BASHH/BHIVA guidelines on the use of HIV pre-exposure prophylaxis (PrEP) (2024)

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Executive Summary and Recommendations

The UK has committed to end HIV transmissions by 2030(1) and we have, in recent years, seen declines in HIV incidence, most markedly in gay, bisexual and other men who have sex with men (GBMSM)(2, 3). Increased provision of pre-exposure prophylaxis (PrEP) has been a key component contributing to this success.

However, reductions in HIV incidence and access to HIV prevention, treatment and care are not equally experienced across all communities. For example, young people, those from ethnic minority communities, heterosexual men and women, trans and non-binary people and people who inject drugs often having lower knowledge of, access to and uptake of PrEP. UK data on HIV diagnoses in 2022 show an increasing proportion of first ever diagnoses in populations other than GBMSM(2), emphasising the need to ensure that HIV prevention interventions including PrEP extend across all those at risk and to areas and communities of the UK with low as well as high overall HIV prevalence.

In developing the 2024 PrEP guidelines we have purposefully included a new chapter on PrEP equity. We have also written a new chapter on PrEP suitability and risk assessment that moves away from PrEP eligibility based on the inclusion criteria used for clinical trials. Avoiding the restrictions of basing eligibility on the limits necessarily applied in a trial situation and the potential barriers to access that brings, will help to support a more inclusive and accessible approach to PrEP provision, especially for already underserved and marginalised groups.

Chapters 5 to 8 are intended to offer practical guidance in risk assessment, starting and stopping PrEP, ongoing management and monitoring while on PrEP and considerations for post-exposure prophylaxis in people taking PrEP. In view of the availability of PrEP formulations other than oral tablets, in particular the anticipated approval of long-acting injectable cabotegravir (CAB-LA)(4, 5) in the near future, we have added a final chapter (Chapter 10) to support the use of new therapies. However, when we use the term ‘PrEP’ throughout these guidelines we are referring to TD/FTC or TAF/FTC oral tablets, unless otherwise stated.

Recommendations and Good Practice Points

Recommendations for PrEP Equity

1. We recommend ensuring the fair distribution of provision and support for PrEP (PrEP equity) by addressing all factors that affect access to and uptake of PrEP and related healthcare (Grade 1C).

2. We recommend that all health providers, including policy makers, commissioners and community partners should identify and address how health service organisation and delivery can play a role in addressing persistent PrEP inequity. (1D)

Good practice points

- We suggest that, with clear governance connections to specialist level 3 GUM services, PrEP provision should be expanded, with evaluation, to settings outside of specialist sexual health services including but not limited to, online services, in community pharmacies, drug and alcohol services, in primary care and in community settings likely to be accessed by people who would benefit from PrEP.
- We suggest that sexual and reproductive health promotion information should include information and advice about PrEP that is co-designed with communities who would benefit from PrEP and be targeted at those groups who have poorer access to PrEP.
- We suggest that organisations who work with communities who would benefit from PrEP and/or who deliver outreach work should ensure that information on PrEP is integrated into their work.

We suggest that anyone who offers information/support to potential PrEP users, or designs or delivers services should consider:

- Who attends (and *who does not attend*) your clinic or service?
- What is the physical and social environment when they arrive at your clinic or service?
- What demands (resources, knowledge, behaviour, etc) are asked of them within the clinic or service?
- What support do they need in understanding and using PrEP within their sexual and social lives?
- How might the physical and social settings in which they live affect their PrEP access and use?

Recommendations for PrEP Efficacy

3. We recommend that PrEP should be offered to people, regardless of their gender or sexual orientation, who would benefit from a reduction in HIV risk* This includes:

- HIV-negative gay, bisexual and other men who have sex with men who are at elevated risk of HIV-acquisition through condomless sex (1A)
- HIV-negative individuals having condomless sex with HIV positive partners whose plasma viral load is not <200 copies/ml on ART (1A)
- Heterosexual men and women at greater risk of HIV acquisition*. See Section 5. (1B)
- Trans women (1B), trans men and nonbinary people (1D) at greater risk of HIV acquisition*
- People who inject drugs and who might share injecting equipment (1B)
- People who, regardless of gender or sexual orientation, are likely to have condomless sex with people at risk of HIV (2B)

