodes vaginal intercourse with HIV-positive partner in the past 3 months) with no chronic HBV infection. HIV-negative women who were breastfeeding, pregnant or planning to become pregnant were excluded from the study. The study also excluded HIV-negative participants with glycosuria or proteinuria, ongoing therapy with certain drugs, and a history of pathological bone fractures not related to trauma. HIV-positive sexual partners were >18 years old, sexually active, with CD4 cell counts ≥250 cells/mL, no history of AIDS-defining Illnesses (ADIs) and not using antiretrovirals (ARVs). The HIV incidence in the control arm was 1.99 per 100 person-years. Overall, the study found the efficacy of PrEP using TDF alone was 67% (95% CI 44–81; *P*<0.001) compared to placebo, and had comparable efficacy to PrEP using TDF-FTC 75% (95% CI 55–87; *P*<0.001). The study team subsequently reported an analysis of efficacy stratified by TDF and TDF-FTC levels in plasma in the intervention arms in the 29 seroconverters compared to 196 randomly selected controls who were uninfected. The estimated protective effect of PrEP against HIV based on drug levels >40 mg/mL (i.e. consistent with daily dosing), was 88% (95% CI 60–96; *P*<0.001) for TDF and 91% (95% CI 47–98; *P*=0.008) with TDF-FTC [5]. A secondary analysis of Partners PrEP data found oral TDF-based PrEP reduced HSV-2 acquisition by 30% among initially HSV-2 seronegative people [6].

3.2.1.2.2 TDF-2

TDF-2 was a double-blind placebo controlled Phase 3 RCT comparing dual agent PrEP (TDF-FTC) with placebo [2]. The trial was undertaken in Botswana from 2007 to 2009 where around 40% of adults aged 30–44 years old are infected with HIV. Participants in the RCT were sexually active men and women aged 18–39 years old, without HIV infection, with normal serum chemistry and haematology results, negative HBV surface antigen, and without any chronic illness or long-term medication. Women were required to use effective contraception and could not be pregnant or breastfeeding. The HIV incidence in the control arm was 3.1 per 100 person-years. The TDF-2 study experienced difficulties in getting participants to complete the study protocol and was concluded early, which led to the study being underpowered to determine efficacy. However, in the modified intention-to-treat analysis, the efficacy of TDF-FTC was found to be 62% (95% CI 21–83). However, the efficacy differed in men and women, with 49% efficacy in women (95%CI 22–81) and 80% in men (95%CI 25–97).

3.2.1.2.3 FEM-PrEP

FEM-PrEP was a double-blind, placebo-controlled, Phase 3 RCT comparing PrEP (TDF-FTC) with placebo in 2120 sexually active heterosexual women aged 18–35 years in Kenya, South Africa and Tanzania from 2009 to 2011 [3]. The HIV incidence in the TDF-FTC arm was not significantly different to the placebo arm (HR 0.94, 95%CI 0.59–1.52).

3.2.1.3 ***VOICE***

VOICE was a double-blind, placebo-controlled Phase 2b RCT with daily oral TDF (300 mg), daily oral TDF-FTC (300 mg/200 mg) and vaginal tenofovir gel (1%) [4]. The trial took place in South Africa, Uganda and Zimbabwe from 2009 to 2011, in 5029 sexually active heterosexual women aged 18–45 years. None of the interventions reduced HIV acquisition. Hazard ratio for efficacy was 1.49 (95%CI 0.97–2.29) for TDF, 1.04 (95%CI 0.73–1.49) for TDF-FTC, and 0.85 (95%CI 0.61–1.21) for tenofovir gel.

Both FEM-PrEP and VOICE excluded pregnant and breastfeeding women. Both trials failed to demonstrate efficacy of either TDF or TDF-FTC and this is believed to be due to insufficient levels of drug measured in participants' plasma. Fewer than 40% of participants in Fem-PrEP had evidence of recent pill use, and drug was detected in only 25–30% of a sample of VOICE participants.

3.2.1.4 PrEP efficacy and contraception use

PrEP efficacy in women using depot medroxyprogesterone acetate (DMPA) was assessed in two of the RCTs. In Partners PrEP, Heffron *et al.* reported a 64.7% reduction in risk of HIV acquisition among women using DMPA in the intervention arm compared to the placebo arm (HR: 0.35, 95% CI 0.12–0.1.05) [7]. PrEP efficacy estimates were similar among women using DMPA and those using no hormonal contraception (64.6% and 75.5%, p=0.65) suggesting no impact of DMPA on PrEP efficacy. In FEM-PrEP, there was no evidence that TDF-FTC affected serum DMPA levels in participants using DMPA [8].

In HIV-negative women taking PrEP in the Partners PrEP study, there was no evidence that PrEP affected hormonal contraceptive effectiveness (oral contraceptive pill, DMPA and hormonal implants) [9]. There was no difference in pregnancy incidence between women in the study groups, (10.0 per 100 person-years placebo, 11.9 per 100 person-years in participants assigned to TDF; *P*=0.22 vs placebo, and 8.8 per 100 person-years in participants assigned to TDF-FTC; *P*=0.39 vs placebo).

In a prospective cohort study of South African VOICE participants, Noguchi *et al.* found higher risk of HIV acquisition among DMPA users (incidence 8.62 per 100 person-years, 95% CI 6.61–8.68) than among norethisterone enanate (NET-EN) users (6.57 per 100 person-years, 95% CI 4.35–7.38, HR: 1.53, 95% CI 1.12–2.08; *P*=0.007) [10]. The association persisted when adjusted for confounding variables (adjusted hazard ratio [aHR]: 1.41, 95% CI 1.06–1.89; *P*=0.02). The authors suggest that ENT-EN might be an alternative injectable drug to DMPA for women in settings with high HIV incidence. Given the low adherence to PrEP in VOICE, these data probably reflect the findings of a meta-analysis that shows an increased risk of HIV acquisition in women using DMPA when compared to other forms of contraception or non-use [11].

3.2.1.5 Observational data on efficacy of PrEP as a bridging intervention to TasP

Baeten *et al.* reported on a prospective study where just over 1000 serodifferent heterosexual couples in Kenya and Uganda were offered antiretroviral therapy (ART) (either as PrEP for the seronegative partner or as treatment as prevention [TasP] for the seropositive partner) [12]. The study discontinued PrEP for the seronegative partner once the seropositive partner had completed 6 months of ART. Findings demonstrated the feasibility of integrated delivery of time-limited PrEP as a bridge to suppressive ART, which resulted in near elimination of HIV transmission, with an observed HIV incidence of <0.05% per year compared to an expected incidence of >5% per year (estimated through modelling) [12].

3.2 Evidence for safety and efficacy in heterosexual populations: recommendations

4. **We recommend that daily oral TDF-FTC should be offered to HIV-negative heterosexual men and women having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)**
5. **We suggest that PrEP with daily oral TDF-FTC should be offered on a case-by-case basis to heterosexual men and women with current factors that may put them at increased risk of HIV acquisition. See Section 4. (2B)**
6. **We recommend that TDF alone can be offered to heterosexual men and women where FTC is contraindicated. (1A)**

Good practice point

- **For women using DMPA, PrEP is likely to counteract an increase in HIV acquisition. However, women at risk of HIV acquisition should be offered an alternative form of contraception if available, whether or not they opt to take PrEP.**

3.2.2 Adherence in heterosexual populations

Adherence in heterosexual populations: summary

- **Poor adherence has been reported in two trials in sub-Saharan Africa and this restricted the effectiveness of PrEP.**
- **Other trials in sub-Saharan Africa have demonstrated that good adherence to daily oral PrEP is possible and sustainable.**
- **Good adherence is helped by understanding perceived risk of HIV, partner and peer support, trust in PrEP and varied external strategies such as external reminders, drug-taking routines and adherence counselling.**
- **Poor adherence is associated with lack of peer and partner support, low risk perception, limited or lack of drug-taking routines, mistrust of medication, misunderstanding of the role of ARVs in prevention and wider HIV stigma.**
- **Support for varied tools and approaches to facilitate adherence will be required, including those that address factors at individual, partner, peer and community level.**
- **Low levels of PrEP literacy for potential users and the wider community will also need to be addressed to support PrEP uptake and effective use.**

3.2.2.1 Adherence to daily PrEP

Partners PrEP reported good adherence, measured by counts of returned bottles and pills. Medication was reported to have been taken as prescribed during 92.1% of total study follow-up time. A Partners PrEP sub-analysis reported high continued PrEP use amongst those in serodifferent partnerships [13]. Amongst partnerships where the HIV-positive partner had not yet initiated ART, participants' continued PrEP use remained high at 6- (91%) and 12- (84%) month follow-up visits. Reasons for discontinuation of PrEP included ART use by HIV-infected partner (41%), loss to follow-up (30%), pregnancy and breastfeeding (9%), partner preference (8%) and partnership dissolution (6%). A Partners PrEP sub-study reported high adherence with active adherence monitoring with unannounced home-based pill counts (99.1%, interquartile range [IQR] 96.9–100%) and electronic pill bottle monitoring (97.2%, IQR 90.6–100%) [14]. Low adherence was associated with not having sex, having sex with another person besides study partner, younger age, and heavy alcohol use. A subgroup of 96 participants who received daily short SMS text messaging over 60 days found that 96.9% reported taking PrEP on ≥80 % of the days, with 69.8% missing at least one dose [15].

Adherence rates in the TDF-2 study were similar for both the TDF-FTC and placebo groups when measured by pill count (84.1% in TDF-FTC group and 83.7% in placebo group; *P*=0.79) and self-reported adherence over the

preceding 3 days (94.4% and 94.1%, respectively; *P*=0.32). As with Partners PrEP, efficacy was dependent on adherence to medication, as assessed by measure of plasma drug concentrations with non-seroconversion drug levels of 30.5 ng/mL for TDF and 103.3 ng/mL for 3TC.

3.2.2.2 Adherence to daily vs time or event-driven dosing

The ADAPT RCT (HPTN 067) compared daily and non-daily PrEP dosing among 179 women enrolled in the South African arm of this trial. Regimens included: (i) daily (D); (ii) time driven: twice weekly with post-intercourse boost (T); or (iii) event driven: before and after intercourse (E). Coverage was defined as more than one pill in 4 days before and more than one pill taken 24 hours after intercourse [16]. Participants were aged between 18 and 52 years old (median age 26), with 80% unmarried and 83% unemployed. In this study, reported adherence to PrEP was greater in D regimens, compared with T and E (*P*<0.001), and adherence to post-intercourse dosing was low. Amico *et al.* report specific challenges to non-daily dosing in the ADAPT study, centring on the context in which participants had sex (e.g. unplanned, as available and typically outside the home) and the context surrounding post-sex (e.g. where relaxation takes precedence over action-oriented prevention behaviours such as dosing) [17].

3.2.2.3 Lessons learned from low adherence to daily PrEP in VOICE and FEM-PrEP

Although VOICE and FEM-PrEP do not provide evidence about the efficacy of TDF-based PrEP, they do offer important insights into some of the barriers and facilitators to taking daily oral PrEP in sub-Sahara African populations. Research from both trials identified a range of barriers to initiating and sustaining adherence to PrEP, which may have relevance to a UK context.

- Perceived harm of ARVs: within the VOICE trial, taking ARVs was perceived to be associated with illness, and seen as harmful to those who were HIV negative, in spite of acknowledged benefits for people with HIV.
- Distinguishing between prevention and treatment: female participants described difficulties in distinguishing between ARVs for prevention and treatment, for both themselves and their sexual partners [18].
- Social/community pressures: FEM-PrEP participants described being discouraged from taking PrEP by members of their social network because of the investigational nature of the study and potential drug side-effects [19].

These studies, which are supported in their findings by a systematic review of adherence interventions [20], highlight the importance of clear communication with patients and community groups about what PrEP is, and how it works, to ensure appropriate and successful uptake and continued use.

3.2.2.4 Facilitators for adherence

Corneli *et al.* used qualitative semi-structured interviews to identify facilitators linked to adherence to PrEP in the FEM-PrEP study including personal motivation (HIV risk reduction and general interest in the outcome of the research) and adherence strategies [21,22]. These strategies included: external cues, reminders and support such as partner awareness, encouragement and support or assistance, established routines and tools, and adherence counselling.

High adherence (measured using a pill-dispensing device that recorded opening, and weekly interviews) in African women in HPTN 067 was associated, in a qualitative study, with: levels of perceived safety and efficacy of PrEP; trust in those providing PrEP; and investment in protecting one's community with PrEP [17]. Adherence strategies (e.g. daily timer on mobile phone, aligning daily routine to television programmes, social/family support) were reported to support adherence. The authors suggest wider community engagement, transparency in discussions around safety and efficacy, and peer-led programmes of debate and engagement in implementation might contribute to sustained engagement in care and adherence.

Guest *et al.* reported on adherence in a randomised, double-blind, placebo-controlled, TDF trial conducted in Ghana with women who engaged in sex work and transactional sex [23,24]. Findings highlight the importance in allowing time for users to establish good patterns of use (up to 6 months), which was associated with good adherence in the study.

3.2.2.5 Acceptability of PrEP to heterosexual populations in high-resource settings

Acceptability studies in the UK and USA in heterosexual populations reiterate findings from RCT studies in relation to:

- The need for clear understandings of what PrEP is and how it works for potential users; and
- The need to address potential social barriers to continued PrEP use amongst sexual partners, peers and the wider community.

In a study with African men and women living in Scotland, Young *et al.* identified inequalities in HIV literacy that might affect uptake and sustained use of PrEP. Limited awareness and mistrust of pharmaceutical-based prevention led to scepticism of PrEP as a viable HIV prevention option. Concerns about how sexual partners and the wider community might view PrEP were seen as a significant barrier to PrEP use, highlighting the need to address wider community concerns around sexual norms and HIV prevention [25]. Similarly, in a study with American women across multiple sites in the US, Auerbach *et al.* identified lack of communication among community members, mistrust of medical institutions and potential HIV-stigma related to an unfamiliar HIV prevention method as key barriers to supporting PrEP uptake and adherence [26].

3.2.3 Safety

Safety: summary

- **RCTs in sub-Saharan Africa have shown good safety data for daily oral TDF-FTC as PrEP in men and women, with any small changes occurring in renal function or bone mineral density likely to reverse following discontinuation of PrEP.**
- **The existing data suggest that PrEP can be used safely in women who are pregnant or breastfeeding and with current factors that may put them at increased risk of HIV acquisition.**

3.2.3.1 Adverse events and grade 3–4 safety data

To date, studies of TDF-FTC PrEP suggest evidence for short-term safety.

3.2.3.2 Renal function

TDF exposure has been associated with a small but statistically significant decline in estimated glomerular filtration rate (eGFR) in HIV-uninfected persons receiving TDF-based PrEP for HIV prevention. In Partners PrEP, all participants had creatinine clearance of ≥60 mL/min at study entry [1], and there were 3924 individuals with serum creatinine measurements in whom differences were noted between study groups which, although statistically significant, were unlikely to be clinically significant. Mean eGFR at last on-study drug visit was 129 mL/min/1.73 m^2 for TDF, 128 mL/min/1.73 m^2 for TDF-FTC, and 131 mL/min/1.73 m^2 for placebo groups, such that the overall mean decline for those receiving PrEP compared to placebo was estimated to be 2–3 mL/min/1.73 m^2 ($P \leq 0.01$) [27], and the differences had disappeared on testing 4 weeks later. Overall, in Partners PrEP, the proportions of participants with a confirmed ≥25% decline in eGFR from baseline by 12 and 24 months were 1.3% and 1.8% for TDF, 1.2% and 2.5% for TDF-FTC, and 0.9% and 1.3% for placebo (not statistically significant) [28].

A subgroup analysis of 1549 men and women participating in Partners PrEP assessed the effect of TDF on renal proximal tubular dysfunction that was predefined as ≥2 of the following: tubular proteinuria, euglycaemic glycosuria, increased urinary phosphate, and uric acid excretion. Even using these very detailed markers of tubular proteinuria they found that there was no difference in tubulopathy frequency between the group receiving daily oral TDF-FTC and the placebo group over a median of 2 years' follow-up (1.7% for TDF-FTC versus 1.3% for placebo, OR: 1.30, 95%CI 0.52–3.33; *P*=0.68). The authors also report that tubulopathy did not predict a clinically relevant eGFR decline (defined as ≥25% eGFR decline from baseline) [29].

Although these data are reassuring, clinicians prescribing PrEP should consider whether patients have any pre-existing renal disease or risk factors for future renal disease, and ensure appropriate monitoring in these cases.

3.2.3.3 Bone mineral density

A subset of 220 women enrolled in TDF-2 (108 TDF-FTC and 112 placebo) had bone mineral density (BMD) measurements with low baseline scores found among 7% [30]. In the group receiving TDF-FTC, there was a slight, but statistically significant reduction in the mean percentage change in BMD from baseline compared to the control group at month 30 (forearm –0.84%, spine –1.62%, hip –1.51%). In the VOICE study, BMD data were available for a subset of 81 women with detectable drug in serum samples in the combined active arms and 158 in the placebo group [31]. Similar findings were reported, showing that the mean percentage BMD change from baseline at 48 weeks was 1.4% lower for those receiving active drug than for placebo. This difference had reversed when measurements were repeated 48 weeks after ceasing treatment. No bone fractures were reported. These data mirror findings from studies in MSM and other groups.

3.2.3.4 PrEP safety in pregnancy

Among HIV-negative women taking PrEP in the Partners PrEP study, there was no difference in pregnancy incidence between women in the study groups: 10.0 per 100 person-years in the placebo arm, 11.9 per 100 person-years in participants assigned to TDF arm (*P*=0.22) and 8.8 per 100 person-years in participants assigned to TDF-FTC (*P*=0.39). There was also no difference in pregnancy outcomes (preterm birth, congenital anomaly and growth) between those receiving PrEP and those receiving placebo in Partners PrEP [32]. However, the relatively small sample sizes resulted in wide confidence intervals for some pregnancy outcomes, including preterm birth and congenital anomalies. In addition, in Partners PrEP, PrEP was discontinued once pregnancy was confirmed, so that *in utero* exposure after conception was typically short (average 35 days in early pregnancy) and therefore these findings can only be generalised to periconception exposure to PrEP [33]. There is no evidence that TDF-FTC adversely affects male fertility [34].

Although there are no formal studies investigating safety of oral TDF-based PrEP throughout pregnancy, two clinics from the USA have reported on offering PrEP to women at high risk of acquiring HIV through preconception, during pregnancy and postpartum. Of the 27 women referred to their service, 18 women chose to take PrEP with a median length of time on PrEP of 30 weeks. No PrEP-related pregnancy complications were identified [35].

In a systematic review examining the safety of TDF during pregnancy for mother and foetus in women with HIV and/or hepatitis B infection, the authors conclude that TDF is safe in pregnancy [36]. In addition, a systematic review and meta-analysis investigating the safety of TDF in HIV-negative women on antiretrovirals for chronic hepatitis B infection found no significant differences in congenital malformations, prematurity rate or Apgar scores [37].

3.2.4.5 PrEP safety during breastfeeding

In a prospective study of daily TDF-FTC taken for 10 days by 50 HIV-negative breastfeeding women who were between 1 and 24 weeks postpartum, TDF concentrations were extremely low in breast milk and below the level of detection in infant plasma. FTC levels, on the other hand, were higher in breast milk and detectable in infant plasma, but still more than 200-fold lower than proposed infant therapeutic doses [38]. Although more research is warranted to understand the clinical safety for infants who are breastfed by women on PrEP, there is extensive experience of FTC-TDF use in women with HIV who are breastfeeding. These data confirm very low median concentrations of FTC and TDF secreted in breast milk (2% and 0.03% respectively of proposed oral infant treatment doses for HIV infection) [39].

3.2.3.6 Drug resistance

The meta-analysis by Fonner *et al.* reviewed six studies that reported cases of TDF or FTC drug resistance using standardised genotypic laboratory assays [26]. RCTs conducted in heterosexual populations found that selected drug resistance occurs rarely, and that this may be either in subjects initiating PrEP with an undetected HIV infection or in those with breakthrough infections after starting PrEP. For example, in TDF-2, one case of TDF and FTC drug resistance was reported. The participant was subsequently found to have had undetected HIV infection at enrolment [2]. In Partners PrEP, among those receiving PrEP, three of 12 subjects subsequently found to be HIV positive at enrolment had TDF or FTC resistance detected, and four of 51 who acquired HIV after enrolment had resistance detected [40,41].