*defined as where HIV risk is likely to be in excess of the background UK population and where benefit outweighs clinical risk of PrEP (see Chapter 4)(1-3)

4. We recommend that young people (aged 15-22) should be offered PrEP in accordance with their reported risk (1B) and that those aged under 18 years should be offered TAF-FTC as PrEP (1B)
5. We recommend that young people on PrEP should be offered additional support and monitoring to optimise adherence (1B)

6. We recommend that PrEP using TD alone can be offered to heterosexual men and women if FTC is contraindicated (1A)
7. We recommend that TD alone should not be offered as PrEP to GBMSM. This is based on lack of evidence, rather than evidence of lack of effect (2C)

Good practice points

- We suggest that, as bone formation continues into the early 20s, TAF-FTC PrEP when commenced before the age of 18 years should be continued until the individual is aged 20 years.
- We suggest that specific reassurance should be given to trans people that there are no expected drug–drug interactions between PrEP and gender affirming hormone therapy (GAHT).

Recommendations for PrEP Suitability and Risk Assessment

Who should be offered PrEP?

8. We recommend that PrEP should be offered to people, regardless of their gender or sexual orientation who would benefit from a reduction in HIV risk* including:

- people who request PrEP (2B)
- people at risk of HIV*(1A/1B depending on group)
- people who, regardless of gender or sexual orientation, are likely to have condomless anal or vaginal sex with people at risk of HIV* (2B)
- people who inject drugs who might share injecting equipment (1A)

*defined as where HIV risk is likely to be in excess of the background UK population and where benefit outweighs clinical risk of PrEP (see Chapter 4)(1-3)

When should PrEP be prescribed?

9. We recommend that PrEP should be prescribed for people in whom it is suitable as soon as HIV risk is identified as benefit is immediate and toxicity is uncommon and delayed. (1A)

Good practice points

- **PrEP offer:** We suggest that PrEP should be considered in people identifying or identified as being at risk of HIV infection. For example, where HIV testing is performed, or an individual presents for regular or emergency contraception or STI testing
- **Reviewing PrEP risk/benefit:** We suggest that there is ongoing consideration and review of risk and benefit as this can change over time
- **Assessment of PrEP suitability:** We suggest that assessment of HIV and STI risk and suitability for PrEP should be integrated into the broader sexual and reproductive health context. People who could benefit from PrEP will be encountered in community healthcare, general practice, and sexual and reproductive health services. HIV risk may become apparent in the context of care related to contraception, pregnancy or abortion, or in the emergency setting in the context of HIV testing or PEPSE provision. This particularly applies to women and other people who would benefit from a reduction in HIV risk but do not attend sexual health services. It also includes people in whom HIV or STI testing is stigmatised or who had not previously considered HIV risk.

Recommendations for baseline testing and management

HIV testing

10. We recommend that baseline HIV testing with a combined antigen/antibody serology test is undertaken prior to commencing PrEP (1A)
11. For individuals who have no history of a high-risk sexual exposure in the preceding 6 weeks, or for those in whom high risk exposure has not involved the use of PrEP or PEP, we recommend that PrEP can be safely initiated on the same day in the presence of a negative 3rd generation or higher or blood based POCT pending the results of laboratory HIV antigen/antibody test (1A)

12. We recommend HIV viral load testing should be considered where a high-risk exposure has happened in the preceding 6 weeks, PEP has been taken or PrEP has been inconsistently used and/or there are symptoms consistent with HIV seroconversion. (1B)
13. We recommend that patients with symptoms suggestive of seroconversion should be investigated with a combined HIV antigen/antibody test and HIV viral load and PrEP initiation be deferred until HIV infection has been excluded. Atypical testing results should be discussed with a regional expert. (1C)

STI and BBV testing

14. We recommend that testing for STIs should be undertaken at baseline. (1B)
15. We recommend that testing for hepatitis B should be undertaken at baseline (1A)
16. We recommend that testing for hepatitis C should be undertaken at baseline in GBMSM and other at-risk groups (1B)