3.2.4 Risk behaviour/STIs

Risk behaviour: summary

- **There are few data available to understand whether risk compensation might occur in heterosexual populations and the likely effect on STI rates.**

It has been suggested that behaviour change leading to increased acquisition of STIs might occur due to risk compensation associated with the efficacy of PrEP. However, data to assess this risk are limited. To investigate whether knowledge of PrEP efficacy might influence sexual behaviour, a Partners PrEP subgroup analysis compared reported sexual behaviour during the 12 months before and the 12 months after the study was unblinded and the efficacy of PrEP was reported publicly. Overall, 3024 men and women contributed 56,132 person-months to this study, and the frequency of condomless sex with the HIV-infected study partner fell from 59 acts per 100-person months to 53 acts per 100-person months (non-significant), and there were no changes in STIs or pregnancies detected [42]. There was a small but significant increase in the estimated frequency of condomless sex acts with partners other than the study partner (predicted using a counterfactual scenario had unblinding not occurred). Overall, there is a lack of data available to understand whether risk compensation occurs in heterosexual populations and, if so, what the impact is on rates of STI infections.

3.2.5 References

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3.3 Evidence for safety and efficacy in people who inject drugs (PWID)

Evidence for safety and efficacy in people who inject drugs (PWID): summary

- **There are no data on the efficacy of PrEP in PWID in the UK.**
- **There is limited evidence for safety and efficacy in people who inject drugs (PWID) with only one reported RCT (TDF vs placebo) performed in PWID in Bangkok, which demonstrated a 49% reduction in HIV incidence.**
- **Efficacy was strongly linked to adherence.**
- **It is difficult to separate the impact of PrEP on parenteral HIV transmission from sexual transmission in PWID.**
- **The authors of the Bangkok Tenofovir Study acknowledge that, although the study was designed to measure the impact on parenteral transmission, participants may have become infected sexually.**
- **In 2015, PWID made up 3% (210) of new HIV diagnoses in the UK, but overall, the number of people acquiring HIV through injecting drug use in the UK remains low.**
- **Chemsex and slamming (the act of injecting the drugs used in chemsex) are more commonly seen in MSM and are associated with risk behaviours for HIV acquisition.**

3.3.1 Efficacy

3.3.1.1 Phase 3 clinical study

One randomised, double-blind, placebo-controlled Phase 3 trial (The Bangkok Tenofovir Study) assessed the efficacy of daily TDF versus placebo in PWID in Thailand [1]. Participants were enrolled from drug treatment centres in Bangkok and were eligible if they were aged 20–60 years, were HIV-negative, and reported injecting drugs during the previous year. Participants were randomised 1:1 to receive either TDF or placebo and could choose daily directly observed treatment (DOT) or monthly visits and completed an adherence diary. The majority were on DOT for which attendance was reimbursed, which would not be the case in routine practice, so adherence may be overestimated. Participants received monthly HIV testing and individualised risk-reduction and adherence counselling, blood safety assessments every 3 months, and were offered condoms and methadone treatment. The study enrolled 2413 participants, assigning 1204 to TDF and 1209 to placebo. The median age of

enrolled participants was 31 years (20–59), 80% were male, and 63% reported that they injected drugs during the 3 months before enrolment. Among those who injected, 53% injected methamphetamine and 35% heroin. An open-label extension study offered study participants a subsequent 1 year of TDF, which was taken up by 787 (35%) participants.

Two participants had HIV at enrolment and 50 became HIV infected during follow-up; 17 in the TDF arm (incidence: 0.35, 95% CI 0.21–0.56, per 100 person-years) and 33 in the placebo arm (incidence: 0.68, 95% CI 0.47–0.96, per 100 person-years), indicating a 48.9% reduction in HIV incidence (95% CI 9.6–72.2).

3.3.1.2 Data on PWID in the UK

There are no data on the efficacy of PrEP in people who inject drugs in the UK. Generalisability of other studies to a UK population is difficult as the injecting risk behaviours differ and the UK has effective needle-exchange and opiate substitution programmes, which have successfully contained the HIV epidemic in PWID.

In 2015, PWID made up 3% (210) of new HIV diagnoses in the UK [2]. This was an increase on the previous year (160 new infections) and was largely due to an HIV outbreak among PWID in Glasgow, which led to the diagnosis of over 50 people. Overall, the number of people acquiring HIV through injecting drug use in the UK remains low and PrEP use in the UK relates to sexual transmission risks except in an outbreak situation in PWID such as in Glasgow in 2015.

3.3.2 Adherence

As in other studies, efficacy was closely correlated with adherence in the Bangkok Tenofovir Study (as measured by a study drug diary) [1]. The risk reduction for people on TDF PrEP was 84% in those with at least 98% adherence [3]. Participants took study drug an average of 84% of days; 84% while in daily follow-up and 89% while in monthly follow-up. In multivariate analysis, men were less adherent (94%, 95% CI 79–99%) than women (96%, 95% CI 81–99%; *P*= 0.04). Adherence was better in participants aged 40 years and older (median 98%, 95% CI 94–99.5%) than it was in participants 30–39 years old (median 94.2%, 95% CI 82.2–98.6%) and those aged 20–29 years old (median 90%, 95% CI 69%–98%; *P*<0.001). Other factors significantly associated with poor adherence included incarceration in prison (OR: 1.3, 95% CI 1.1–1.7; *P*=0.02), and injecting methamphetamine (OR: 1.2, 95% CI 1.0–1.5; *P*=0.04). Participants in a methadone programme at enrolment were more likely to report at least 95% adherence (OR: 0.7, 95% CI 0.6–0.9; *P*=0.003) [4]. In the open-label extension study, one participant became HIV-infected after starting PrEP giving an estimated HIV incidence of 2.1 (95% CI 0.05–11.7) per 1000 person-years [5]. This participant had not taken tenofovir during the 60 days before the reactive HIV test. In the open-label study 28% of participants did not return for any follow-up visits, which suggests engagement and adherence remain a challenge in this group.

3.3.3 Safety

In the Bangkok RCT the occurrence of serious adverse events was similar between the two groups (*P*=0.35). Renal function was assessed using the Cockcroft–Gault, Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[6]. There were small but significant decreases in cross-sectional measures of creatinine clearance (CrCl) and eGFR at 24, 36, 48 and 60 months in the TDF group compared with the placebo group. Creatinine clearance measured when study drug was stopped was lower in the tenofovir group (89.7 mL/min, 95% CI 86.7–92.7) than the placebo group (97.9 mL/min, 95% CI 95.1–100.7; *P*<0.001), but the difference resolved when tested a median of 20 months later. Nausea was more common in participants in the tenofovir group (8%) than in the placebo group (5%; *P*=0.002).

There were no reported TDF resistance mutations in any of the participants in the Bangkok Tenofovir Study who were either HIV positive at enrolment or who subsequently seroconverted in either group [1].

3.3.4 Risk behaviour

In the Bangkok Tenofovir Study the proportion of participants injecting drugs, sharing needles, and reporting sex with more than one partner significantly declined during follow-up [7]. Multivariable analysis showed that younger age (i.e. 20–29 years; HR: 1.9, 95% CI 1.1–3.4; *P* = 0.02), sharing needles (HR: 8.9, 95% CI 4.1–19.3; *P*<0.001), and incarceration in prison (HR: 2.7, 95% CI, 1.4–4.9; *P*= 0.002) were independently associated with incident HIV infection. Sexual activity was not associated with HIV infection, suggesting that the reduction in HIV incidence among participants taking daily oral TDF was as a result of preventing parenteral transmission. Participants reporting sex with a partner of the opposite sex (OR: 1.1, 95% CI 0.6–1.9; *P* = 0.79), sex with a live-in partner (OR: 0.6, 95% CI 0.4–1.1, *P* = 0.11), sex with a casual partner (OR: 1.6, 95% CI 0.9–3.0; *P*= 0.13), or men reporting sex with male partners (OR: 0.0, 95% CI 0.0–5.9; *P*=0.50) were not at a higher risk of HIV infection compared to those who did not report these behaviours.

3.3.4.1 Chemsex and slamming

Chemsex is the use of three specific drugs ('chems') in a sexual context. These three drugs are methamphetamine (crystal, meth, Tina), mephedrone (meph/drone, miaow miaow, m-cat) and GHB/GBL (G, Gina). Chemsex and slamming (the act of injecting the drugs used in chemsex) should be distinguished from injecting drug use involving heroin as the drugs, demographics of users and risks for STIs, HIV and other blood-borne viruses are different. Chemsex is frequently reported in MSM who are at risk of HIV [8,9]. In the PROUD study, at baseline, drugs commonly associated with drug use in a sexual context (mephedrone, GHB/GBL and methamphetamine) were used by 231/525 (44%) participants in the previous 3 months [10]. Strategies to identify to those at risk and to provide support and interventions should form part of PrEP consultation [11].

3.3 Evidence for safety and efficacy in people who inject drugs (PWID): recommendations
7. PrEP is not recommended for people who inject drugs where needle exchange and opiate substitution programmes are available. (2C)
8. We recommend that existing harm-reduction strategies such as needle exchange and opiate substitution programmes should be encouraged for people who inject drugs. (1D)
Good practice points
• **Consider PrEP on a case-by-case basis in people who inject drugs in an outbreak situation or with other factors that put them at increased risk of HIV acquisition. See Section 4.**
• **Interventions for chemsex should be encouraged for people who are identified as being at elevated risk of HIV acquisition through report of injecting drug use during chemsex (slamming).**

3.3.6 References

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3.4 Evidence for safety and efficacy in trans people

Evidence for safety and efficacy in trans people: summary

- **Transgender women (TGW) only formed a minority of PrEP RCT participants.**
- **In a subgroup analysis of iPrEx and iPrEx-OLE, daily oral TDF-FTC had lower effectiveness in TGW than MSM, primarily linked to lower adherence as measured by drug concentrations.**
- **An interaction between TDF-FTC and feminising hormones is unlikely to be due to differing metabolism and clearance.**
- **The possibility of a drug–drug interaction between PrEP and female hormones remains a concern for TGW and clinicians should be aware that TGW may prioritise this over other health concerns, which may impact on PrEP adherence.**
- **There are no data on PrEP effectiveness in transgender men (TGM).**
- **There are no data on PrEP effectiveness for frontal (vaginal) sex in either TGW or TGM.**

3.4.1 Efficacy in trans women

While there are no data from the UK, it is estimated that transgender women (TGW) are 49 times more likely to be infected with HIV than the general population worldwide [1]. Globally, TGW also experience high levels of discrimination, structural barriers to healthcare, violence, poverty, high unemployment and housing instability, which all contribute to the high burden of HIV among TGW [2].

3.4.1.1 Phase 3 clinical studies

Although a number of Phase 3 RCTs included the option to recruit TGW [3-5], in reality, TGW have formed only a minority of trial participants. In 2015, the iPrEx study group carried out an unplanned subgroup analysis considering efficacy specifically in this group [6]. The randomised phase of iPrEX compared daily oral TDF-FTC with

placebo. Of the 2499 participants in iPrEx, 339 (14%) were classified as TGW. Amongst TGW there were 11 HIV infections in the PrEP group and ten in the placebo group (HR: 1.1, 95% CI 0.5–2.7), indicating minimal efficacy of PrEP in TGW. It is notable however that none of the TGW in the active arm who became infected with HIV had detectable drug at the time of seroconversion.

There are no studies in TGW of intermittent or on-demand dosing.

3.4.1.2 Other studies

The subgroup analysis of iPrEx [6] also considered the open-label extension of the study. During this phase, 192 TGW enrolled and were eligible to take PrEP. Of those receiving PrEP, TGW had lower drug concentrations than did MSM overall [7]. Protective drug concentrations (indicating use of four or more pills per week) were detected in 17% of person-years of follow-up in transgender women compared 35% of person-years follow-up in MSM (P<0.0001). There were no seroconversions in TGW with drug concentrations commensurate with 4 or more tablets per week. Seroconversion occurred only among TGW having drug concentrations compatible with less than two tablets of TDF-FTC per week. The study authors concluded that the lack of PrEP efficacy in TGW was primarily a result of low adherence as measured by drug concentrations.

3.4.1.2 Adherence

In both iPrEx and iPrEx-OLE, adherence in TGW was low. Of concern, the subgroup analysis of iPrEx [6] showed that MSM with the highest risk behaviours were more adherent to PrEP, but this was not the case in TGW at highest risk. Lower TDF concentrations were observed among TGW using feminising hormones compared with other TGW not using hormones (OR: 0.32, 95% CI 0.16–0.66; P= 0.002). This may reflect less PrEP adherence among TGW whose concerns about drug–drug interactions were not fully addressed during the trial. However, no systemic drug–drug interactions are expected between TDF-FTC, which is cleared in the kidney, and oestrogens and progestogens, which are metabolised in the liver.

3.4.3 Safety in trans women

3.4.3.1 Adverse events and grade 3–4 safety data

The iPrEX subgroup analysis [6] showed that moderate and severe adverse events in TGW were rare, and there was no difference between the PrEP and the placebo group (31 vs 28 events; P=0.73).

3.4.3.2 Renal function

In iPrEx, there was a non-significant mean difference from baseline in estimated creatinine clearance at week 24 of –1.0 mL/min (95% CI –3.8–1.8; P=0.48) in TGW in the active arm, which was similar to differences in MSM [8]. However, presence of TDF in the active arm was low among TGW.

3.4.3.3 Bone mineral density

Dual-energy X-ray absorptiometry (DEXA) scans were performed in a subset of participants enrolled in the iPrEx study (246 TDF-FTC, 251 placebo arms) of whom 11% were TGW. Bone mineral density at the hip increased by 0.5% (95% CI -0.5–1.5) from baseline in TGW at week 24, compared with a decrease of 0·4% (95%CI -0.7– -0.2) among MSM and at the spine, bone mineral density increased by 0.3% (-0.8–1.3) from baseline in TGW and decreased 0.7% (–0.3–1.2) among MSM (P=0.08) [6]. At week 24, intracellular tenofovir diphosphate (TFV-DP) was detected in only 53% of sub-study participants randomised to TDF-FTC and TFV-DP levels exhibited a statistically significant inverse relationship with changes in BMD.

3.4.3.4 Interaction with female hormones

Interaction between PrEP and female hormones is a concern for TGW, and many will prioritise hormone use over other health concerns such as aquisition of HIV. In a PrEP acceptability study comprising 107 TGW in Thailand [9], three-quarters feared that PrEP might interact with other medications, including female hormones.

Co-administration of TDF-FTC and oestradiol has not been studied, but based on metabolism and clearance, a clinically significant interaction is unlikely [10]. Oestradiol is metabolised by CYP1A2 and CYP3A4, whereas both TDF and FTC do not impact cytochrome P450 activity, and are excreted via the kidney.

In the Partners PrEP study, there was no difference in PrEP efficacy between women using hormonal contraception versus those who were not [8]. No trials to date have studied efficacy at hormonal levels used for feminisation. There are two demonstration projects planned for transwomen in California and Brazil. These studies will include an examination of possible drug interactions between PrEP use and feminising hormones [11,12].

The University of Liverpool (www.hiv-druginteractions.org) has released an updated guide on interactions between ARVs and oestrogen and anti-androgen preparations used in male-to-female gender reassignment therapy, indicating there is no clinically significant interaction expected between TDF or FTC and hormone therapies used for gender transitioning except for ethinylestradiol. (See link for more details: https://liverpool-web-production.s3.amazonaws.com/printable_charts/pdfs/000/000/024/original/Hormone_Chart_2017_Apr.pdf?1491312832).

Any concerns about drug–drug interactions should be fully explored and addressed with reassurance given to optimise adherence. For further information and current national good practice guidelines for general assessment and treatment of trans adults see the following document [13].

3.4.3.5 Drug resistance

Among the TGW participants with incident infections in the iPrEx study, none had FTC or TDF selected mutations or reduced phenotypic susceptibility. Among the two TGW with acute HIV infection at randomisation to the active arm, M184V or I mutations were predominant at seroconversion, but waned to background levels within 24 weeks after discontinuing drug [14].

3.4.3.6 Risk behaviour

In the iPrEx subgroup analysis, TGW more frequently reported transactional sex or commercial sex work which can be associated with a higher risk of HIV acquisition, receptive anal intercourse without a condom, or more than five partners in the past 5 months when compared with MSM. The study authors did not comment upon risk compensation over time or STI incidence [6].

3.4.4 Trans men

To date, there are no clinical trials that include transgender men (TGM) as participants. PrEP efficacy in this group is therefore unknown. Transgender MSM solely having anal sex could be assumed to have similar levels of protection from PrEP as cis gender MSM, if achieving similar levels of adherence.

Under the influence of testosterone therapy, there may be vaginal atrophy, theoretically increasing the risk of HIV transmission. There is evidence to suggest that daily dosing of TDF-FTC is needed to achieve effective concentrations in vaginal tissue and the lead-in time to achieve steady state is longer [15].

3.4 Evidence for safety and efficacy in trans people: recommendations

9. **We recommend that PrEP with daily oral TDF-FTC should be offered to HIV-negative trans women who are identified as being at elevated risk of HIV acquisition through condomless anal sex in the previous 3–6 months and ongoing condomless sex. (1A)**
10. **We recommend that daily oral TDF-FTC should be offered to HIV-negative trans women and trans men having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)**

Good practice points

- **PrEP could be considered on a case-by-case basis in trans women and trans men with current factors other than condomless anal sex that may put them at increased risk of HIV acquisition. See Section 4.**
- **For both trans women and trans men a discussion should be had regarding unknown PrEP efficacy for frontal (vaginal) sex.**
- **A discussion should be had, both at PrEP initiation and maintenance visits, that there are no known interactions between TDF-FTC and feminising or masculinising hormones except for ethinylestradiol.**

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3.5 Evidence for safety and efficacy in young people (15–25 years)

Evidence for safety and efficacy in young people (15–25 years): summary

- **Data regarding safety and efficacy for oral TDF-FTC PrEP in young people is available only for MSM age 15–22 years through Project PrEPare, which had two phases: a randomised placebo-controlled feasibility and acceptability phase (ATN 082); and an open-label PrEP demonstration project (ATN 110).**
- **Adherence as measured by self report and dried blood spots decreased over time. By week 48 in ATN 110, only 34% of participants had drug levels consistent with four or more pills per week.**
- **Indices of renal function in ATN 117 did not differ between high- or low-TDF exposure groups supporting the short-term renal safety of TDF-based PrEP in adolescent boys and young men.**
- **Bone density showed progressive decline in high vs low TDF exposure groups over 48 weeks, but discontinuation of TDF-FTC led to recovery of bone mineral density changes over a 48-week follow-up period. This suggests PrEP-related bone loss in young men is reversible.**
- **However, the persistently lower Z scores in the spine, even at 48 weeks off PrEP, suggest that the use of TDF PrEP may be a particular risk for adolescents as this is a critical period for attainment of peak bone mass.**

3.5.1 Efficacy

Despite the majority of large PrEP studies recruiting from the age of 18 years, few were designed to report safety and efficacy specifically in the younger age group. When reported, younger age is associated with poorer adherence and lower TDF-FTC levels [1,2]. This is not surprising, as adherence to medication is known to be a challenge for young people, whether for treatment of disease or pregnancy prevention [3-7]. Recent Phase 3 studies of the dapavirine ring reported that efficacy was lower in the younger age groups [8,9].

The only study to date to report on adherence and safety specifically in young people is Project PrEPare. This is composed of two phases: a randomised placebo controlled feasibility and acceptability phase (ATN 082)[10]; and Project PrEPare 2 (ATN 110) [11], an open-label PrEP demonstration project and Phase 2 safety study in MSM. For Project PrEPare 2 (ATN 110), HIV-negative young men who have sex with men (YMSM) age 18–22 years were recruited from 12 urban cities in the United States. Of 2186 screened, 400 were eligible and 200 were enrolled into the study (mean age 20.2 years; 54.5% Black, 26.5% Latino). Eleven individuals were diagnosed with HIV at

baseline (4%) and two participants were prematurely discontinued due to diagnosis of acute HIV via RNA at enrolment visit.

There were four HIV seroconversions during the study giving an HIV incidence rate of 3.29 per 100 person-years (95% CI 0.07–6.52). None of the participants who seroconverted had detectable levels of tenofovir diphosphate (TFV-DP) in the sample that was drawn closest to the seroconversion date.

3.5.2 Adherence

Project PrEPare (ATN 082) [10] and Project PrEPare 2 (ATN 100) [11], both reported adherence. Both studies included an evidence-based behavioural HIV prevention intervention, Many Men Many Voices (3MV)[12], with participants in PrEPare 2 also receiving personalised cognitive counselling [13].

Follow-up of the 58 participants randomly recruited to Project PrEPare, occurred every 4 weeks for 24 weeks. Self-reported adherence to study pill fluctuated, ranging from five missed doses (weeks 16 and 20) to 17 missed doses (week 24). The rates of detectable TFV-DP in the plasma of the TDF-FTC arm decreased over the study visits: 63.2% at week 4 to 20% at week 24.

Study visits for Project PrEPare 2 occurred monthly for the first quarter and then quarterly to 48 weeks. TFV-DP was measured using dried blood spots: the majority of participants had detectable drug over the course of the study; 90% had detectable drug at 12 weeks; 81% at week 24; and 69% at week 48. By week 48, only 34% of participants had a drug level consistent with at least four pills per week, the level consistent with no HIV infections in iPrEx-OLE [1]. Of note, the median level for African American participants was below this protective threshold at all time points. Participants reporting recent condomless sex had consistently higher TFV-DP levels (P=0.01).

ATN 113 (Project PrEPare) was a demonstration project and Phase 2 safety study that aimed to obtain data on safety and to evaluate rates of adherence, and patterns of sexual risk behaviour among young MSM aged 15–17 [14]. The study combined PrEP with behavioural risk reduction and adherence support in 78 HIV-uninfected MSM aged 15–17 years [14]. More than 95% had detectable drug levels and more than half had highly protective levels (at least four doses per week) during the first 3 months, but this dropped to about 75% and 32%, respectively, after they switched to quarterly follow-up.

3.5.3 Safety

3.5.3.1 Overall adverse events and grade 3–4

Of 258 participants in Project PrEPare [10] and Project PrEPare 2 [11], there were seven grade 3 adverse events thought to be possibly or probably related to study drug: one increased bilirubin, two headache (one migrainous), one nausea, one weight loss and two instances of decreased creatinine clearance in the same participant. For that participant, the estimated creatinine clearance was 180 mL/min/1.73 m^2 at baseline and showed considerable variation over the course of the study, but never declined below 110 mL/min despite continuation of study drug. More nausea was noted in the TDF-FTC group (23.5%) of Project PrEPare vs placebo (0%) and no-pill (5.9%) groups.

The ATN 110 extension study followed BMD in young men who either lost or failed to gain bone mineral content or BMD at week 48 of the initial study (n=102) for an additional 48 weeks, of whom 72 patients discontinued PrEP and were eligible for inclusion in the final bone extension analysis [15]). As men reach peak bone mass at approximately 25 years of age, it would be abnormal not to gain bone during this period of early adulthood, and important to determine if any effects of TDF on BMD are reversible upon discontinuation.

3.5.3.2 Renal function

Metabolic data were collected from a subset of participants in ATN 110 [11] and ATN 113 [14] (15–17 year old participants in Project PrEPare). This sub-study (ATN 117 [16]), aimed to characterise the relative roles of renal (glomerular and tubular) versus endocrine (calcium phosphate–vitamin D metabolism) changes in TDF-associated bone toxicity. Using TFV-DP concentrations in dried blood spots, they categorised participants into high (>861 fmol/punch), moderate (≤861–≥345 fmol/punch) and low (<345 fmol/punch) exposure categories. Serum creatinine rose slightly during the first 12 weeks, but eGFR did not decline significantly at any time point. There were no significant changes in any other measure of renal toxicity. None of the indices of renal function (urine glucose, retinol-binding protein, β2-microglobulin, protein/creatinine or calcium/creatinine ratio; serum creatinine, calcium, or phosphate; or calculated eGFR) differed by drug-exposure category.

The authors conclude that these findings support the short-term renal safety of TDF-based PrEP in HIV-negative adolescent boys and young men. They comment that a lack of renal effect could result from higher baseline eGFR in the young study group, and also that duration of follow-up was short, postulating that a longer exposure may be required to reveal a relationship between tubular impairment and bone loss.

3.5.3.3 Bone mineral density

Compared to the low drug-exposure group, the high drug-exposure group (as measured by measured by red blood cell TFV-DP concentrations) exhibited greater and more consistent change in biochemical markers of calcium (PTH), phosphate (FGF23), and bone turnover (osteocalcin) than markers of renal glomerular or tubular dysfunction over 48 weeks of TDF-FTC PrEP, suggesting that endocrine disruption (PTH-FGF23) is a primary contributor to TDF-associated BMD decline in this age group [16].

In terms of BMD, the ability of TDF to decrease or impair accrual of BMD in this young study cohort was demonstrated by the greater than 3% difference in change in BMD (percentage difference from the baseline value) and BMD Z-score in the total hip and femoral neck from baseline to week 48 in the high drug-exposure group compared to the low drug-exposure group (−1.59 [2.77]% vs +1.54% [3.34]%, respectively; *P*=0.001). Spine BMD changes followed a similar pattern, but did not achieve statistical significance (*P*=0.19 at week 48). The authors suggest that this pattern of BMD change suggests a stronger effect of TDF on cortical bone (the hip is a predominantly cortical site) and a lesser effect on trabecular bone (predominant in the spine) in young men, some of whom were aged 15 years.

Following discontinuation of TDF-FTC, changes in bone mass of 72 participants of ATN 110 (mean age 20.1 years), was assessed at 24 and 48 weeks post discontinuation via DEXA scanning [15]. Among this group, average BMD changes from baseline to week 48 of the PrEP treatment phase were: spine −0.25% (*P*=0.23); hip −1.43% (*P*=0.002); whole body (WB) −0.63% (*P*=0.03).

However, in the 48 weeks after PrEP was stopped at the end of the extension phase (48 weeks on TDF-FTC followed by 48 weeks off TDF-FTC), BMD increased significantly at all sites: +1.15% in the spine (*P*=0.003), +1.02% in the hip (*P*=0.04), and +0.64% in the whole body (*P*=0.01).

When comparing net changes in BMD from baseline to the end of the extension phase, these were not significant in the hip −0.35% or whole body −0.11% , but a significant increase in BMD for the spine (+0.87%, *P*<0.05) was reported at the end of 48 weeks off PrEP when compared to baseline [15].

In terms of Z-scores, which measure the number of standard deviations a person is away from an age-, sex-, and race-matched population, with a normal Z-score being 0, there was however a suggestion of some persistent effects of PrEP on BMD at end of follow-up (48 weeks post PrEP), with small, but statistically significant net decreases from baseline in Z-scores in the spine (−0.164, *P*<0.001) with no significant change in the hip (−0.03) or whole body (−0.07). There is therefore some evidence of impact on bone density caused by exposure to TDF-FTC

over 48 weeks in 18–22-year-old males, but discontinuation of TDF-FTC led to recovery of bone mineral density changes over a 48 week follow-up period. These results suggest that the effect of PrEP on bone loss in young men is reversible. However, the persistently lower Z scores in the spine, even at 48 weeks off PrEP at the end of follow-up, suggests that the use of TDF PrEP may be a particular risk for adolescents as this is a critical period for attainment of peak bone mass.

The authors suggest that endocrine-focused interventions might be reasonable to consider for young men taking TDF-FTC for PrEP, and that supplementation with calcium and vitamin D may lessen TDF-related BMD decline, but the data is lacking in HIV-negative individuals and a study of the effect of vitamin D supplementation on BMD decline in TDF-FTC PrEP is warranted, particularly as vitamin D and calcium supplementation lessens BMD decline at TDF-containing ART initiation [17].

3.5.4 Risk behaviour

In Project PrEPare [10], sexual-risk behaviour declined in all study arms from baseline through to week 24. The baseline rates of HIV transmission risk behaviour and STI prevalence were high in Project PrEPare 2 [11]; these behaviours remained largely stable over time. However, the fact that ongoing HIV transmission risk behaviour remained high, PrEP adherence counselling in this group was extremely important.

3.5 Evidence for safety and efficacy in young people (15–25 years): recommendations

11. **We recommend that PrEP with daily oral TDF-FTC should be offered to young MSM and TGW women (15–25 years) who are identified as being at elevated risk of HIV acquisition through condomless anal sex in the previous 3–6 months and ongoing condomless anal sex. (1A)**
12. **We recommend that PrEP with TDF-FTC should be offered to young people having condomless anal sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)**
13. **Routine BMD scanning in young people initiating PrEP is not recommended. (1D)**

Good practice points

- **Consider PrEP with daily oral TDF-FTC on a case-by-case basis to young people with current factors other than condomless anal sex that may put them at increased risk of HIV acquisition. See Section 4.**
- **The risk and benefits of providing PrEP for adolescents should be weighed carefully in the context of UK laws and judgements about autonomy in healthcare decision-making (e.g. Fraser competency), and balanced against protecting young people from harm.**
- **A discussion about side effects including impact upon bone density in young people should be held at PrEP initiation and maintenance visits.**

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3.6 Evidence for the timelines for starting and stopping PrEP

Evidence for the timelines for starting and stopping PrEP: summary

- **The time to achieve a protective concentration is determined by the drugs used, the dose, the frequency of dosing and the target tissue.**
- **Available data suggest that time to clinical protection for TDF and FTC (and active metabolites) is shortest in the lower gastrointestinal tract, followed by peripheral blood mononuclear cells (PBMCs) and then in the female genital tract (FGT).**
- **The active metabolite of TDF concentrates to much higher levels in the lower gastrointestinal mucosa relative to PBMCs whereas FTC concentrates in the FGT.**
- **The time to clinical protection for anal sex has been evaluated in a single RCT (IPERGAY), starting with double-dose of TDF-FTC 2–24hrs before sex. This is supported by pharmacokinetic data in animal studies.**
- **The time to clinical protection for vaginal sex has been extrapolated from pharmacokinetic studies of TDF-FTC and there is consensus for a lead-in time for protection of 7 days.**
- **Data from IPERGAY demonstrates that, when PrEP is taken to prevent HIV acquisition from anal sex, dosing can be stopped when an oral dose has been taken 24 hours and 48 hours after the last episode of potential exposure. This is supported by animal and pharmacokinetic studies when the person is receptive, but there are fewer data for foreskin and urethra.**
- **There is consensus that, when taken to prevent HIV acquisition from vaginal sex, TDF-FTC can be stopped when a daily oral dose has been taken for 7 days after the last episode of potential exposure.**

There are several well-conducted pharmacokinetic studies which have used diverse methodology to address the question of time to clinical protection. There is considerable heterogeneity across the results, but a consensus with respect to the concentration of the active metabolites of TDF and FTC in colonic and cervico-vaginal tissue relative to PBMCs, the shorter time it takes to achieve the peak concentration of FTC-TP compared to TFV-DP, and the longer half-life of TFV-DP in all tissues. There is also consensus that concentrations of active metabolites in the genital and colonic tissues are probably the most important in averting infection.

3.6.1 Blood PBMCs

Anderson *et al.* combined data from the iPrEX effectiveness trial and the STRAND pharmacokinetic study to determine the relationship between PrEP efficacy and TFV-DP concentration in PBMCs. They deduced that an intracellular concentration of TFV-DP (the active metabolite) of 16 fmol per million in cryopreserved PBMCs was associated with a 90% reduction (EC_{90}) in HIV acquisition relative to the placebo arm, and derived effect sizes of 76% for two doses a week, 96% for four doses and 99% for seven doses, respectively [1]. A similar approach was used to evaluate the time to clinical protection in PBMCs and rectal mononuclear cells, and the duration of protection after stopping PrEP by Seifert *et al.* [2]. TFV-DP concentrations in PBMCs (and rectal mononuclear cells) were measured in twenty-one HIV-uninfected adults in an intensive pharmacokinetic study of 30 days of daily TDF-FTC followed by 30 days off drug. Using the iPrEx drug-detection efficacy model described above, the inferred HIV risk reduction derived from PBMC TFV-DP concentration reached 99% (95% CI, 69–100%) after five daily doses, and remained >90% for 7 days after stopping drug from steady-state conditions. In contrast to the effect described by Anderson *et al.* (described above) and using the same drug-detection efficacy model, the proportion of participants reaching the EC_{90} was 77% after five doses and 89% after seven doses [3].

The HPTN 066 study sought to establish drug concentrations within PBMCs (and also reproductive and gastrointestinal tracts) when oral TDF-FTC was given at different doses and at different dose schedules under direct observation for 5 weeks. Forty-nine study participants (29 females and 20 males) were randomly assigned to one of four oral regimens of fixed-dose FTC-TDF. Participants received one tablet weekly (1/week), one tablet twice weekly (2/week), two tablets twice weekly (4/week), or one tablet daily (7/week) with sampling prior to the second dose, at day 7 and every 7 days through to day 49. All regimens achieved steady-state concentrations for the active metabolites in PBMCs at 7 days, earlier than predicted from similar studies in HIV positive populations. With daily dosing, iPrEX EC_{90} concentrations of TFV-DP in unfractionated PBMCs were also achieved in all participants after 7 days. Two weeks after the final dose, TFV-DP in PBMCs was above the lower limit of quantification in seven of eight in the 4/week group and eight of 10 in the daily group whereas FTC-TP was only detected in the daily group at this timepoint [4].

Comparable results were seen in an intensive 60-day pharmacokinetic study of 40 individuals (19 HIV-negative and 21 HIV-positive individuals) receiving daily TDF-FTC where drug concentrations were analysed in blood, genital and rectal compartments. This study included an earlier sampling timepoint in all participants at day 3. The estimated time to steady state in PBMC was 3 days for FTC-TP and 11 days for TFV-DP. There were small differences between HIV-negative and -positive populations but these were not thought to be clinically meaningful [2].

3.6.2 Female and male genital tract

Similar EC_{90} values for 'protective concentrations' are not well defined for the female genital tract (FGT), urethra, glans or foreskin, and may vary from that in blood PBMCs. Several papers have shown that TFV-DP achieves much higher concentrations in rectal tissues relative to vaginal tissues.

Paterson *et al*. evaluated the concentrations in blood and genital secretions of TFV and TFV-DP plus FTC and FTC-TP in 15 HIV-negative individuals, including seven women, given a single oral dose of TDF-FTC [5]. Drug levels and their active metabolites were also measured in homogenates prepared from vaginal and cervical tissues and compared with rectal homogenates. Following single dose of TDF-FTC, the area under the concentration–time curve from 24 hours to 14 days (AUC 1–14 days) for FTC in genital secretions was 27-fold greater than in blood plasma and 10- to 15-fold higher than in rectal tissue. Levels of FTC-TP were, however, only detected for 2 days after dosing in vaginal and rectal tissues [5]. Thus, FTC and FTC-TP levels seem to accumulate rapidly in cervicovaginal tissues and fluid but decay rapidly (terminal half-life of FTC, $T_{1/2}$ = 40 hours). In addition, results suggest the role of FTC in protection in vaginal tissues may be of greater significance, particularly in the early stages after starting oral TDF-FTC.

In contrast to FTC, following a single dose of TDF-FTC, the AUC 1–14 days for TFV was only 2.5-fold greater in genital secretions than in blood plasma whereas in rectal tissue, TFV and TFV-DP concentrations were 100-fold higher than the concentrations in vaginal and cervical tissues [5]. In addition, TFV-DP levels were detectable out to 14 days (terminal half-life $T_{1/2}$ = 71 hours), again suggesting the active metabolite plays a more important role than FTC-DP in averting infection after cessation of oral TDF-FTC after last time of exposure [5].

Time-to-steady state in the FGT has been extrapolated from pharmacokinetic data studies on samples taken from the FGT following a single oral dose of TDF 300 mg and microdose of radiolabelled ^{14}C-TDF to six HIV-negative women [6]. Blood was collected at multiple time points within the first 24 hours, then at 4, 8, 11, and 15 days post-dosing. Rectal and vaginal biopsies plus luminal fluid and blood on days 1, 8 and 15 were assayed for TFV and TFV-DP; no data were collected on FTC. Data were used to estimate the rate of absorption, and rate of formation and decay of TFV-DP. Results demonstrated anatomical variation in pharmacokinetics across CD4 cells extracted from PBMCs, colon biopsies and female genital tract biopsies. Respectively, the $T_{1/2}$ of TFV-DP was markedly

longer in vaginal tissues than PBMCs (139 hours vs 112 hours) and also longer than that seen in colonic samples (139 hours vs 60 hours), underlying the importance of the terminal decay of TFV-DP in averting infection [6,7].

HPTN 066 also sought to establish drug concentrations within reproductive tissue when oral TDF-FTC was given at different doses [4]. Of 49 study participants recruited, 29 were female. Samples, including vaginal tissue (biopsy) and cervicovaginal fluid (direct aspirate), were collected for drug assessment at end of dosing and 2 weeks later in a subset of participants who underwent a 'washout period'[4].

Although no assessment of lead-in times was performed in the FGT, HPTN 066 did establish that, except for vaginal homogenate TFV and FTC concentrations with daily dosing, nearly all vaginal samples were below quantitative limits, implying that only daily dosing is likely to be effective and by inference, lead-in time is likely at least a week [4].

Finally, by combining an *in vitro* efficacy model with mucosal tissue PK data and mathematical modelling, Cottrell *et al*. attempted to determine the number of doses required for effective PrEP. Mucosal concentrations of TDF and FTC (including vaginal, cervical and colorectal samples) and their metabolites were measured in 47 HIV-negative women administered a single dose of TDF-FTC. Results were compared with competing endogenous nucleotides. *In vitro* models (using TZM-bl and CD4+ cells) were then used to identify EC_{90} ratios for protection [8]. By contrast to HPTN 066, the model predicted that in the FGT, at least 98% of the population achieved protective mucosal tissue exposure by the third daily dose of TDF-FTC. Aligning with conclusions of HPTN 066, however, a minimum adherence to six of seven doses/week (85%) was required to protect lower FGT from HIV [4].

No data exist on double dosing on day 1 of lead-in for women wishing to use PrEP; however, such an approach is biologically plausible in order to load more rapidly. No data exist on penetration of TDF or FTC into the male genital tract.

3.6.3 Rectal tissues

Seifert *et al*. examined TFV-DP concentrations in rectal mononuclear cells among 21 HIV-negative adults over 30 days of daily TDF-FTC followed by 30 days off drug [3]. The percentage of steady state reached for TFV-DP in rectal tissue was 71% after three doses, 88% after five and 94% after seven doses; it is speculated, however, that protective concentrations of TDF in the rectal mucosa will be achieved more rapidly.

Earlier time to achieving protective concentrations is supported by results in a study by Patterson *et al*. in which 15 HIV-negative individuals were given a single oral dose of TDF-FTC [4]. Here, both drugs were measured in homogenates prepared from rectal (and vaginal and cervical tissues). In rectal tissue, high penetration of TFV-DP was demonstrated at the end of the first 24-hour period after dosing (median 206,950 fmol/g); FTC-TP concentrations, however, were substantially lower than TFV-DP at 24 hours (124 ng/g). Rectal TFV-DP concentrations were 100-fold higher than the vaginal and cervical concentrations.

Further data on time to steady state for FTC and TDF in rectal tissues comes from the Cell-PrEP study; in the 60-day pharmacokinetic study with daily oral TDF-FTC, steady state concentrations for TFV-DP were achieved in rectal mononuclear cells by day 5 and was 10-fold that seen in PBMCs. Significantly, however, FTC appeared to reach steady state 2 hours into the first dose within rectal mononuclear cells [2].

This rapid accumulation of FTC in rectal tissues may explain the findings within the IPERGAY study where an apparent lead-in time of 2–24 hours with a double dose of TDF-FTC conferred 86% risk reduction in HIV acquisition and thus may play an important role in event-based dosing [9].

3.6.4 Duration of PrEP use following last possible exposure

Duration of continued PrEP depends on site of last potential exposure. Data from IPERGAY suggests that where exposure occurs through anal sex, a high protective effect is achieved when daily oral doses are taken 24 hours

and 48 hours after the first double dose (in cases of multiple consecutive sexual intercourse, participants were instructed to take one pill per day until the last sexual intercourse and then to take the two post-exposure pills) [9]. Evidence in relation to duration of continued use following exposures at other anatomical sites, however, remains less clear and has not been clearly addressed in clinical trial settings. Importantly, the duration of time for HIV to be cleared from mucosal sites following last potential exposure is unknown and as such, the duration of time that PrEP should be continued to cover this time can only be inferred. Although it is recommended to continue post-exposure prophylaxis for 28 days after exposure, this is based on the premise that the early stages of HIV lifecycle may have occurred by the time PEPSE has been initiated and consequently, a longer duration of treatment is required until the virus can be cleared. In the instance where a person is receiving PrEP however, early stages of the viral lifecycle are inhibited and thus, a shorter duration of continued PrEP use is likely to be required following last potential HIV exposure.

Data from Cottrell *et al*. suggests high adherence is needed in women (at least six of seven doses/week) because drug concentrations quickly drop (particularly FTC-DP) in vaginal tissue thus suggesting a longer duration of continuation is needed in following potential vaginal exposure [8]; to date, expert opinion estimates a continued duration of TDF-FTC of 7 days after last potential exposure.