Renal function

17. We recommend that serum creatinine and eGFR should be performed at baseline. Renal function should be checked on the same day or as close to PrEP initiation as possible and the results checked as soon as possible, but PrEP can be commenced while waiting for the results (1A)
18. We recommend that eGFR for individuals starting TD-FTC should be ≥60 ml/min/1.73m^2 (2A)
19. We recommend that if eGFR ≥ 90ml/min/1.73m^2 at baseline and the person is aged < 40 years, with no risks for renal disease, then annual eGFR testing should be conducted (1A) [***See flow chart on page 53]***
20. We recommend that if eGFR is ≥ 90 ml/min/1.73m^2 at baseline and the person is ≥ 40 years or has risks for renal disease then eGFR should be repeated at 6 months (2B) [***See flow chart on page 53]***
21. We recommend that if eGFR is between 70 – 89ml/min/1.73m^2 at baseline then risks for renal disease should be checked, reduced exposure to oral PrEP be considered (e.g. with event based or intermittent dosing) of oral PrEP and eGFR repeated at 3 months (2B) ***See flow chart on page 53***
22. We recommend that if eGFR is 60 - 69 ml/min/1.73m^2 at baseline then eGFR should be repeated in 2-4 weeks, having stopped any creatine/protein supplements, assessing risks for renal disease and consider reduced to exposure to oral PrEP with event based or intermittent dosing (2B) **See flow chart on page 53**
23. We recommend that individuals with an eGFR between 30 - 60 ml/min/1.73m^2 at baseline have the full assessment recommended in the ***flow chart on page 53*** and are recommended TAF-FTC PrEP (1A)

Bone function

24. We recommend that oral PrEP recipients should be informed of the risk of reduction in BMD of around 1.5–2% at the hip and spine following 48 weeks of TDF-FTC PrEP (1B) but that there is no evidence of an increased risk of fractures while taking PrEP (1A)
25. We recommend that all oral PrEP recipients should be assessed for markers of increased absolute fracture risk e.g. previous fracture(s) at wrist, spine or hip, smoking, high alcohol intake, menopause, high-dose oral or high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer), or other causes of secondary osteoporosis (1D)
26. We recommend that those aged under 18 should be offered TAF-FTC as PrEP (1B)
27. We recommend that in those aged > 50 and/or with risk factors for osteoporosis, fracture risk should be calculated using the QFracture® (preferred) or FRAX® online assessment calculators. Those at high risk (risk score greater than 10%) should be offered a DXA scan(6) *
28. We recommend that in people with markers of increased fracture risk and/or with confirmed osteoporosis on DXA scanning (see GPP) who require continuous daily oral PrEP, alternatives to TD-FTC PrEP (currently TAF-FTC only) should be advised (2B)

29. We recommend that in those with risk factors for reduced BMD in whom DXA scanning is not indicated, options for reduced exposure to TD through event-based or interval dosing should be supported where appropriate for risk reduction (2C)

Pregnancy

30. We recommend that if an individual is pregnant when starting PrEP that they initiate PrEP during pregnancy and breastfeeding if there is an ongoing risk of HIV acquisition, after discussing the potential risks of TD-FTC. (2B)

*From NICE Clinical Guideline 146: Osteoporosis; ungraded recommendation

Good practice points

- We suggest that PrEP should be offered as part of a package of care including condom provision, regular HIV and STI testing and monitoring of renal function.
- We suggest that people who could benefit from PrEP should be informed of the evidence for effectiveness and safety of PrEP
- We suggest that a thorough medical history before initiating PrEP is essential to identify people at greater risk of adverse events who might require closer renal or bone monitoring including a medication history for concomitant nephrotoxic drugs
- We suggest that the possibility of reduced renal function with TD-FTC is discussed with individuals who have pre-existing chronic renal disease or risk factors (diabetes, hypertension, ≥40 years of age, eGFR < 90 ml/min/1.73m^2)
- We suggest that routine monitoring of BMD is not recommended in individuals taking PrEP with no other risk factors for reduced BMD.
- We suggest that people at intermediate risk whose fracture risk is close to but under 10% who have risk factors that may be underestimated by FRAX®, such as people taking high doses of oral corticosteroids, should be offered a DXA scan.
- We suggest that people at low risk (risk score less than 10%) should not be offered a DXA scan, but given lifestyle advice and fracture risk checked annually whilst on PrEP
- We suggest that vitamin D and calcium supplementation is recommended to PrEP recipients of all ages with risk factors for reduced BMD, particularly those under the age of 25 years.
- We suggest that PrEP initiation in the presence of a negative blood POCT and absence of Acute HIV Infection (AHI) symptoms should not be delayed whilst awaiting laboratory or confirmatory results.
- We suggest that access to PrEP amongst people at high risk of HIV infection is not delayed; wherever possible aim to initiate on same day of testing. Take all tests at the time of PrEP initiation, review results as soon as possible and modify PrEP prescription accordingly once results become available.
- We suggest that clinicians remain alert to acute HIV infection amongst people at risk of HIV, particularly in the presence of any symptoms, which are often non-specific in nature, and counsel and manage accordingly.
- We suggest that assessment for pregnancy is conducted in women and other people who can get pregnant who are not using reliable contraception if indicated.
- We suggest that adverse events should be reported through the yellow card scheme (https://yellowcard.mhra.gov.uk/).