Seifert *et al* estimated the time taken for TFV-DP levels to fall below the protective threshold after stopping PrEP in PBMCs extrapolated from iPrEx data [3]. At 2 days after stopping drug, 80% of TFV-DP concentrations remained above protective thresholds (EC_{90}), decreasing to 48% at 7 days after discontinuation. In sensitivity analyses, the proportion of concentrations above the EC_{90} ranged from 86% to 91% at 2 days after stopping drug, and 48% to 63% at 7 days after stopping drug.

3.6 Evidence for the timelines for starting and stopping PrEP: recommendations

14. **We recommend that if the risk of HIV acquisition is through anal sex, PrEP can be started with a double dose of TDF-FTC taken 2–24 hours before sex and continued daily until 48 hours after the last sexual risk. (1B)**

15. **We recommend that if PrEP for anal sex has been interrupted and it is less than 7 days since the last TDF-FTC dose then PrEP can be re-started with a single dose of TDF-FTC. (1B)**

16. **We recommend that if the risk of HIV acquisition is through vaginal sex, PrEP should be started as a daily regimen 7 days ahead of the likely risk and continued daily for 7 days after the last sexual risk. (1C)**

Good practice points

- **Individuals whose risk is through vaginal sex should still be informed about starting oral PrEP with a double dose of TDF-FTC in case there are times when it is not possible to take for a full 7 days before a potential risk, but advised that the evidence currently only supports this regimen for anal sex.**

- **Individuals at risk through injecting drug use as well as sexual risk should be informed that it takes longer to achieve protective concentrations in the blood, and that 7 days before and 7 days after is advisable.**

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4 Baseline risk-assessment

4.1 How to target those at risk of HIV transmission

PrEP is indicated for those at greater risk of HIV acquisition and therefore comprehensive history taking and risk assessment, including both sexual and drug taking histories, is required to identify those most likely to benefit. Clinicians will need to make pragmatic decisions with patients about future HIV risk, their need for PrEP and individual–level assessment of the benefit versus potential harms of PrEP. At a population level, given limited resources and a desire to achieve the maximum impact of PrEP, clinicians should use clinical criteria and recommendations as outlined in these guidelines, along with local and national criteria for NHS or clinical trial eligibility to provide PrEP to those at highest risk of HIV acquisition.

It is well recognised that there are other risk behaviours and vulnerability factors that increase the risk of HIV acquisition and these should be taken into consideration on a case-by-case basis by clinicians when considering eligibility for PrEP and assessing HIV risk. Although this lacks a clear evidence base, the writing group has considered this in terms of those who are 'high risk' and therefore PrEP would be recommended and those who are at 'medium risk' where PrEP should be considered (Tables 4.1.1 and 4.1.2).

Table 4.1.1. Summary table of recommendations for PrEP

<table>
<tr><td colspan="2">High risk: recommend PrEP</td></tr>
<tr><td colspan="2">(i) HIV-negative MSM and trans women who report condomless anal sex in the previous 3–6 months and ongoing condomless anal sex. (1A)
(ii) HIV-negative individuals having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies. (1A)</td></tr>
<tr><td colspan="2">Medium risk: consider on a case-by-case basis</td></tr>
<tr><td colspan="2">PrEP may be offered on a case-by-case basis to HIV-negative individuals considered at increased risk of HIV acquisition through a combination of factors that may include the following:</td></tr>
<tr><td>Population-level indicators
Heterosexual black African men and women
Recent migrants to the UK
Transgender women
People who inject drugs
People who report sex work or transactional sex</td><td>Clinical indicators
Rectal bacterial STI in the previous year
Bacterial STI or HCV in the previous year
Post-exposure prophylaxis following sexual exposure (PEPSE) in the previous year; particularly where repeated courses have been used</td></tr>
<tr><td rowspan="2">Sexual behaviour/sexual-network indicators
High-risk sexual behaviour: reporting condomless sex with partners of unknown HIV status, and particularly where this is condomless anal sex or with multiple partners
Condomless sex with partners from a population group or country with high HIV prevalence (see UNAID definitions) [1]
Condomless sex with sexual partners who may fit the criteria of 'high risk of HIV' detailed above
Engages in chemsex or group sex
Reports anticipated future high risk sexual behaviour
Condomless vaginal sex should only considered high risk where other contextual factors or vulnerabilities are present</td><td>Drug use
Sharing injecting equipment
Injecting in an unsafe setting (outside safe injection facilities)</td></tr>
<tr><td>Sexual health autonomy
Coercive and/or violent power dynamics in relationships (e.g. intimate partner violence)
Inability to negotiate and/or use condoms (or employ other HIV prevention methods) with sexual partners</td></tr>
</table>

Table 4.1.2. Estimated HIV prevalence (diagnosed and undiagnosed infection) in adults aged 15–59 years in the UK in 2015 [2]

Population group*	HIV prevalence (per 1000) (95% credible interval, CrI)
Total population	
• **All ages**	1.6 (1.5–1.6)
• **Those aged 15–74**	2.1 (2.0–2.2)
• **Men**	2.3 (2.2–2.5)
• **Women**	0.98 (0.95–1.02)
Men who have sex with men (MSM)	
• **UK**	58.7 (51.2–68.0)
• **London**	135 (101–184)
• **Elsewhere in the England and Wales**	39.1 (33.4–46.5)
Heterosexuals	
• **All**	1.0 (1.0–1.1)
• **Black African heterosexual men**	22.2 (21.3–23.6)
• **Black African heterosexual women**	42.6 (41.0–44.3)

*These data are for England and Wales only

4.2 Associations with HIV transmission in UK populations

4.2.1 MSM and transgender women

Inclusion criteria for PROUD were MSM and TGW who reported condomless anal sex on one or more occasions in the previous 90 days and the likelihood of future condomless anal sex [3]. IPERGAY included MSM and TGW who reported anal sex with at least two sexual partners, without systematic condom use, in the previous 6 months [4]. In the PROUD study the baseline predictors of HIV infection in the deferred PrEP group (overall HIV incidence of 9.1 per 100 person-years) were: having a rectal STI (incidence 17.4/100 person-years), two or more condomless anal sex partners in the previous 90 days (incidence 13.6/100 person-years), taking PEPSE in previous 90 days (incidence 12.5/100 person-years) and participating in chemsex (incidence 11.6/100 person-years).

In the IPrEX study, where the overall number needed to treat (NNT) was 62 (95% CI 44–147), NNTs were lowest for MSM and TGW who reported receptive anal intercourse without a condom in the 3 months before screening (NNT 36), cocaine use (12), or a sexually transmitted infection (41) [5]. There is also a clear correlation between previous STIs and sexual behaviour and on-going risk of HIV acquisition. Using GUMCAD data (England and Wales) from 2014, HIV incidence overall in MSM was 1.8 per 100 person-years (Table 4.2.1). This increased to 3.3/100 person-years in those who had a bacterial STI and 4.9/100 person-years in those with a rectal bacterial STI in the previous 12 months (S. Desai and H. Mitchell, personal communication).

Table 4.2.1. HIV incidence in MSM

MSM GUM clinic attendees	Numbers (2014)	HIV incidence per 100 person-years (95% confidence interval)
HIV negative or unknown	104,480	1.8 (1.7–2.0)*
HIV test in previous year (42–365 days prior) [A]	24,235	1.9 (1.6–2.2)
• **Subset of [A] with recent* bacterial STI [B]**	7,949	3.3 (2.7–4.0)
• **Subset of [B] with recent** rectal bacterial STI [C]**	2,125	3.9 (2.8–5.6)
Recent bacterial STI**	21,002	3.3 (2.9–3.9)
Recent rectal bacterial STI**	5,425	4.9 (3.9–6.2)

*HIV incidence estimated in England and Wales using May 2016 GUMCAD extract. Analyses included 36,541 repeat testers and 421 seroconversions

**Recent STI is one in the prior year and/or at first attendance in 2014

4.2.2 Heterosexual men and women

The evidence to support PrEP efficacy and inform detailed risk assessment in heterosexual populations in the UK setting is not as robust as that for MSM. There are no PrEP studies in UK heterosexual populations or in high-income countries. The RCTs evaluating the efficacy of PrEP among heterosexuals have been undertaken in sub-Saharan Africa where HIV prevalence is very high and this substantially limits the ability to generalise these findings to the UK setting.

The estimated prevalence of HIV among all heterosexuals in the UK is low at 1.0 per 1000 (95% credible interal [CrI] 1.0–1.1), but greater among black African adults; 22.2 (95% CrI 21.3–23.6) per 1000 among black African heterosexual men and 42.6 (95% CrI 41.0–44.3) per 1000 among black African heterosexual women [2]. The clinical and cost effectiveness of PrEP depends upon providing PrEP to those at high risk of HIV acquisition. However, it is quite difficult to identify using sufficiently specific clinical criteria for any group of heterosexual people in the UK who would be at sufficient risk. The WHO recommends PrEP for those at 'substantial risk' of HIV acquisition, which is defined as an HIV incidence greater than 3 per 100 person-years [2]. Even among GUM clinic black African attendees, the incidence of HIV is 0.17 per 100 person-years [6], which is far lower than the 2–5% reported in the RCTs. However, we know that black African women are at substantially more risk of transmission than men and those at risk may not attend GUM clinics.

Factors that may indicate the use of PrEP is appropriate include having an HIV-positive partner not on suppressive ART, recent bacterial STI and multiple sexual partners where condoms are not used. In addition, clinicians should consider the risk of any of the patients' sexual partners being HIV positive, as HIV transmission is not determined solely at the individual level but is affected by a more complex interaction within sexual networks and at a population level especially if a patient's sexual partners are from a community or demographic group with a higher HIV prevalence.

4.2.3 People who use recreational drugs or people who inject drugs

In considering HIV risk in people who inject drugs, we have considered separately those who inject heroin in particular from those who engage in drug taking specifically with sex (chemsex). As discussed in Section 3.3 HIV incidence in people who inject drugs in the UK is low, outside specific outbreak situations. People who engage in chemsex however, especially MSM, often engage in higher-risk sexual practices.

Participants in the PROUD and IPERGAY studies reported high levels of recreational drug use and, in particular, drugs associated with chemsex [4,7]. Chemsex is associated with high-risk sexual practices, including group sex, high partner numbers and condomless anal sex.

In PROUD, those reporting chemsex were significantly more likely to be diagnosed with a bacterial rectal STI compared to non-users (41% vs 28%; *P*=0.003) and in the no-PrEP group had a higher HIV incidence (11.6/100 person-years).

A cohort study undertaken in California on 8905 HIV-negative MSM demonstrated that the 754/8905 men who reported methamphetamine use in the previous 12 months scored significantly higher on an evaluated sexual risk behaviour score than the 5922 MSM who reported never using methamphetamine (*P*<0.001). The authors concluded that methamphetamine use increases sexual risk behaviour and these patients may represent ideal candidates for PrEP [8].

4.2.4 People with HIV-positive partners who are not on suppressive therapy

Both HPTN052 and the PARTNER study demonstrated the efficacy of suppressive ART therapy at preventing HIV transmissions through condomless sex in heterosexual and MSM couples [9,10]. The Partners PrEP study demonstrated that PrEP can be an effective strategy to prevent HIV transmission in HIV serodifferent couples where the positive partner has recently started therapy and not yet achieved a suppressed HIV viral load. Partners PrEP demonstrated a relative reduction of 67% in the incidence of HIV-1 with TDF (95% CI 44–81; *P*<0.001) and of 75% with TDF-FTC (95% CI 55–87; *P*<0.001) in heterosexual HIV-1 serodifferent couples from Kenya and Uganda [11].

In the Partner Demonstration project 1013 serodifferent heterosexual couples in Kenya and Uganda were offered ART (as PrEP) for the HIV-negative partner and as TasP for the HIV-positive partner. The study discontinued PrEP for the partner without HIV once the partner with HIV had completed 6 months of ART. Findings demonstrated the feasibility of integrated delivery of time-limited PrEP as a bridge to sustained ART, which resulted in near elimination of HIV transmission, with an observed HIV incidence of <0.05% per year compared to an expected incidence of >5% per year (estimated through modelling) [12].

4.2.5 Vulnerability factors in trans people

Transgender women have a high estimated worldwide HIV prevalence of 19% [13]. Few data are available for transgender men or other transgender populations. However, trans MSM are likely to have the same or similar risk for HIV acquisition as other MSM populations. Transgender people have low rates of access to health and HIV services owing to a range of socio-economic and cultural issues. Trans and non-binary people commonly experience violence and stigma (including, abuse perpetrated by clients of sex workers and intimate partner violence) and may experience rejection from family and lack of cultural support. Trans communities also experience higher rates of unemployment, poverty, housing insecurity, marginalisation and social isolation. All these factors can have a negative impact on mental health and wellbeing, could potentially increase vulnerability to HIV and should inform adherence support and engagement with services while taking PrEP [14].

4.2.6 Sexual health autonomy and sexual networks

An assessment of an individual's sexual health autonomy and their involvement in wider sexual networks, which both may impact on HIV risk, should be undertaken with the patient when assessing their eligibility for PrEP. In particular, consideration should be given to:

- The existence of any coercive and/or violent power dynamics in their relationship(s) (e.g. intimate partner violence);
- Whether they engage in any paid or transactional sex;
- Whether there are drug and alcohol or mental health issues that may negatively impact on their autonomy;
- Their current ability to negotiate and/or use condoms (or employ other HIV prevention methods) with sexual partners;
- Any potential impact of PrEP on future ability to negotiate condom use (or employ other HIV prevention methods).

Consideration should also be given to those whose HIV risk may be elevated as a result of engaging within a higher-risk sexual network. Individuals may be at elevated risk of HIV acquisition when engaging in condomless sex with partners from a population group or country with high HIV prevalence. In addition, an individual may have an elevated HIV risk as a result of condomless sex with partners who fit the criteria of 'high risk of HIV' as detailed above.

4.2.7 Risk assessment (Table 4.2.2 and proforma). See Appendix 2

Table 4.2.2. At baseline (and during follow-up) detailed history and risk assessment is required to include:

Sexual behaviour	• **Gender and sexuality of partners** • **Number of sexual partners in previous 3–6 months** • **Condomless sex in previous 3–6 months (anal or vaginal)** • **Sexual partners who are HIV positive and not on ART for >6 months with an HIV viral load <200 copies/mL** • **History of chemsex**
STI history	• History of bacterial STI • History of rectal bacterial STI • HIV and STI testing history • History of PEP in the previous 12 months
Medical and other relevant history	• Past medical history (with particular reference to renal and bone problems) • Drug history (with particular reference to nephrotoxic drugs) • History of injecting drug use including details of sharing needles or injecting equipment

4.1 How to target those at risk of HIV transmission: recommendations

17. **We recommend that PrEP with regular or event-based oral TDF-FTC is offered to MSM and TGW at elevated risk of HIV acquisition through recent (3–6 months) and ongoing condomless anal sex. (1A)**

18. **We recommend that PrEP with daily oral TDF-FTC is offered to HIV-negative people having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)**

Good practice point

- **Consider PrEP with oral TDF-FTC on a case-by-case basis for people with other factors that place them at increased risk of HIV acquisition.**

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5 Initiating PrEP

5.1 Overview

Initiation of PrEP should occur within the context a comprehensive package of prevention services including level 3 sexual health services and access to substance misuse and counselling services. Provision of PrEP should be preceded by addressing risk factors (e.g. inconsistent condom use, recreational drug use), screening and referral for treatment for other STIs and viral hepatitis, vaccination against hepatitis A and B (if indicated), education on limitations of PrEP (including adherence and lead-in times), management of possible side effects, education on long-term safety of medications, drug resistance and symptoms of primary HIV infection (PHI).

In addition to confirming that any person starting PrEP medication is not infected with HIV, assessments of renal function and testing for infection with hepatitis B virus (HBV) are required because both decreased renal function and active HBV infection are potential safety issues for the use of TDF-FTC as PrEP. Adherence may be promoted through text message reminders or use of mobile app devices to record taking medications. The need for PEPSE should be excluded in all individuals considering starting PrEP.

5.2 Education, behavioural support and adherence

Education, behavioural support and adherence: summary

- **Education prior to starting PrEP should include information on HIV transmission, how PrEP works, potential side effects of PrEP medication, adherence and efficacy, dosing schedule, lead-in time to protection, STI/HIV testing and other HIV prevention strategies.**
- **PrEP efficacy is strongly linked to adherence. People starting PrEP who may need greater adherence support should be identified and offered enhanced adherence support interventions.**
- **Access to a health advisor, or psychosexual support through counselling, should be available and offered.**
- **Referrals into specialist services should also be used where appropriate to support and compliment clinical advice around PrEP, including MSM, black African or trans people, sexual health peer support, drug (including chemsex), alcohol and mental health services.**

5.2.1 Education

Education has been a key component of many PrEP trials. Educational interventions in the PROUD study covered HIV prevention, HIV testing, treatment, side effects of TDF-FTC adherence, PEP, STI testing and other HIV prevention strategies [1]. In services supporting PrEP use (generic, private or NHS), the following topics should be covered in brief to ensure the patient has sufficient knowledge before starting PrEP:

- HIV transmission;
- HIV testing and window periods;
- Side effects of TDF-FTC
- Efficacy of PrEP and link to adherence;
- Daily dosing and event-based regimens;
- PEP for risks with suboptimal PrEP adherence;
- Wider PrEP provision, including generics, national programmes and trials;
- STI testing
- PrEP information resources (see below)

Both internationally and within the UK PROUD study, uptake of PrEP has been greater amongst MSM with higher levels of formal education and associated socioeconomic resources (e.g. caucasian, full-time employment). Educational needs of MSM beyond those seen in the PROUD study may be greater.

Similarly, it seems likely that other communities, particularly those who experience more stigma or have less engagement with HIV, may have significantly different and greater educational needs [2,3]. More research is needed in a UK context around knowledge, attitudes and acceptability of PrEP within other groups at risk of HIV acquisition, especially, but not limited to, black African or trans people.

Useful resources to signpost people to include:

i-base	http://i-base.info/prep and http://i-base.info/guides/prep
Prepster	http://prepster.info/
I Want PrEP Now	https://www.iwantprepnow.co.uk/

5.2.2 Behavioural support

In the UK PROUD study, all trial participants were offered the opportunity to see a health advisor or access psychosexual support through counselling at the level 3 sexual health services. A high proportion of PROUD trial participants also reported recreational drug use, particularly those closely associated with chemsex. It is important, therefore, that people accessing PrEP have access to behavioural change services, which may have an impact on their wider, holistic sexual health (and which are not solely focused on condomless sex).

It is recommended that all services either prescribing PrEP or supporting its use are able to offer behavioural change services, including: (i) health advisor or nurse-led brief interventions (with optional use of motivational interviewing); and (ii) psychological support services. Although these represent the ideal, it is recognised that some clinics may not have their own counselling services, and this should not be a barrier to a clinic providing support around PrEP.

Referral pathways into relevant community or specialist services should also be used to support and complement clinical advice around PrEP, i.e.:

- Sexual health peer support;
- Community behavioural change (e.g. motivational interviewing) or therapeutic change (e.g. counselling) services;
- Chemsex services;
- Community online support and trans specific clinics where available;
- Drug and alcohol, and/or mental health services.

5.2.3 Adherence

Specific cultural or situational contexts remain an important factor in determining adherence. Within African heterosexual studies, a huge variation in adherence was seen between the Fem-PrEP study [4], which was discontinued due to poor adherence, and the serodifferent African Partners study [5], which reported good levels of adherence and efficacy. Variations in cohorts within a community, around issues such as perceived risk, gender, HIV stigma or knowledge, may all have profound impacts on adherence and the feasibility of PrEP as an intervention. Different populations or individuals may need significantly different or greater interventions to support adherence.

While adherence was not highlighted as a concern in the UK PROUD study in MSM, it was noted that trial participants had higher levels of further education, and engagement with sexual health services (seen in testing frequency and PEP usage) compared to the wider MSM population [6]. Concerns about side effects of PrEP or low

perception of need for PrEP may reflect that extra adherence support is required. Similarly, the IPERGAY study reported good levels of adherence among a similar cohort to that recruited to PROUD. Expansion of PrEP use to different populations or beyond the demographics seen within the PROUD study may see greater numbers of users who require more support around adherence. For example, the subgroup analysis of iPrEx [7] reported low TDF concentrations among transgender women who use feminising hormones, possibly reflecting concerns about drug interactions.

Robust adherence support is required at PrEP initiation and follow-up, but some individuals starting PrEP may require extensive counselling and support to explore potential barriers to adherence and to provide support and strategies to improve adherence. This may be particularly relevant to transgender men and women, young people and some heterosexual men and women to ensure PrEP literacy and maximise adherence.

5.2.3.1 Adherence interventions

In a review of adherence interventions that might be adapted to support PrEP adherence in the UK [8], the strongest evidence for two types of interventions was found.

1. Complex, resource-intensive interventions shown to be effective combined multiple adherence support approaches. In the case of PrEP, this could include: education about PrEP and the importance of adherence; counselling to improve adherence skills, such as incorporating pill taking into a daily routine and developing strategies for remembering doses when travelling; and/or provision of feedback on medication adherence (e.g. providing results from drug-level testing).

2. Effective, low-cost, low-intensity interventions with the strongest evidence included the provision of education or telephone calls for adherence support. Education-based interventions for PrEP users, in the form of either printed materials or brief discussion with a provider, could focus on improving users' understanding and self-perception of HIV infection risk, information about the drug, the regimen's requirements, potential side effects, and the signs and symptoms of acute HIV infection.

For those who express moderate concerns or difficulties with adherence, the following adherence support interventions should be used:

- Use of support tools, more commonly used by people living with HIV:
    - Alarms or reminders on phones;
    - Routine planning (taken at set times each day or with an activity (e.g. bedtime, or when brushing teeth);
    - Storage options (keyring pill capsules, supplies in multiple locations);
- Access to behavioural change services (see above).

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5.3 Settings and context to administer PrEP

In the UK, the PROUD study demonstrated the feasibility of administering PrEP in level 3 sexual health clinics. The clinics offered PrEP, monitoring of renal and other drug toxicity and medication adherence embedded into a routine risk-reduction support package including testing for HIV and STIs [1].

Provision of PrEP in these settings also provides opportunities to deliver a combination prevention package, which includes other specialist services that may only be available in this setting, such as drug and alcohol services and psychological support.

Data from the Gay Men's Sexual Health cross-sectional survey of MSM indicates that more than half of MSM surveyed (54.8%) reported attending a sexual health clinic in the past year [2]. Those who reported high-risk sexual behaviours such as 10 or more partners or condomless anal intercourse with casual partners in the past year were more likely to have attended a sexual health clinic, suggesting that sexual health clinics are a suitable setting for the delivery of PrEP. However, data from cross-sectional surveys in Scotland show that two-fifths (34/78) of MSM newly diagnosed with HIV had never previously engaged with specialist sexual health services and one-third had never previously tested for HIV prior to diagnosis [3].

In addition, limiting provision of PrEP to level 3 sexual health clinics risks widening health inequalities, disproportionately among black, Asian, and minority ethnic (BAME) populations. In a recent survey by Public Health England of 1379 MSM and 362 black African respondents, one in seven (14%) MSM and a quarter (23%) of black Africans had never had an HIV test [4]. These communities could be enabled to access PrEP and prevention services through collaboration with outreach and community-based support for PrEP services and offered alternative HIV testing strategies such as self-sampling and self-testing.

In other high-income settings, such as the USA, PrEP has been successfully delivered across a variety of settings, including community-based HIV/STI testing sites, health maintenance organisations (HMOs), HIV clinics, LGBT clinics, primary care and STI clinics [5]. Although experience of delivering PrEP in a range of settings is currently lacking in the UK, these options should be explored and evaluated to ensure widest possible access.

5.3 Settings and context to administer PrEP: good practice points

- **Robust adherence support is required at PrEP initiation and maintenance. Some individuals starting PrEP may require extensive counselling and support to explore potential barriers to adherence and to provide support and strategies to improve adherence. This may be particularly relevant to some trans people, some young people and some heterosexual men and women to ensure PrEP literacy and maximise adherence.**
- **Information should be provided to all patients on:**
  - **PrEP medication dose and schedule;**
  - **Lead-in time to protection;**
  - **Potential side effects of PrEP medication and management of common side effects;**
  - **Relationship of adherence to PrEP efficacy;**
  - **Risks of HIV infection and antiretroviral resistance from suboptimal adherence;**
  - **Symptoms of HIV seroconversion that require assessment.**
- **PrEP provision should include condom provision and behavioural support.**
- **People receiving PrEP should receive advice on the potential risk of other STIs and the need for regular testing.**
- **Although level 3 sexual health services are recognised as preferable for PrEP delivery these settings may restrict access for some and, where appropriate, alternative models of delivery should be explored.**

5.3.1 References

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5.4 Baseline assessment and testing

5.4.1 Assessment for consideration of post-exposure prophylaxis following sexual exposure (PEPSE)

If an individual has had a high-risk exposure within the previous 72 hours, it may be appropriate to consider a course of PEPSE [1] prior to transitioning to PrEP. Testing for HIV should be performed in line with current PEPSE guidelines [1]. If immediately transitioning to PrEP after a course of PEPSE, HIV testing should be performed at the end of the 4 weeks of PEPSE and again 4 weeks after starting PrEP.

5.4.2 HIV testing

Baseline HIV testing is mandatory prior to starting PrEP since initiation in the context of undiagnosed HIV infection could lead to development of antiretroviral resistance. All individuals must have a 4th or later generation laboratory HIV enzyme-linked immunoassay (EIA) test at baseline or a recorded negative test within the previous 4 weeks. Service providers may obtain rapid results through blood-based point-of-care tests (POCTs) to allow same-day initiation, although caution must be given to the higher possibility of both false–positive, and, in early infection, false–negative results. If blood-based POCT is negative, and the patient has no symptoms suggestive of seroconversion illness, clinicians can consider starting same-day PrEP while awaiting the results of the laboratory 4^{th} generation HIV antigen/antibody test. Oral POCT tests should not be used because of lower sensitivity particularly during the window period. Clinicians should not accept self-reported negative results.

Where a high-risk exposure (e.g. condomless anal sex) has occurred within the previous 4 weeks, an HIV viral load could be considered in addition to sending a 4^{th} /5^{th} generation test. In the absence of symptoms of PHI [2] and in the presence of a negative 4^{th}/5^{th} generation or blood-based POCT test and ongoing risk of HIV, PrEP can be started immediately to mitigate against the risk of infection. A 4^{th} / 5^{th} generation HIV test result can be repeated 4 weeks after PrEP initiation in those where a risk occurred in the 4 weeks prior to initiating PrEP.

A person with a positive HIV test at baseline should be managed in accordance with current guidelines with referral for specialist HIV care [3].

5.4.3 Acute HIV infection

PrEP is indicated for individuals at risk of HIV acquisition. Clinicians should therefore have a high level of suspicion for acute HIV infection (AHI) and take an appropriate symptom history, noting that a proportion (40–90%) with AHI will be symptomatic. The symptoms most strongly associated with PHI are fever and rash [2]. Other symptoms include headache, malaise, arthralgia and sore throat. Symptoms of AHI may be non-specific, however, and patients may fail to report them, so diligence is required to exclude AHI at the time of starting PrEP.

A history of condomless anal sex within the HIV window period of the test is not an exclusion criterion to starting PrEP, although starting PrEP should be deferred in those with signs or symptoms consistent with AHI currently, or in the previous 4 weeks, until HIV infection can be reliably excluded with additional HIV viral load nucleic acid amplification testing (NAAT) to avoid development of drug-resistant virus.

5.4.4 Assessment of renal function

Among HIV-positive persons prescribed TDF-containing regimens, tenofovir can cause decreased renal function and occasional cases of acute renal failure, including Fanconi's syndrome [4]. In the context of treating HIV, the TDF 'Summary of Product Characteristics' recommends standard dosing in mild renal impairment (creatinine clearance of 50–80 mL/min) and dose reductions where creatinine clearance is less than 50 mL/min [4]. In some

of the PrEP trials among otherwise healthy, HIV-negative adults, an estimated GFR ≥60 mL/min/1.73 m^2 was an eligibility criterion [5,6]).

Although a good renal safety profile for TDF has been demonstrated across all PrEP trials, safety data for TDF-FTC prescribed to HIV-negative persons with reduced renal function are not available. Mild progressive renal impairment has been seen in PrEP studies, which reversed on stopping study medication [5-10]

It is necessary to assess the risk of chronic kidney disease at baseline. Factors that may indicate an individual is at higher risk of CKD include being aged 40 years old or more being on concomitant medication associated with renal impairment, or the presence of comorbidities such as hypertension, and diabetes [11,12]. Prior to initiating PrEP, clinicians should discuss the possibility of kidney disease with individuals who have pre-existing risk factors. A thorough medication history should be obtained to ascertain any concomitant nephrotoxic drugs or drugs that have interactions with TDF-FTC.

Serum creatinine and eGFR should therefore be performed at baseline. PrEP may be started pending results of serum creatinine and eGFR, but results should be reviewed at the soonest possible time.

A number of studies have demonstrated that CKD-EPI equation is more accurate than the Cockcroft–Gault formula or the MDRD estimate, especially at higher GFR >60 mL/min/1.73 m^2 [11]. The most effective way to calculate eGFR is therefore using the CKD-EPI equation.

The CKD-EPI equation (www.kidney.org/professionals/kdoqi/gfr_calculator)

For women with a plasma creatinine ≤0.7:

$(\text{plasma creatinine}/0.7)^{-0.329} \times (0.993)^{\text{age}}$ (× 166 (if black) × 144 (if white or other))

For women with a plasma creatinine >0.7:

$(\text{plasma creatinine}/0.7)^{-1.209} \times (0.993)^{\text{age}}$ (× 166 (if black) × 144 (if white or other))

For men with a plasma creatinine ≤0.9:

$(\text{plasma creatinine}/0.9)^{-0.411} \times (0.993)^{\text{age}}$ (× 163 (if black) × 141 (if white or other))

For men with a plasma creatinine >0.9:

$(\text{plasma creatinine}/0.9)^{-1.209} \times (0.993)^{\text{age}}$ (× 166 (if black) × 144 (if white or other))

It is recognised that most clinicians will be likely to use lab eGFR, but CKD-EPI equation can be calculated using an online calculator (e.g. https://www.qxmd.com/calculate/calculator_251/egfr-using-ckd-epi). It should also be noted that the CKD-EPI does not take weight into account, and in people with extremes of muscle mass, for example in bodybuilders, the eGFR may need to be interpreted with caution [12].
Baseline urinalysis is not recommended as detection of proteinuria, as measured in routine dipstick urinalysis, has a very low PPV (0.7%) in predicting elevation of creatinine [8].

5.4.5 STI screen

STI testing is recommended at baseline including NAAT for gonococcal and chlamydial infection at sites of exposure (genital, rectal, pharyngeal) and syphilis serology in accordance with national recommendations and guidelines [13].

5.4.6. Assessment of viral hepatitis status

TDF-FTC may be used simultaneously as treatment for chronic active HBV infection and as PrEP. However, discontinuation of TDF-FTC requires close monitoring in patients with chronic hepatitis B infection because of the risk of rebound viraemia and fulminant liver damage.

Screening for hepatitis B should be undertaken at baseline, if no evidence of current or previous infection or immunity then HBV vaccination should be offered as per current guidelines [14]. PrEP may be started pending results of HBsAg, but results should be reviewed at the soonest possible time as both TDF and FTC are active against HBV and stopping these drugs may cause severe hepatic flares. Individuals found at baseline to have undiagnosed HBV infection should be referred to specialist hepatology services for assessment. Individuals with chronic HBV on PrEP should be counselled regarding adherence to PrEP to prevent possible hepatic flares. Event-based or on demand PrEP dosing should not be considered in people with chronic HBV infection.

High background prevalence of HCV has been reported in HIV-negative MSM before starting PrEP in both clinical trials and PrEP demonstration projects [15,16]. Screening for Hepatitis C should be undertaken at baseline. People with previously undiagnosed HCV should be referred to specialist services for assessment and consideration of directly acting antiviral (DAA) treatment, if appropriate.

Routine hepatitis A virus screening and immunisation is not recommended except in context of risk or outbreak (e.g. in MSM where increased rates of infection have been recognised locally) [14]. All MSM attending GUM services should be vaccinated against HAV (unless they have a reliable history of vaccination or infection) and a default screening step is not required.

5.4 Baseline assessment and testing: recommendations

19. **We recommend that baseline HIV testing with 4th generation serology test is undertaken prior to commencing PrEP. (1A)**

20. **We recommend that same-day initiation of PrEP may occur where an individual has a negative blood-based POCT on the day, or 4th generation test within the past 4 weeks. (1A)**

21. **We recommend that an HIV viral load should be considered where a high-risk exposure has occurred within 4 weeks. (1B)**

22. **We recommend that initiation of PrEP is deferred in people reporting condomless anal sex in the previous 4 weeks who have symptoms suggestive of HIV seroconversion until an HIV RNA result is available. (1A)**

23. **We recommend that baseline screening for hepatitis B should be undertaken in those of unknown hepatitis B status to exclude active hepatitis B infection with vaccination initiated in those who are non-immune. (1A)**

24. **We recommend that baseline screening for hepatitis C should be undertaken. (1B)**

25. **We recommend a full STI screen at baseline including syphilis serology for all, STI testing NAAT for gonococcal and chlamydial infection at sites of exposure (genital, rectal, pharyngeal). (1A)**

26. **We recommend that baseline renal function is assessed with a serum creatinine and eGFR but PrEP can be commenced while waiting for the results of baseline creatinine measurements. (1A)**

27. **We suggest that the eGFR for individuals starting TDF is >60 mL/min/1.73 m^2. (2A)**
28. **We suggest that individuals with eGFR <60 mL/min/1.73 m^2 should be started on PrEP only on a case-by-case basis and after a full assessment and discussion with the patient of the risk and benefits and obtaining specialist renal advice. (2B)**

Good practice points

- **A thorough medical history before initiating PrEP is essential to identify patients at greater risk of adverse events who might require closer renal or bone monitoring.**
- **Discuss possibility of kidney disease with TDF-FTC with individuals who have pre-existing chronic kidney disease or risk factors (>40 years of age, eGFR <90 mL/min/1.73 m^2 at baseline, hypertension, or diabetes).**
- **Obtain a thorough medication history for concomitant nephrotoxic drugs or drugs that have interactions with TDF-FTC. Discuss risk and benefits.**
- **PrEP should be offered as part of a package of care including regular HIV and STI testing and monitoring of renal function.**

5.4.7 References

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5.5 Other considerations

5.5.1 Pregnancy or trying to conceive

PrEP may be one option to prevent HIV seronegative partners from acquiring HIV infection in serodifferent couples during attempts to conceive if the positive partner is not on suppressive ART. Assessment for pregnancy status should be undertaken if indicated at baseline. If a person is pregnant when starting PrEP or becomes pregnant while on PrEP, discuss the known risks and benefits of taking TDF-FTC during pregnancy. After discussing the potential risks of TDF-FTC, recommend continuation of PrEP during pregnancy or breastfeeding for those with ongoing risk for HIV. Report information regarding use of PrEP during pregnancy to the Antiretroviral Pregnancy Registry.

5.5.2 Bone health

Bone loss is associated with tenofovir use. In addition, low bone mineral density (BMD) has been reported in participants in PrEP trials at baseline [1]. Pre-existing risk factors for bone loss include: age over 50 years (particularly women); use of some medications including steroids; having a low body weight; smoking and excess alcohol use [2]. Clinicians should discuss risk of bone loss with individuals with pre-existing risk factors or demonstrated osteoporosis, osteomalacia or osteopenia. Individuals with low BMD or risk factors should be counselled to reduce factors associated with low BMD such as reducing alcohol intake and stopping smoking as well as ensuring adequate levels of vitamin D and calcium in the diet and undertaking weight-bearing exercise. A person with osteoporosis on TDF-based PrEP will require careful monitoring at clinician discretion.

5.5 Other considerations: recommendations

29. **We suggest that if an individual is pregnant when starting PrEP or becomes pregnant while on PrEP, we suggest continuation of PrEP during pregnancy or breastfeeding for those with ongoing risk for HIV after discussing the potential risks of TDF-FTC. (2B)**

Good practice points

- **Report information regarding use of PrEP during pregnancy to the Antiretroviral Pregnancy Registry.**
- **Discuss risk of bone loss with individuals with pre-existing risk factors or young people or demonstrated osteoporosis/osteomalacia/osteopenia.**

5.5.3 References

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5.6 Prescribing PrEP

5.6.1 What to use

We recommend that TDF-FTC is used for PrEP for MSM, TGW, TGM, and heterosexual men and women. For heterosexual men and women only, TDF alone may be considered.

When first starting PrEP (and when re-starting), dispensing a 90-day supply of medication is recommended. Follow-up should be planned for 4 weeks later (either face to face or by telephone) to review adherence and side effects.

5.6.2 Lead-in period

FTC-DP concentrates more rapidly than TFV-DP in all tissues. In general, time to protection of TFV-DP is shortest in lower gastrointestinal tract tissues, followed by blood PBMCs and then the female genital tract tissues (FGT). The time to clinical protection has only been evaluated for anal sex in a single RCT (IPERGAY), starting with double-dose of TDF-FTC 2–24 hours before sex and stopping with a single tablet taken at 24 hours and again at 48 hours after the first dose [1]. The time to clinical protection is estimated as 7 days for vaginal tissue [2-4]. There is no data in trans women or trans men.

5.6.3 Frequency of dosing to attain benefit

Although complete adherence to daily PrEP is not required to attain benefit for anal sex, protective effects diminish incrementally as adherence declines. In IPrEX, when TDF is taken twice, four times and seven times a week, estimated HIV risk reduction is 76%, 90% and 99%, respectively [5]. In the iPrEx-OLE study, plasma drug levels corresponding with adherence of two to three tablets per week were associated with an 84% risk reduction (95% CI 21–99) whereas more than four doses per week were associated with 100% risk reduction [6]. Where there is a preference to avoid daily dosing by a PrEP user having only anal sex, and in the knowledge that effective protection is obtained by at least four doses per week, consensus opinion is that TDF-FTC should be taken on alternate days rather than four consecutive days with then three days off.
For exposures other than anal sex, intermittent use TDF-FTC has not been studied and it is currently recommended that TDF-FTC should be taken daily.

5.6.4 On-demand dosing

On demand, or 'event-based', PrEP dosing led to an 86% reduction in new HIV infections in MSM in the IPERGAY study [1], similar to daily dosing. A loading dose of two TDF-FTC was taken 2 to 24 hours before sex, followed by a third dose at 24 hours and a fourth at 48 hours. In the event of multiple consecutive episodes of sexual intercourse, participants were instructed to take one pill per day until the last sexual intercourse and then two post exposure pills frequent sexual intercourse, participants are instructed to continue taking one tablet daily

until 48 hours after the last sexual intercourse. When restarting PrEP, participants were advised to take a loading dose of two pills unless the last PrEP dose was less than 1 week earlier, in which case they were instructed to take only one pill [1]. Event-based dosing has not been investigated in heterosexual men and women and based on this and pharmacokinetic concerns we do not recommend event-based PrEP in these groups. In the absence of data, trans women and trans men should also not be offered event-based PrEP.

Table 5.6.1. Options for dosing schedules and lead-in times [references]

		Insertive anal sex	**Receptive anal sex**	**Insertive vaginal sex**	**Receptive vaginal sex***
Dosing schedule	Daily dosing	✓ [6-8]	✓ [6-8]	✓ [9,10]	✓ [9,10]
	Event-based dosing (≥4 tablets around sex)	✓ [1]	✓ [1]	Not recommended	Not recommended
	Intermittent dosing (≥4 tablets per week)	✓ [6]	✓ [6]	Not recommended	Not recommended
Starting and stopping PrEP	Lead in times to protection	2–24 hours before condomless sex [1]	2–24 hours before condomless sex [1]	7 days [2-4]	7 days [2-4]
	Stopping PrEP	One tablet 24 hours and one 48 hours after last condomless sex [1]	One tablet 24 hours and one 48 hours after last condomless sex [1]	7 days after last condomless sex [2]	7 days after last condomless sex [2]

*Includes frontal sex in trans women and trans men.

5.6 Prescribing PrEP: recommendations

30. **We recommend that tenofovir/emtricitabine (TDF-FTC) fixed-dose combination, dosed appropriately, is used for HIV pre-exposure prophylaxis for men who have sex with men (MSM), transgender women (TGW) and heterosexual men and women who are at high risk of HIV acquisition. (1A)**
31. **We recommend that for heterosexual men and women only, tenofovir alone may be considered. (1A)**
32. **We recommend the following lead in periods:**
    - **For event-based or daily dosing in anal sex, the time to clinical protection in rectal tissues is estimated as 2–24 hours following a double dose of TDF-FTC. (1A)**
    - **For daily dosing (with single dose TDF-FTC), the time to protection for vaginal sex is estimated as 7 days. (1B)**
33. **Frequency of dosing:**
    - **We recommend daily PrEP can be offered to MSM, trans men, trans women and heterosexual men and women at high risk of HIV. (1A)**
    - **MSM and TGW should be advised that minimal benefit from daily dosing will not be attained if fewer than four doses are taken per week. There is no evidence in other populations that four doses instead of seven per week is adequate. (1B)**
    - **We recommend that event-based PrEP can be discussed and offered to MSM. A loading dose of two tablets of TDF-FTC taken 2–24 hours before sex, followed by a third (single) tablet 24 hours and a fourth (single) tablet 48 hours later is advised. Where potential exposure is sustained over more than a 24-hour period, one pill per day should be taken until the last sexual intercourse and then to take the two post exposure pills. (1A)**
    - **In the absence of data, we do not recommend event-based dosing in heterosexual men and women, trans men or trans women.**

5.6.5 References

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6 Clinical follow-up and monitoring on treatment

6.1 Overview

In addition to undertaking monitoring investigations, regular review permits review of adherence (e.g. through pill counts, review of pill app reminder), side effects and facilitates discussions around changes in risk behaviour to determine the need for ongoing PrEP use. In providing repeat courses of PrEP, providers should obtain a thorough sexual and drug use history, and assist in the decision of when to use PrEP (especially in cases of event based use) and when to discontinue use.

In most circumstances a 3-month supply (90 tablets) of TDF-FTC should be provided in order to promote return for review of adherence, tolerability and to ensure 3-monthly HIV testing is conducted to minimise prolonged use of PrEP in the presence of a new HIV infection.

Monitoring of individuals receiving PrEP should focus on excluding HIV, monitoring for side effects and toxicities, screening for and treating sexually transmitted infections, risk reduction and promoting adherence. At a population level, surveillance is required to understand how PrEP is used and monitor clinic attendance and other characteristics of PrEP users and non-users, and will enable follow-up to estimate HIV incidence in these groups.

6.2 Continued prescribing

When first starting PrEP (and when re-starting), dispensing a 90-day supply of medication is suggested. Further maintenance prescriptions for 90 days should be given after obtaining a negative 4^{th}/5^{th} generation HIV test result. Following visits should be every 3 months. PrEP should be continued where there is ongoing high-risk for HIV transmission as per the baseline assessment. The length of use will depend on the individual's behaviours and choices, which are likely to change over time. For those who started PrEP because they have a partner who is HIV positive, an ongoing assessment should be made of when PrEP can be stopped (partner on ART for 6 months and HIV viral load <200 copies/mL). This should take account of risks taken outside the primary relationship.

6.3 Assessing adherence and adverse events

Assessment 1 month after commencing PrEP (face-to-face, telephone, email or text) provides the opportunity to review adherence, adverse events and HIV/STI window periods. Reasons for non-adherence including adverse events should be elicited and documented at each follow-up visit. Additional support, practical or psychological may be required. Adherence must be reviewed at each follow-up visit. For MSM and TGW on event-based PrEP, providers should ensure this is being taken correctly and that a switch to daily PrEP (and vice versa) is not appropriate. In MSM and TGW taking the daily PrEP regimen who are having only anal sex, providers should ensure that a minimum of four tablets a week (on alternate days not consecutively) are being taken to ensure continued efficacy.

6.4 Management of short-term side effects

TDF-FTC can have short-term side effects, although in clinical trials these were short-lived. Side effects can include nausea, flatulence, abdominal pain, dizziness and headache. These symptoms usually occur early but mostly disappear within the first month. They can often be managed with simple analgesia or anti-emetics, but patients should also be made aware of symptoms that may indicate more serious toxicities such as renal injury.

Flow chart

Wanting to start PrEP

↓

First visit assessment and documentation

- Reasons for seeking PrEP
- Medical history relevant to TDF-FTC including bone and renal health, concomitant medications
- Risk assessment and eligibility for PrEP
- Consideration of AHI and eligibility for PEPSE
- Details of HIV/STI screens last 12 months
- Timing of condomless sex acts last 3 months
- If MSM: discussion of both regimens (daily and on demand)
- Reasons adherence is important before and after risk of exposure
- Potential toxicities and how to manage
- Risks and benefits of online purchase and community websites with information about online purchase if required
- Results HIV/STI screen
- Decision to start and time to start
- Recommended follow-up at 1 or 3 months after starting PrEP for HIV/STI screen, adherence check and serum creatinine and eGFR
- Code using GUMCAD codes (See Appendix 1)

Baseline testing

- HIV testing using 4th generation (POCT if same day initiation is preferable)
- STI screen including HCV and HBV testing
- Serum creatinine and eGFR
- Pregnancy testing if indicated

↓

Quarterly visit documentation

- Reason for continuing PrEP
- Regimen followed and reasons for non-adherence including adverse events
- Support provided for medication adherence
- HIV risk-reduction advice
- Recreational drug or alcohol use with referral to support services, if required
- Results HIV/STI screen
- Prescription for 90 days
- Arrange follow up for 3 months
- Code using GUMCAD codes (Appendix 1)

Monitoring

- Result of HIV testing using 4th generation
- Results of STI screen (including anti-HCV in MSM/TGW)
- Serum creatinine and eGFR annually if >90 mL/min/1.73 m^2 and aged <40, more frequently if 60–90 mL/min/1.73 m^2 or >40 years or risk factors for renal disease.

6. Clinical follow-up and monitoring on treatment: good practice points

- **When first starting PrEP (and when re-starting), dispensing a 90-day supply of medication is suggested.**
- **Follow-up should be planned for 4 weeks later if indicated – via phone or email is sufficient – to review side effects, adherence and that daily and on-demand based regimes are being taken appropriately.**
- **Reasons for non-adherence including adverse events should be elicited and documented at each follow-up visit. Additional support, practical or psychological may be required.**
- **PrEP should continue where there is on-going high-risk for HIV transmission.**
- **Recipients should be advised of the possibility of transient nausea, vomiting, or headache and encouraged to manage this through the use of simple analgesics and anti-emetics**

6.5 Monitoring on PrEP

The following monitoring guidance is the same for both on-demand dosing and daily dosing (Table 6.5.1).

6.5.1 HIV testing

HIV testing should be undertaken every 3-months with a laboratory 4th generation test or blood-based POCT. Further PrEP prescriptions should not be issued without repeat HIV testing every 90 days. Atypical testing results should be discussed with a regional expert, for possible further investigation for seroconversion.

6.5.2 Management of HIV seroconversion

Comprehensive adherence support should minimise the risk of HIV seroconversion on PrEP and regular HIV testing should detect any new infections as early as possible. HIV seroconversion should be considered in any individual presenting with symptoms suggestive of primary HIV infection and investigated with an HIV viral load in addition to a 4th generation HIV test.

A full assessment of those who seroconvert while being prescribed PrEP should include intended PrEP use (daily versus event-based dosing), adherence to intended regimen and assessment and timing of recent risks for HIV transmission. Baseline resistance testing should be undertaken as early as possible to look for evidence of resistance-associated mutations to tenofovir or emtricitabine. Therapeutic drug monitoring should be considered in order to assess whether the individual has detectable levels of tenofovir and emtricitabine. Any new HIV infections should be managed in line with existing BHIVA HIV treatment guidelines [1].

In addition, Public Health England have introduced enhanced public health surveillance to further investigate factors associated with seroconversion among PrEP users. Clinicians are advised to complete the questionnaire in for all patients who seroconvert whilst taking PrEP or for patients who seroconvert and have a history of having taken PrEP in the past.

6.5.3 STI screening

Given the high rates of bacterial STIs observed in PROUD and IPERGAY and as part of a comprehensive risk reduction strategy, 3-monthly STI screening (chlamydia, gonorrhoea and syphilis) are advocated for MSM and TGW. For heterosexual individuals receiving PrEP, STI screening should be offered at each 3-month review in particular, if there has been a change in partner or other risks for STI acquisition [2].

6.5.4 Viral hepatitis

There is recognition of the risk of HCV incidence amongst HIV negative MSM using PrEP [3]. Within the PROUD study, incident HCV infections were found in 3.1% [4]. Similarly, within the IPERGAY study, there was a 1% incidence of new HCV infections [5]. No data exist for heterosexual PrEP studies however the incidence is unlikely to be increased in the absence of specific risk factors such as intravenous drug use.

Amongst MSM and TGW using PrEP, it is recommended to screen for HCV every 3 months. If anti-HCV is positive then HCV RNA should be tested and, if positive, the patient referred to specialist services for further investigation and consideration of early treatment.

6.5.5 Renal monitoring

To date, large clinical trials investigating the use of PrEP have not demonstrated any major clinical concerns with regards to renal toxicities. A small, but statistically significant decrease in creatinine clearance (CrCl) may be seen from baseline, which resolves after stopping PrEP. However, there are no data for people with eGFR <60 mL/min/1.73 m^2 so continuing PrEP if eGFR falls to below 60 mL/min/1.73 m^2 is not advised and should only be done on a case-by-case basis with a full discussion of the risk and benefits and ongoing monitoring of renal function. Referral to specialist renal service for investigation and management is advised.

It is advised to measure serum creatinine and eGFR at baseline and if eGFR >90 mL/min/1.73 m^2 and the person is aged under 40 years with no concomitant factors for renal disease, then eGFR can be conducted annually [6].

Where additional risk factors for renal disease are present (e.g. aged over 40 years, use of nephrotoxic drugs, hypertension or diabetes) more frequent monitoring of eGFR and creatinine is required (at least 6 monthly). A rise in serum creatinine and/or fall in eGFR is not a reason to stop PrEP treatment if eGFR remains ≥60 mL/min/1.73 m^2, but more frequent monitoring is indicated.

It is recognised that most clinicians will use lab eGFR, but CKD-EPI equation can be calculated using an online such as https://www.qxmd.com/calculate/calculator_251/egfr-using-ckd-epi. It should also be noted that the CKD-EPI does not take into account weight and in people with extremes of muscle mass, for example in bodybuilders, the eGFR may need to be interpreted with caution [7].

Routine urinalysis for proteinuria is not recommended during follow-up, as detection of proteinuria has a very low positive predictive value (PPV) for creatinine elevation (0.7%) [8]. In addition, testing for specific renal proximal tubular dysfunction seen with TDF, using detailed markers of tubular proteinuria, is also not recommended as it does not predict a clinically relevant eGFR decline [9].

6.5.6 Pregnancy testing

Assessment for pregnancy status should be undertaken if indicated.

6.5.7 Bone monitoring

BMD in HIV-negative MSM has been examined within iPrEx, iPrEx-OLE and CDC safety studies [10-13]. Patients aged under 25 years suffered the greatest loss in BMD although BMD at both hip and spine recovered following PrEP discontinuation, slower recovery was observed in those over 25 years old versus those under 25 years [10]. BMD changes in young HIV-negative African women who had detectable TDF in 75–100% of plasma samples, was 1.4% lower in those receiving TDF or TDF-FTC after 48 weeks of follow-up. Importantly, 48 weeks after treatment discontinuation, effects on BMD appeared to be reversible [12,13].

Based on the above, no routine bone density monitoring is recommended for PrEP users, although supplementation with vitamin D and calcium may be considered, particularly if additional risks for osteopenia or osteoporosis as a good practice point although there is no evidence currently to support this.

Table 6.5.1. Monitoring and clinical follow of people prescribed PrEP

	(Baseline) Week 0	Follow-up			
		Month 1	Month 3	Every subsequent 3 months on PrEP	Frequency while on PrEP
HIV testing	X	X*	X	X	3 monthly
Assessment for symptoms of AHI	X	X	X	X	3 monthly
Hepatitis B (+ vaccination if non immune)	X				
STI screen to include hepatitis C (MSM, TGW, other risks for HCV)	X		X	X	3 monthly
STI screen (non MSM/TGW)	X			X	3 monthly
Serum creatinine/eGFR	X				Annual if eGFR>90 mL/min/1.73 m^2 and aged <40. More frequent monitoring required (at least 6/12) if eGFR 60–90 mL/min/1.73 m^2 or aged >40 years or concomitant risk factors for renal impairment. If <60 mL/min/1.73 m^2 seek specialist renal advice.
Urine pregnancy test (if indicated)	X	X	X	X	3 monthly if indicated

*If risk in 4 weeks prior to starting PrEP.

6.5.8 Coding and data collection

Public Health England has developed new Sexual Health and HIV Activity Property Type (SHHAPT) codes to be returned as part of the Genitourinary Medicine Clinic Surveillance System, which should be completed for all patients to allow national monitoring of the eligibility, uptake, and duration of use of HIV pre-exposure prophylaxis (PrEP). The codes have been designed to minimise the data-entry burden on clinicians while capturing essential public health information about the use of PrEP among GUM clinic attendees, including those who may be enrolled in a PrEP-related trial or who have purchased PrEP drugs over the internet. These codes will be used to understand clinic attendance and other characteristics of PrEP users and non-users, and will enable follow-up to estimate HIV incidence in these groups. For details of the codes see Appendix 1.

The new PrEP codes should only be considered for clinic attendees who belong to sub-populations at high HIV risk including cis- and transgender men and transgender women who have sex with men, black African heterosexuals, people in serodiscordant relationships, and others whose risk of HIV may be greater than or equal to 2% per

annum. The codes should be completed at each PrEP visit or for each new episode of care. PrEP codes should be recorded for all patients who are eligible for PrEP and include a record of starting PrEP, continuing on PrEP, stopping PrEP, declining an offer of PrEP, or taking PrEP from another source. Where PrEP is being prescribed, the number of tablets being prescribed should also be coded. Parallel codes have been adopted in Scotland and are entered using the STISS module of the NaSH system, although medication data is derived directly from the prescribing module.

6.5 Monitoring on PrEP: recommendations

34. **We recommend HIV testing should be undertaken every 3 months with a laboratory 4th or 5th generation test (1A) or a blood-based POCT. (1B)**

35. **We recommend patients with symptoms suggestive of seroconversion should be investigated with a 4th generation HIV test and HIV viral load. Atypical testing results should be discussed with a regional expert. (1C)**

36. **We recommend that in confirmed primary HIV infection, baseline resistance testing should be undertaken. This is to look for evidence of resistance-associated mutations to tenofovir or emtricitabine along with other transmitted mutations. (1B)**

37. **We recommend 3-monthly screening for bacterial STIs (chlamydia, gonorrhoea and syphilis) and for HCV is recommended for MSM and TGW. (1B)**

38. **We recommend STI screening should be offered annually for heterosexual men and women, or more frequently if change of partner or other risks for STI acquisition are present. (1B)**

39. **Renal recommendations:**
    - **If eGFR >90 mL/min/1.73 m^2 at baseline (and follow up) and the person is aged <40 years then annual eGFR should be conducted. (1A)**
    - **If eGFR 60–90 mL/min/1.73 m^2, aged >40 years or concomitant risk factors for renal impairment recommend more frequent monitoring of renal function at physician discretion, but at least 6 monthly. (1B)**
    - **If eGFR <60 mL/min/1.73 m^2, the risks and benefits of continuing PrEP should be assessed on a case-by-case basis. Specialist renal input should be obtained to determine further investigations and frequency of monitoring. (1C)**

Good practice points

- **Assessment of pregnancy status in people not using reliable contraception should be conducted if indicated.**
- **Bone health:**
    - **Patients should be informed of the risk of reduction in BMD of around 1.5–2% at the hip and spine following 48 weeks of treatment.**
    - **Routine monitoring of BMD is not recommended in individuals taking TDF for PrEP with no other risk factors for reduced BMD.**
- **Adverse events should be reported through the yellow card scheme (https://yellowcard.mhra.gov.uk/).**
- **PrEP Sexual Health & HIV Activity Property Type (SHHAPT) codes should be completed for all patients to allow national monitoring of the eligibility, uptake, and duration of use of HIV pre-exposure prophylaxis (PrEP).**

6.6 Indications for stopping PrEP

Contraindications to continued PrEP use include a reduction in risk of HIV acquisition as defined by eligibility criteria, HIV infection and poor adherence where attempts at adherence support have failed. Relative contraindications include side effects and change in risk behaviour (i.e. PrEP is no longer indicated). Continuation of PrEP if eGFR declines to below 60 mL/min/1.73 m^2 should be considered on a case-by-case basis with specialist renal input. Pregnancy is not an indication to stop PrEP especially if there is ongoing risk of HIV.

Both TDF and FTC are active against HBV. Thus, in individuals who do not have vaccine-induced HBV immunity, HBV infection should be excluded before stopping PrEP. If HBV infection is identified, TDF-FTC should be continued, as long as no contraindications exist, and referred to a physician with expertise in management of hepatitis B. If patients with active HBV infection decide to stop taking TDF-FTC, liver function must be closely monitored because reactivated HBV infection can result in hepatic damage.

6.6 Indications for stopping PrEP: recommendations
40. We recommend that a positive HIV test is an absolute contraindication to continued PrEP. Referral to specialist HIV services should be undertaken immediately for investigation and management including intensification of ART regimen. (1A)
41. We suggest that for those at high risk of HIV acquisition, suboptimal adherence is a relative contraindication to continued use. (2B)
42. We recommend that in those without vaccine-induced immunity, HBV infection should be excluded prior to stopping TDF-FTC. (1B)

6.7 References

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13. 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**: 572–580.

7 Buying generics

- There are no peer reviewed papers on this subject.
- Information in this section is drawn from conference presentations and personal communication with members of the writing group, BASHH MSM Special Interest Group, Clinicians PrEP Support Group and Community Group consultation

7.1 Importing medicines bought online

The Medicines and Healthcare products Regulatory Agency (MHRA) advise that it is legal to buy up to 3 months of medicines from outside the European Union for personal use. There is no requirement for a certificate or authorisation. The MHRA also advise that a prescription and/or a letter from the patient's doctor explaining why the product(s) are required is helpful. They suggest that the package is clearly labelled on the outside stating the contents of the package and that the products are for personal use. MHRA strongly advise that the medicines are kept in their original packaging and that they are transported in accordance with storage conditions specified by the manufacturer because this not only helps identify the medicines, but also helps ensure the product's stability.

It is possible to import generic PrEP from certain suppliers without the need for a prescription.

There have been some occasions when medicines have been impounded by the UK Border Agency and customs duty charged. This is increasingly common and should be taken into consideration when ordering generic PrEP online.

There are reports of delays in delivery of TDF-FTC bought online, and occasional issues with stock running out.

7.2 Authenticity of tenofovir-emtricitabine bought online

There are several manufacturers of generic TDF-FTC who import into the UK. These generic manufacturers have their own quality control in place and meet standards satisfactory to the WHO and the FDA [1].

Despite the above, there have been concerns that PrEP bought online could be substandard (contain less or variable amounts of active ingredients) or be counterfeit. To support people choosing to buy generic PrEP online certain clinicians and Trusts have carried out therapeutic drug monitoring (TDM). The largest cohort of PrEP users having TDM was seen at 56 Dean Street. When comparing pharmacokinetic (PK) data for branded Truvada from historic controls, with PK data for 212 generic PrEP users, the PK levels are equivalent for both tenofovir and emtricitabine [2].

Clinical trials of PrEP were undertaken using tenofovir disoproxil fumarate. In October 2016 the European Medicines Agency reported the tenofovir disoproxil maleate salt, which is contained in generic formulations, to be bioequivalent to tenofovir disoproxil fumarate [3].

The writing group is not aware of any reports to date stating that generic PrEP is counterfeit.

7.3 Ethical aspects regarding clinician recommendation to buy PrEP online

7.3.1 General Medical Council

Communication from the GMC states that

- Doctors are responsible for their decisions and actions when they supply and administer medicines or authorise or instruct others to do so.
- Raising the possibility of obtaining medicines for PrEP online as part of the wider discussion of HIV prevention options for patients with high-risk behaviours is consistent with GMC guidance on consent and decision-making [4]. In particular, the GMC states that 'doctors should give patients the information they want and need about options for treating and managing their condition, the potential benefits, burdens and risks for each option, and any treatments that they think has greater potential benefit for the patient than they or their organisation can offer.'

7.3.2 Imperial College Healthcare NHS Trust Clinical Ethics Committee

Clinicians at Imperial College (St Mary's) asked the specific question of their Clinical Ethics Committee (CEC) about providing PrEP support services for people accessing generic PrEP and their response was (O. Dosekun and N. Mackie, personal communication):

- The CEC agrees that the HIV/GUM clinical teams have a duty of care to hold informed discussions about PrEP with patients who are at high risk of HIV infection (where PrEP would not be otherwise contraindicated), in addition to offering other core risk-reduction strategies.
- The CEC agrees that the clinicians proactively and routinely ask only the high-risk cohort of patients if they are aware of, already taking, or would consider taking PrEP in addition to other preventative practices.
- The CEC advises that it is the clinical team's duty of care to fully monitor individuals under their care who have purchased and are taking PrEP. Engaging and supporting high risk patients taking PrEP would be an opportunity to promote risk reduction, and enable regular STI testing in line with national guidelines.

7.4 Specific websites

The GMC advice states that:

- As regards directing patients to specific websites, much will depend on how sure you can be that the medicines obtained from a particular source will be safe and effective.

They note that whether the existing information gained from monitoring patients who have independently acquired medicines for PrEP online provides sufficient assurance is a matter for individual professional judgement.

A number of clinicians (including members of the writing group) approached their defence unions for advice with regard to generic PrEP bought online. Defence unions have concerns about clinicians endorsing a specific website, because quality assurance cannot be absolutely guaranteed, and this could be a risk in the event of an adverse incident. This is also the stance of the Imperial College Healthcare Clinical Ethics Committee.

It is the experience of the writing group however, that if patients choosing to source generic PrEP do not buy via accepted websites, then they are more likely to obtain medicines that are not recommended. Examples include obtaining tenofovir alone rather than TDF-FTC, therefore potentially putting themselves at increased risk of HIV

acquisition. Patients should therefore be encouraged only to use sellers listed on iwantprepnow.co.uk as selling FDA-approved TDF-FTC.

Iwantprepnow.co.uk (IWPN) is the only website in the UK which has a 'click to buy' section. This site only links to an online seller if the website founders know that users have purchased TDF-FTC via that seller, and have had a satisfactory TDM result. They also only link to a seller if the sales/delivery process has been tested and deemed satisfactory. The only sellers listed on IWPN are those selling FDA-approved TDF-FTC.

7.5 Renal monitoring of patients choosing to buy PrEP online

The writing group agrees with the Imperial College Healthcare NHS Trust Clinical Ethics Committee, that denying full monitoring of care while on PrEP would be in breach of the medical profession's duty of care.

7.6 References

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8 Cost effectiveness of PrEP in high-income countries

8 Cost effectiveness of PrEP in high-income countries: summary

- **Overall, the cost-effectiveness of PrEP among MSM populations in high-income countries was found to be highly dependent on HIV incidence of the population taking up PrEP (and therefore their age and level of condom use), HIV prevalence, PrEP drug cost, PrEP efficacy (sometimes expressed in terms of adherence to PrEP), rate of HIV diagnosis in the population and cost of antiretroviral treatment for the HIV-positive population.**
- **Two of the four analyses set in Europe (both using dynamic models) found that the introduction of PrEP in a selected group of MSM at high risk of HIV could not only be cost-effective but cost-saving when appropriately used considering a long time horizon, high PrEP effectiveness and event-based use. Given the efficacy of event-based PrEP was found to be similar to the effectiveness of the daily regimen, but with a lower number of pills, an event-based regimen is considered more cost-effective than the daily regimen.**
- **Cost-effectiveness of PrEP among people who inject drugs has been investigated only in the US. Both studies concluded that PrEP should not be prioritised to this group.**
- **Among couples who wish to conceive where the woman is HIV negative and the man is HIV positive and virologically suppressed on treatment, PrEP, even limited to fertile days, does not represent a cost-effective option at the current cost given the very low risk of transmission if the HIV-positive male partner is virologically suppressed.**

8.1 Men who have sex with men

Several studies assessed the cost-effectiveness of PrEP among MSM in high income countries: most looked at PrEP delivered to a target group of high-risk MSM, with Juusola *et al.* [1], Schneider *et al.* [2] and Cambiano *et al.* [3] also evaluating the cost-effectiveness of PrEP given to MSM at risk of HIV, but without targeting specific higher-risk subgroups.

In order to evaluate the cost-effectiveness of interventions it is necessary to use mathematical models. Models for infectious diseases are generally classified as dynamic or static. Dynamic models reproduce explicitly the transmission of the disease (by modelling the interactions between contacts through which infection can happen) and can therefore take into account the secondary infections averted. Static models are those commonly used to assess the cost-effectiveness of non-communicable diseases and do not capture the transmission of the disease, therefore they do not consider the benefit for people who are not directly receiving the prevention intervention. It is important to bear in mind which type of model is used because static models by definition do not capture the full benefit of interventions such as PrEP that prevent new transmissions.

Nine cost-effectiveness studies were based on dynamic models [1-9], four used a static model [10-13], two used number needed to treat, respectively based on the iPrEx trial and the ANRS IPERGAY trial to estimate cost-effectiveness [14,15] and for one it was not clear (only available as an abstract)[16].

The identified studies considered the MSM population in the US generally [1,4,5,10,11,13] or in specific cities (New York City [7,8] and Los Angeles County [16], Canada [14], Australia [6] and in particular New South Wales [2], the Netherlands [9], France [15] and the UK [3,12]). The settings to which they refer are characterised by different HIV incidence in the MSM population, and different costs for treatment of people living with HIV and for

PrEP, and these factors have been found to be crucial in determining the cost-effectiveness of this prevention intervention.

Another crucial parameter in determining the cost-effectiveness of PrEP is clearly the efficacy assumed. The studies conducted before the PROUD and IPERGAY trials reported, where indicated, assumed a level of PrEP efficacy in line with what was reported at the time: base case ranging from around 44% to 50%, although in sensitivity analyses additional levels of efficacy were considered (e.g. 92% [10]; 10–90% [11], 90% [6]). More recent studies [3,5,9,12,15] considered higher levels of efficacy (80–86%) consistent with the new trials.

In terms of the PrEP regimen, most studies assumed a daily regimen, and only some of the recent studies also considered event-based PrEP use [5,9,15]. (Ouellet *et al.* investigated the use of daily dosing for on-demand PrEP, the most expensive on-demand scenario). All of the peer-reviewed papers were thought to be of high/acceptable quality using the SIGN checklist (www.sign.ac.uk/checklists-and-notes.html), it was not possible to assess it for the conference abstracts [3,6,12,13,15,16] and the correspondence [7].

In cost-effectiveness analyses the costs and health benefits of alternative options are compared and the ratio between the difference in cost (between the two alternatives) and the difference in health is reported. This ratio is called the incremental cost-effectiveness ratio (ICER) and is expressed usually as the cost per quality-adjusted life year (QALY) gained.

In the papers that evaluated PrEP targeted at MSM only, the ICER depended on assumptions about the target population: their age, HIV incidence, HIV prevalence, PrEP drug cost, level of condom use, adherence to PrEP or efficacy, rate of HIV diagnosis in the population and PrEP toxicity.

Eight of them [1-3,9-12,15] explicitly investigated the impact of reduction in the cost of PrEP and all agreed it could have a large impact on the ICER. Desai *et al.* [4] in particular noted that the ICER was inversely proportional to the cost of treating an HIV-positive patient: the higher the cost of treatment the more PrEP is cost-effective. Reduction in the cost of PrEP could be achieved by using event-based PrEP rather than daily PrEP (in IPERGAY on average 16 pills/months were taken) or due to the introduction of generic tenofovir or TDF-FTC. The patent for FTC expired in 2016. The patent for tenofovir disoproxil (TD) expires in July 2017. The patent for TDF (with the salt) expires in the middle of 2018. There are granted Supplementary Protection Certificates (SPCs) based on this patent that is for combinations of TD and FTC and generally the SPCs expire around February 2020.

A few papers highlighted explicitly the importance of targeting PrEP in order to make it cost-effective [1,2,5,8]. They also found that PrEP coverage had important implications for the epidemiological impact, budget impact and the ICER: the greater the number of people on PrEP, the higher the number of HIV infections averted and the budget impact (the additional cost in the first years of implementation). The cost-effectiveness of PrEP is largely dependent on the HIV incidence in the group of PrEP uptakers, therefore if the offer PrEP to a larger number of people is due to less stringent criteria in terms of HIV risk (or in other words lower HIV incidence in the group taking up the offer of PrEP) the cost-effectiveness of PrEP tends to be reduced. Nichols *et al.* and Cambiano *et al.* found that targeting to smaller group at higher risk was more cost-effective than if provided to a less targeted but larger group [3,9]. However, Desai *et al.* reported that a PrEP programme with a low coverage (2.5% of the very high-risk MSM population of New York City, *n*=1500) had limited impact on the number of infections prevented, which would not provide sufficient justification for investing in a PrEP programme.

A potential challenge that was raised was whether it would be realistic to offer PrEP by risk level, the potential challenge of identifying the target population, and how policy could be implemented selectively to prioritise access to PrEP given the substantial budgetary implications [1].

Two analyses [3,12] specific to the UK MSM context have been developed to estimate PrEP cost effectiveness and to explore the sensitivity of cost-effectiveness to changes in critical conditions. The abstract by Cambiano *et al.* [3] was based on a UK-based dynamic model. The authors concluded that PrEP use among MSM was cost-effective

when targeted at MSM reporting five or more condomless sex partners in the last year, when presenting with a bacterial STI, or in men having condomless sex if the cost of antiretrovirals (for treatment and for use as PrEP) was reduced by 50% of the current (2015) British National Formulary list price or in the context of PrEP being available for men having CLS in the past 3 months if there is no increase in CLS and men do not actively seek an HIV test, as a consequence of PrEP becoming available. The abstract by Ong *et al.* [12] used a static model to evaluate cost-effectiveness of a 1-year programme offered to selected GUM clinic attendees in England. The authors concurred with Cambiano *et al.* in concluding that a substantial price reduction of antiretroviral drugs used for PrEP would provide the necessary assurance of cost-effectiveness for an affordable public health programme of sufficient size.

8.2 People who inject drugs

Only two studies considered the cost-effectiveness of PrEP among PWID: one in the US, where PWID represent less than 1% of the population, but with a considerable HIV prevalence (9.8%) [17] and one that considered different subgroups of the populations at high risk of HIV including PWID in New York City [8]. They both considered an efficacy around 50% with a wide range and both found that PrEP should not be prioritised to this group.

As this population in the US is characterised by a very low level of ART coverage (10% in the early stages of the disease), the authors [17] investigated the cost-effectiveness not only of PrEP on its own and with frequent screening but also with enhanced ART (50% of newly diagnosed in the early stages of HIV receive prompt sustained ART) and found this last scenario to dominate the others and to prevent a substantial number of HIV infections among PWID and the whole US population. However, they concluded that at current drug prices (cost of Truvada of US$10,000/year [range: US$7,150–13,320]), this strategy is too expensive both in absolute terms and in terms of cost per QALY gained ($253 000/QALY gained), but if drug costs are reduced by 65% (possibly due to the introduction of generic drugs), then the ICER would be reduced to around $100,000 per QALY gained.

Kessler *et al.* [8] considered the introduction of PrEP in different group at high risk of HIV: MSM, high-risk MSM, high-risk heterosexuals, PWID and their combinations and found that the introduction of PrEP only in PWID had a small epidemiological impact (2% of infections averted over 20 years compared to around 20% when targeting MSM) and at a high cost-per-infection averted (more than $9 million compared to around $2.1 million when targeting MSM).

8.3 Special populations

Two recent studies evaluated PrEP as a conception strategy for heterosexual serodiscordant couples where the male partner is HIV positive and virologically suppressed on antiretroviral therapy: one in Canada [18] and one in France [19].

In particular, Letchumanan *et al.* [18] considered condomless sex restricted to time of ovulation with PrEP and as other conception strategies: condomless sex restricted to time ovulation, sperm-washing with intrauterine insemination. Similarly, Mabileau *et al.* [19] considered four options: condomless sex (note that the HIV-positive partner is suppressed and on treatment), condomless sex restricted to fertile days, condomless sex with the use of PrEP, condomless sex with PrEP restricted to fertile days and medically assisted procreation (MAP), such as intrauterine insemination.

Both concluded that the use of PrEP as a conception is not a cost-effective option. Letchumanan *et al.* found both condomless sex restricted to time ovulation with PrEP and sperm-washing with intrauterine insemination were too expensive in terms of absolute cost (respectively $438 and $14,910 more expensive than condomless sex

restricted to time ovulation) and cost per QALY gained (both dominated by condomless sex restricted to time ovulation which has an ICER of $101/QALY gained). Mabileau *et al.* recognised that the conception options with the lowest risk of HIV transmission are condomless sex restricted to fertile days (with the positive partner suppressed on ART) with PrEP during those days and MAP. However, they conclude that these options are not cost-effective at the current costs.

8.4 References

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9 Summary of recommendations

3.1 Evidence for safety and efficacy in men who have sex with men (MSM): recommendations

1. **We recommend that PrEP with on-demand or daily oral TDF-FTC should be offered to HIV-negative MSM who are identified as being at elevated risk of HIV acquisition through condomless anal sex in the previous 3–6 months and ongoing condomless anal sex. (1A)**
2. **We recommend that PrEP with on-demand or daily oral TDF-FTC should be offered to HIV-negative MSM having condomless anal sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)**
3. **We suggest that tenofovir alone should not currently be offered as PrEP to MSM. This recommendation is based on lack of evidence, rather than evidence of lack of effect. (2C)**

Good practice point

- **Consider PrEP on a case-by-case basis in MSM with current factors other than condomless anal sex in previous 3–6 months that may put them at increased risk of HIV acquisition. See Section 4.**

3.2 Evidence for safety and efficacy in heterosexual populations: recommendations

4. **We recommend that daily oral TDF-FTC should be offered to HIV-negative heterosexual men and women having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)**
5. **We suggest that PrEP with daily oral TDF-FTC should be offered on a case-by-case basis to heterosexual men and women with current factors that may put them at increased risk of HIV acquisition. See Section 4. (2B)**
6. **We recommend that TDF alone can be offered to heterosexual men and women where FTC is contraindicated. (1A)**

Good practice point

- **For women using DMPA, PrEP is likely to counteract an increase in HIV acquisition. However, women at risk of HIV acquisition should be offered an alternative form of contraception if available, whether or not they opt to take PrEP.**

3.3 Evidence for safety and efficacy in people who inject drugs (PWID): recommendations

7. **PrEP is not recommended for people who inject drugs where needle exchange and opiate substitution programmes are available. (2C)**
8. **We recommend that existing harm-reduction strategies such as needle exchange and opiate substitution programmes should be encouraged for people who inject drugs. (1D)**

Good practice points

- **Consider PrEP on a case-by-case basis in people who inject drugs in an outbreak situation or with other factors that put them at increased risk of HIV acquisition. See Section 4.**
- **Interventions for chemsex should be encouraged for people who are identified as being at elevated risk of HIV acquisition through report of injecting drug use during chemsex (slamming).**

3.4 Evidence for safety and efficacy in trans people: recommendations

9. **We recommend that PrEP with daily oral TDF-FTC should be offered to HIV-negative trans women who are identified as being at elevated risk of HIV acquisition through condomless anal sex in the previous 3–6 months and ongoing condomless sex. (1A)**
10. **We recommend that daily oral TDF-FTC should be offered to HIV-negative trans women and trans men having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)**

Good practice points

- **PrEP could be considered on a case-by-case basis in trans women and trans men with current factors other than condomless anal sex that may put them at increased risk of HIV acquisition. See Section 4.**
- **For both trans women and trans men a discussion should be had regarding unknown PrEP efficacy for frontal (vaginal) sex.**
- **A discussion should be had, both at PrEP initiation and maintenance visits, that there are no known interactions between TDF-FTC and feminising or masculinising hormones except for ethinylestradiol.**

3.5 Evidence for safety and efficacy in young people (15–25 years): recommendations

11. **We recommend that PrEP with daily oral TDF-FTC should be offered to young MSM and TGW women (15–25 years) who are identified as being at elevated risk of HIV acquisition through condomless anal sex in the previous 3–6 months and ongoing condomless anal sex. (1A)**
12. **We recommend that PrEP with TDF-FTC should be offered to young people having condomless anal sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)**
13. **Routine BMD scanning in young people initiating PrEP is not recommended. (1D)**

Good practice points

- **Consider PrEP with daily oral TDF-FTC on a case-by-case basis to young people with current factors other than condomless anal sex that may put them at increased risk of HIV acquisition. See Section 4.**
- **The risk and benefits of providing PrEP for adolescents should be weighed carefully in the context of UK laws and judgements about autonomy in healthcare decision-making (e.g. Fraser competency), and balanced against protecting young people from harm.**
- **A discussion about side effects including impact upon bone density in young people should be held at PrEP initiation and maintenance visits.**

3.6 Evidence for the timelines for starting and stopping PrEP: recommendations

14. **We recommend that if the risk of HIV acquisition is through anal sex, PrEP can be started with a double dose of TDF-FTC taken 2–24 hours before sex and continued daily until 48 hours after the last sexual risk. (1B)**

15. **We recommend that if PrEP for anal sex has been interrupted and it is less than 7 days since the last TDF-FTC dose then PrEP can be re-started with a single dose of TDF-FTC. (1B)**

16. **We recommend that if the risk of HIV acquisition is through vaginal sex, PrEP should be started as a daily regimen 7 days ahead of the likely risk and continued daily for 7 days after the last sexual risk. (1C)**

Good practice points

- **Individuals whose risk is through vaginal sex should still be informed about starting oral PrEP with a double dose of TDF-FTC in case there are times when it is not possible to take for a full 7 days before a potential risk, but advised that the evidence currently only supports this regimen for anal sex.**

- **Individuals at risk through injecting drug use as well as sexual risk should be informed that it takes longer to achieve protective concentrations in the blood, and that 7 days before and 7 days after is advisable.**

4.1 How to target those at risk of HIV transmission: recommendations

17. **We recommend that PrEP with regular or event-based oral TDF-FTC is offered to MSM and TGW at elevated risk of HIV acquisition through recent (3–6 months) and ongoing condomless anal sex. (1A)**

18. **We recommend that PrEP with daily oral TDF-FTC is offered to HIV-negative people having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)**

Good practice point

- **Consider PrEP with oral TDF-FTC on a case-by-case basis for people with other factors that place them at increased risk of HIV acquisition.**

5.3 Settings and context to administer PrEP: good practice points

- **Robust adherence support is required at PrEP initiation and maintenance. Some individuals starting PrEP may require extensive counselling and support to explore potential barriers to adherence and to provide support and strategies to improve adherence. This may be particularly relevant to some trans people, some young people and some heterosexual men and women to ensure PrEP literacy and maximise adherence.**
- **Information should be provided to all patients on:**
  - **PrEP medication dose and schedule;**
  - **Lead-in time to protection;**
  - **Potential side effects of PrEP medication and management of common side effects;**
  - **Relationship of adherence to PrEP efficacy;**
  - **Risks of HIV infection and antiretroviral resistance from suboptimal adherence;**
  - **Symptoms of HIV seroconversion that require assessment.**
- **PrEP provision should include condom provision and behavioural support.**
- **People receiving PrEP should receive advice on the potential risk of other STIs and the need for regular testing.**
- **Although level 3 sexual health services are recognised as preferable for PrEP delivery these settings may restrict access for some and, where appropriate, alternative models of delivery should be explored.**

5.4 Baseline assessment and testing: recommendations

19. **We recommend that baseline HIV testing with 4th generation serology test is undertaken prior to commencing PrEP. (1A)**

20. **We recommend that same-day initiation of PrEP may occur where an individual has a negative blood-based POCT on the day, or 4th generation test within the past 4 weeks. (1A)**

21. **We recommend that an HIV viral load should be considered where a high-risk exposure has occurred within 4 weeks. (1B)**

22. **We recommend that initiation of PrEP is deferred in people reporting condomless anal sex in the previous 4 weeks who have symptoms suggestive of HIV seroconversion until an HIV RNA result is available. (1A)**

23. **We recommend that baseline screening for hepatitis B should be undertaken in those of unknown hepatitis B status to exclude active hepatitis B infection with vaccination initiated in those who are non-immune. (1A)**

24. **We recommend that baseline screening for hepatitis C should be undertaken. (1B)**

25. **We recommend a full STI screen at baseline including syphilis serology for all, STI testing NAAT for gonococcal and chlamydial infection at sites of exposure (genital, rectal, pharyngeal). (1A)**

26. **We recommend that baseline renal function is assessed with a serum creatinine and eGFR but PrEP can be commenced while waiting for the results of baseline creatinine measurements. (1A)**

27. **We suggest that the estimated GFR for individuals starting TDF is >60 mL/min/1.73 m^2. (2A)**

28. **We suggest that individuals with eGFR <60 mL/min/1.73 m^2 should be started on PrEP only on a case-by-case basis and after a full assessment and discussion with the patient of the risk and benefits and obtaining specialist renal advice. (2B)**

Good practice points

- **A thorough medical history before initiating PrEP is essential to identify patients at greater risk of adverse events who might require closer renal or bone monitoring.**
- **Discuss possibility of kidney disease with TDF-FTC with individuals who have pre-existing chronic kidney disease or risk factors (>40 years of age, eGFR <90 mL/min/1.73 m^2 at baseline, hypertension, or diabetes).**
- **Obtain a thorough medication history for concomitant nephrotoxic drugs or drugs that have interactions with TDF-FTC. Discuss risk and benefits.**
- **PrEP should be offered as part of a package of care including regular HIV and STI testing and monitoring of renal function.**

5.5 Other considerations: recommendations

29. **We suggest that if an individual is pregnant when starting PrEP or becomes pregnant while on PrEP, we suggest continuation of PrEP during pregnancy or breastfeeding for those with ongoing risk for HIV after discussing the potential risks of TDF-FTC. (2B)**

Good practice points

- **Report information regarding use of PrEP during pregnancy to the Antiretroviral Pregnancy Registry.**
- **Discuss risk of bone loss with individuals with pre-existing risk factors or young people or demonstrated osteoporosis/osteomalacia/osteopenia.**

5.6 Prescribing PrEP: recommendations

30. **We recommend that tenofovir/emtricitabine (TDF-FTC) fixed-dose combination, dosed appropriately, is used for HIV pre-exposure prophylaxis for men who have sex with men (MSM), transgender women (TGW) and heterosexual men and women who are at high risk of HIV acquisition. (1A)**
31. **We recommend that for heterosexual men and women only, tenofovir alone may be considered. (1A)**
32. **We recommend the following lead in periods:**
    - **For event-based or daily dosing in anal sex, the time to clinical protection in rectal tissues is estimated as 2–24 hours following a double dose of TDF-FTC. (1A)**
    - **For daily dosing (with single dose TDF-FTC), the time to protection for vaginal sex is estimated as 7 days. (1B)**
33. **Frequency of dosing:**
    - **We recommend daily PrEP can be offered to MSM, trans men, trans women and heterosexual men and women at high risk of HIV (1A).**
    - **We recommend that MSM and TGW should be advised that minimal benefit from daily dosing will not be attained if fewer than four doses are taken per week. There is no evidence in other populations that four doses instead of seven per week is adequate (1B).**
    - **We recommend that event-based PrEP can be discussed and offered to MSM. A loading dose of two tablets of TDF-FTC taken 2–24 hours before sex, followed by a third (single) tablet 24 hours and a fourth (single) tablet 48 hours later is advised. Where potential exposure is sustained over more than a 24-hour period, one pill per day should be taken until the last sexual intercourse and then to take the two post exposure pills (1A).**
    - **In the absence of data, we do not recommend event-based dosing in heterosexual men and women, trans men or trans women**

6. Clinical follow-up and monitoring on treatment: good practice points

- **When first starting PrEP (and when re-starting), dispensing a 90-day supply of medication is suggested.**
- **Follow-up should be planned for 4 weeks later if indicated – via phone or email is sufficient – to review side effects, adherence and that daily and on-demand based regimes are being taken appropriately.**
- **Reasons for non-adherence including adverse events should be elicited and documented at each follow-up visit. Additional support, practical or psychological may be required.**
- **PrEP should continue where there is on-going high-risk for HIV transmission.**
- **Recipients should be advised of the possibility of transient nausea, vomiting, or headache and encouraged to manage this through the use of simple analgesics and anti-emetics**

6.5 Monitoring on PrEP: recommendations

34. **We recommend HIV testing should be undertaken every 3 months with a laboratory 4th or 5th generation test (1A) or a blood-based POCT. (1B)**

35. **We recommend patients with symptoms suggestive of seroconversion should be investigated with a 4th generation HIV test and HIV viral load. Atypical testing results should be discussed with a regional expert. (1C)**

36. **We recommend that in confirmed primary HIV infection, baseline resistance testing should be undertaken. This is to look for evidence of resistance-associated mutations to tenofovir or emtricitabine along with other transmitted mutations. (1B)**

37. **We recommend 3-monthly screening for bacterial STIs (chlamydia, gonorrhoea and syphilis) and for HCV is recommended for MSM and TGW. (1B)**

38. **We recommend STI screening should be offered annually for heterosexual men and women, or more frequently if change of partner or other risks for STI acquisition are present. (1B)**

39. **Renal recommendations:**
    - **If eGFR >90 mL/min at baseline (and follow up) and the person is aged <40 years then annual eGFR should be conducted. (1A)**
    - **If eGFR 60–90 mL/min, aged >40 years or concomitant risk factors for renal impairment recommend more frequent monitoring of renal function at physician discretion, but at least 6 monthly. (1B)**
    - **If eGFR <60 mL/min, the risks and benefits of continuing PrEP should be assessed on a case-by-case basis. Specialist renal input should be obtained to determine further investigations and frequency of monitoring. (1C)**

Good practice points

- **Assessment of pregnancy status in people not using reliable contraception should be conducted if indicated.**
- **Bone health:**
    - **Patients should be informed of the risk of reduction in BMD of around 1.5–2% at the hip and spine following 48 weeks of treatment.**
    - **Routine monitoring of BMD is not recommended in individuals taking TDF for PrEP with no other risk factors for reduced BMD.**
- **Adverse events should be reported through the yellow card scheme (https://yellowcard.mhra.gov.uk/).**
- **PrEP Sexual Health & HIV Activity Property Type (SHHAPT) codes should be completed for all patients to allow national monitoring of the eligibility, uptake, and duration of use of HIV pre-exposure prophylaxis (PrEP).**

6.6 Indications for stopping PrEP: recommendations

40. **We recommend that a positive HIV test is an absolute contraindication to continued PrEP. Referral to specialist HIV services should be undertaken immediately for investigation and management including intensification of ART regimen. (1A)**
41. **We suggest that for those at high risk of HIV acquisition, suboptimal adherence is a relative contraindication to continued use. (2B)**
42. **We recommend that in those without vaccine-induced immunity, HBV infection should be excluded prior to stopping TDF-FTC. (1B)**

10. List of abbreviations

AE	Adverse event
aHR	Adjust hazard ratio
BMD	Bone mineral density
CrCl	Creatinine clearance
CSW	Commercial sex worker
DOT	Directly observed therapy
eGFR	Estimated glomerular filtration rate
FGT	Female genital tract
HBV	Hepatitis B
HCV	Hepatitis C
HR	Hazard ratio
ITT	Intention to treat
MSM	Men who have sex with men
OR	Odds ratio
PBMC	Peripheral blood mononuclear cells
PEP	Post-exposure prophylaxis
PEPSE	Post-exposure prophylaxis for sexual exposure
PPV	Positive predictive value
RCT	Randomised controlled trial
RR	Risk ratio
STI	Sexually transmitted infection
TasP	Treatment as prevention
TDF-FTC	Tenofovir-emtricitabine
ULN	Upper limit of normal

Appendix 1. Pre-exposure prophylaxis (PrEP) GUMCAD codes: information for clinics and software providers

New sexual health and HIV activity property type (SHHAPT) codes are being introduced to the GUMCAD surveillance system to allow monitoring of HIV risk assessment and the eligibility, uptake and duration of use of HIV pre-exposure prophylaxis (PrEP) to reduce the acquisition of HIV infection.

Why are the codes needed?

The codes are designed to capture the use of PrEP among GUM clinic attendees who may be enrolled in a PrEP-related trial or have purchased PrEP drugs over the internet. The extent of the use of PrEP in the community is unknown at present. However, a large rise in its use is expected when the NHS England-funded PrEP Impact trial begins in 2017.

The introduction of PrEP SHHAPT codes to GUMCAD will allow the monitoring of the eligibility assessment and uptake of PrEP.

What codes are being introduced?

The additional codes are set out below. They are aligned with the PrEP eligibility criteria introduced in 2016 and are consistent with the current structure of SHHAPT codes.

For whom should codes be completed?

These codes should usually only be considered for clinic attendees who belong to sub-populations at high HIV risk, including cis- and transgender men and transgender women who have sex with men, black African heterosexuals, and people in serodiscordant relationships and others whose risk of HIV may be greater than or equal to 2% per annum. However, some clinic attendees who do not belong to these high-risk sub-populations may be privately purchasing PrEP, in which case some of these codes may also apply to them (e.g. O43: PrEP continued [through other source]).

How often should the codes be completed?

The codes should be completed at each PrEP visit or for each new episode of care.

Table A1. **Codes, descriptions, and definitions and guidance for PrEP SHHAPT codes**

SHHAPT code	Description	Definition and guidance
	PrEP eligibility codes	
O31	PrEP eligibility: criterion 1 (MSM/transgender woman)	High risk (cis- and transgender) men and transgender women who have sex with men: With a current negative HIV test* ***and*** another within the previous year (43–365 days) **AND** Who report condomless sex in the past 3 months** **AND** Who anticipate condomless sex in the next 3 months** * Current test can include a test performed on the day of assessing for PrEP eligibility ** excludes oral sex
O32	PrEP eligibility: criterion 2 (HIV+ partner)	HIV-negative partner of an HIV-positive person who is **not** virally suppressed* * Viral suppression defined as a (reported or documented) HIV viral load <200 copies/mL for more than 6 months
O33	PrEP eligibility: criterion 3 (others at high risk of HIV)	HIV-negative person at risk equivalent* to regular condomless sex with an HIV-positive person who is **not** virally suppressed** *an HIV risk greater than or equal to 2% per annum ** Viral suppression defined as a (reported or documented) HIV viral load <200 copies/mL for more than 6 months
Note: O31/32/33 should be coded at each new episode of care or at each PrEP visit. Only one of these eligibility codes (O31/32/33) should be assigned to a patient at each visit.		
PrEP offer and use codes		
O41	PrEP regimen: starting or continuing DAILY PrEP	For those starting or continuing a daily PrEP regimen
O42	PrEP regimen: starting or continuing EVENT-BASED PrEP	For those starting or continuing an event-based PrEP regimen

O43	PrEP continued (through other source)	For those who are obtaining PrEP from another source (e.g. from a trial other than the Impact trial or clinical service or online source or self-sourced)* * This could include people who do not meet eligibility criteria 1–3
O44	PrEP offered and declined	For those who decline the offer of starting a new course of PrEP* *Those who decline PrEP because they are already obtaining PrEP from another source should be coded O43
O45	PrEP stopped	PrEP stopped at the current attendance
Note: O41/42/44/45 should be coded for anyone assessed as eligible for PrEP (i.e. who has been coded as O31/32/33). O43 and O45 can be coded for those eligible and those not eligible for PrEP		
PrEP prescription codes		
O51*	PrEP prescription: 30 tablets	To indicate the number of tablets prescribed to those starting or continuing PrEP (30 tablets)
O52*	PrEP prescription: 60 tablets	To indicate the number of tablets prescribed to those starting or continuing PrEP (60 tablets)
O53*	PrEP prescription: 90 tablets	To indicate the number of tablets prescribed to those starting or continuing PrEP (90 tablets)
Note: Codes O51/52/53 should only be completed for a PrEP-related visit when PrEP is prescribed		
Patient characteristic code		
O60	Patient characteristic: transgender	Gender identity is not the same as their gender assigned at birth

Where are the codes being introduced?

These codes are being introduced in England and Wales.

Eligibility criteria (within the PrEP Impact trial)

There are three eligibility criteria:

1. **Men (cis-gender and transgender) and transgender women who:**
    1. Have sex with men
    2. Have had an HIV-negative test during an earlier episode of care in the preceding year
    3. Report condomless intercourse in the previous 3 months
    4. Affirm their likelihood of having condomless intercourse in the next 3 months
2. **HIV-negative partners of an HIV-positive person when:**
    1. The HIV-positive partner is not known to be virally suppressed (<200 copies/mL for 6 months or more)
    2. Condomless intercourse is anticipated before treatment of the HIV-positive partner takes effect
3. **HIV-negative persons who:**
    1. Are clinically assessed and considered to be at similar high risk of HIV acquisition as those with a serodiscordant partner who is not known to be virally suppressed

Participants will therefore be considered eligible for trial enrolment if they fulfil all the following individual eligibility criteria:

1. Belong to one of the three high HIV risk populations described above
2. Aged 16 years or over (no upper limit)
3. Considered to be HIV-negative on the day of enrolment
4. Willing and able to provide informed consent
5. Willing to adhere to the recommended PrEP regimen
6. Willing to re-attend the trial clinic at appropriate intervals for risk assessment

For any further questions or to provide feedback on the implementation of these codes, please contact the GUMCAD team (gumcad@phe.gov.uk).

Coding scenarios

Scenario	Coding
i. Patient accessing PrEP in a trial other than the PrEP Impact trial	O31/32/33: as appropriate O43: PrEP continued (through other source)
ii. Patient accessing PrEP online for personal use or through a private clinic	O31/32/33: as appropriate O43: PrEP continued (through other source)
iii. Patient is not taking PrEP, is offered PrEP at the current visit and declines	O31/32/33: as appropriate O44: PrEP offered and declined
iv. Patient started on daily PrEP at the current clinic visit	O31/32/33: as appropriate P1A/T4/T7: as appropriate for the HIV test O41: PrEP regimen: starting or continuing DAILY PrEP O51/52/53 (as appropriate for the number of PrEP tablets prescribed)
v. Patient continuing on event-based PrEP provided by the clinic	O31/32/33: as appropriate P1A/T4/T7: as appropriate for the HIV test O42: PrEP regimen: starting or continuing EVENT-BASED PrEP O51/52/53 (as appropriate for the number of PrEP tablets prescribed)
vi. Patient having a sexual health screen and continuing on daily PrEP though does not receive a PrEP prescription at the current visit	O31/32/33: as appropriate P1A/T4/T7: as appropriate for the HIV test O41: PrEP regimen: starting or continuing DAILY PrEP
vii. Patient stopping PrEP today	O31/32/33: as appropriate O45: PrEP stopped

viii. A black African heterosexual woman attends the GUM clinic with abnormal vaginal discharge and three partners of unknown HIV status from high HIV-prevalence countries in the past 3 months She is told about PrEP and the need to have an HIV test. She would like a course of PrEP but refuses an HIV test.	P1B: HIV antibody test offered and refused PrEP cannot be prescribed without a negative HIV test
ix. A gay man was risk-assessed and prescribed daily PrEP 3 months ago at his first attendance. At his follow-up visit, he reports continued condomless anal sex and anticipates further condomless anal sex. He would like to continue on PrEP prospectively using an event-based regimen. He consents to a rapid HIV test and STI testing.	O31: PrEP eligibility: criterion 1 P1A/T4/T7: as appropriate for the HIV test T10: rapid testing (same day results) O42: PrEP regimen: starting or continuing EVENT-BASED PrEP O51/52/53 (as appropriate for the number of PrEP tablets prescribed)
x. An HIV-negative gay man has recently entered a regular partnership with an HIV-positive man who has not yet started antiretroviral therapy and reports that his HIV viral load has consistently been over 200 copies/mL. They are having condomless anal sex and want to continue to do so. He would like to take PrEP and consents to a rapid HIV test today. His last HIV test was 5 months ago.	O31: PrEP eligibility: criterion 1 P1A/T4/T7: as appropriate for the HIV test T10: rapid testing (same day results) O41/42 (as appropriate for the PrEP regimen) O51/52/53 (as appropriate for the number of PrEP tablets prescribed) * The patient meets the criteria for O31 and O32. He is coded as O31. However, if he had not had an HIV test in the past 42 – 365 days, he would be eligible for PrEP and coded O32.
xi. An HIV-negative black African woman has recently entered a regular partnership with an HIV-positive man who has not yet started antiretroviral therapy and reports that his HIV viral load has consistently been over 200 copies/mL. They want to have condomless sex. She would like to take PrEP and consents to an HIV test today.	O32: PrEP eligibility: criterion 2 P1A/T4: as appropriate for the HIV test O41: PrEP regimen: starting or continuing DAILY PrEP O51/52/53 (as appropriate for the number of PrEP tablets prescribed)

xii. A female sex worker has many clients from high HIV-prevalence countries. She inconsistently uses condoms for vaginal and anal sex. She would like to use PrEP.	SW: Sex worker O33: PrEP eligibility: criterion 3 P1A/T4/T7: as appropriate for the HIV test T10: rapid testing (same day results) O41: PrEP regimen: starting or continuing DAILY PrEP O51/52/53 (as appropriate for the number of PrEP tablets prescribed)
xiii. An injecting drug user who injects opiates attends clinic requesting PrEP. He denies sharing needles or works, does not use 'chems' and has one regular UK-born female partner who last tested HIV-negative 8 months ago. He consents to an HIV test today.	P1A/T4/T7: as appropriate for the HIV test T10: rapid testing (same day results) *The patient would not be eligible for PrEP unless there were additional risk factors that increased his risk of HIV to greater than 2% per annum. Therefore, no eligibility codes would be completed.
xiv. A gay man in a regular partnership with an HIV-negative man attends clinic for a regular sexual health screen. He does not have any other partners. He says that he is taking, and plans to continue taking, PrEP that he has bought over the internet.	P1A/T4/T7: as appropriate for the HIV test T10: rapid testing (same day results) O43: PrEP continued (through other source) *The patient would not be eligible for PrEP and therefore not coded O31/32/33, unless there were additional risk factors that increased his risk of HIV to greater than 2% per annum. However, as he is obtaining PrEP from another source, he should be coded O43.
xv. A gay man is risk assessed as eligible for PrEP. However, he wishes to access PrEP from another clinic.	O31/32/33: depending on risk assessment O44: PrEP offered and declined

Appendix 2: PrEP proformas: initial and follow-up visits

DRAFT

PrEP proforma – initial visit

Patient-identified reason for requesting PrEP:

Gender:

Medical history

Past medical history:

Regular medications: Allergies:

Any symptoms of HIV seroconversion in past 4/52: Yes / No

(If **Yes,** defer PrEP until HIV infection is excluded)

Hepatitis B status reviewed: Vaccinated in past? No □ Commence vaccination course, send hep B CAb

Yes □ Send hep B Sab

Where relevant: LMP: Contraception:

Sexual history:

Most recent Sexual Intercourse: Regular Partner (Y/N) Condom used? Yes □ No

Gender of partner: Partner county of origin

Partners HIV status: If HIV positive, on ART for 6 months with VL<200 copies (Y/N)

Type of sex: Receptive anal/Insertive anal/receptive vaginal/insertive vaginal x

Details of all new sexual partners in the last 3/12 _____

When was last condomless sex if different to above?

STI/HIV Screen

Date last STI screen: DD/MM/YY. Date of last HIV test if different DD/MM/YY. Location _____

Last HIV result: STI history:

Risk Factors

recreational drugs/chemsex? No □ Yes □ When were chems last used? _____

Please specify which (e.g. crystal meth, mephedrone, GBH/GBL)

Any sharing of needles: Y/N

If chemsex identified as a problem offer support

Offered? Y/N Accepted? Y/N

Any use of PEPSE/PEP in past year: Y/N

If yes: Details of when: _____

HIV test results

HIV POCT result today: *Reactive* Non-Reactive

***If reactive do not commence PrEP – send 4th generation HIV test to confirm diagnosis**

DRAFT

PrEP proforma – follow-up

Baseline tests	Tick if sent	Results
HIV		
Hepatitis B screening		
Hepatitis C screening		
STS		
CT/GC testing	Genital	
	Rectal	
	Pharyngeal	
Renal function		Abnormal? Yes No Detail: Action:
Pregnancy test (if indicated)		

Discuss use of nephrotoxic drugs: Y/N

Importance of adherence to dosing schedule discussed: Y/N

Patient information given and adherence support provided as appropriate

Importance of regular HIV testing, STI screening and monitoring of renal function discussed: Y/N

Discussed risk of decrease in bone density (not monitored): Y/N

Counselled on importance of practicing safer sex and condom use while on PrEP: Y/N

Discussed daily PrEP dosing/event-based dosing (EBD): Y/N Patient's choice: Daily / EBD / Intermittent*

Advised that minimum of 4 tablets should be taken per week for adequate protection

Discussed lead-in times (see table below) until PrEP effective: Y/N

	Time to steady state
Anal sex	2 tablets 2 – 24 hours before condomless sex
Vaginal sex	7 days

There are no data on trans men or women

Information given to patient where to purchase PrEP online/private prescription given: Y/N

Follow up

Date next appointment due: Booked today? Y/N

DRAFT

PrEP proforma – follow-up

Review appointment date:

Any change to health information provided at first visit? Y/N

On: Daily PrEP Event-based PrEP Intermittent PrEP

Has patient been sufficiently adherent with PrEP, i.e. >4 doses per week if on daily? Y/N

If no, please detail missed doses _____

Any unwanted side effects? Y/N If yes, please detail _____

Where relevant: LMP:

Contraception:

Sexual history:

Most recent SI: Regular Y/N Condom? Type of sex? Partner from?

☐ ♂ ♀ Yes ☐ No ☐ _____

Details of sexual partners in the last 3/12 _____

_____

When was last unprotected sex (without condom) if different to above?

Tests	Tick if sent	Results
HIV		
Hepatitis B screening		
Hepatitis C screening		
STS		
CT/GC testing	Genital	
	Rectal	
	Pharyngeal	
Renal function		Abnormal? Yes No Detail: Action:
Pregnancy test (if indicated)		

Hepatitis B status reviewed: Y/N

Further prescription given/further medication purchased online: Y/N