Recommendations for on-going clinical management and monitoring

HIV Testing

31. We recommend HIV testing should be undertaken every 3 - 6 months for people taking PrEP with a laboratory combined HIV antigen/antibody test (1A) or a blood based POCT (1B).
32. We recommend 3-monthly testing for bacterial STIs (chlamydia, gonorrhoea and syphilis) for people taking PrEP who have new or multiple sexual partners and regular HCV testing in those at ongoing risk in line with hepatitis testing guidelines(7, 8) (1B)
33. We recommended that following the discontinuation of PrEP, retest for HIV at day 45 (1B)

34. In the presence of indeterminate HIV test results, for people having reported use of intermittent PrEP or PEP, we recommend serology and samples to be sent to the reference laboratory at the UK Health Security Agency for detailed analysis, including Western Blot and HIV DNA testing. We recommend continuation of PrEP until additional results of HIV testing is complete. In complex cases we recommend referral to the UKHSA/IDRIS clinic for expert review (Imperial.IDRIS@nhs.net) (1B)
35. 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)

Testing and management of renal function (*See flow chart on page 59)*

36. We recommend that ongoing monitoring of renal function is assessed with serum creatinine and eGFR (1A)
37. We recommend that if eGFR remains ≥ 90 ml/min/1.73m^2 and the person is aged < 40 years, with no risks for renal disease then annual eGFR should be conducted (1A)
38. We recommend that if an individual has a significant drop in eGFR (defined as a confirmed reduction of 15 ml/min or 25% in eGFR from baseline), more frequent renal monitoring is required (2B)
39. We recommend that where a significant drop in eGFR is experienced, it is confirmed with the CKD-EPI equation to calculate creatinine clearance (2B)
40. We recommend that if a significant drop in eGFR is not confirmed with CKD-EPI that eGFR is repeated at 3 months and ongoing renal monitoring continued as per the flow chart on page 60 (2B)
41. We recommend that if eGFR is between 70 – 89 ml/min/1.73m^2 whilst taking PrEP, then risks for renal disease should be checked, reduced exposure to TD with EBD or intermittent dosing considered, and eGFR repeated at 3 months (2B)
42. We recommend that if eGFR is 60-69 ml/min/1.73m^2 whilst taking PrEP then eGFR should be repeated in 2-4 weeks, having stopped any creatine/protein supplements, assessing risks for renal disease and consider reducing exposure to TDF with EBD or intermittent dosing (2B)
43. We recommend that if eGFR < 60 ml/min/1.73m^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 **See flow chart on page 61**
44. We recommend that individuals with an eGFR < 60 ml/min/1.73m^2 be recommended TAF containing PrEP (1A) **See flow chart on page 61**
45. We recommend that that if eGFR < 60 ml/min/1.73m^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) **See flow chart on page 61**

TAF-FTC PrEP and weight gain

46. We recommend that individuals taking TAF-FTC PrEP should be advised of the risk of modest weight gain compared to TD-FTC (1B).

Testing and management of bone function

47. We recommend that those with markers of increased fracture risk and/or with confirmed osteoporosis on DEXA scanning (see GPP) who are taking continuous daily PrEP, alternatives to TD-PrEP (currently TAF-FTC only) should be advised (2B).
48. We recommend that in those with risk factors for reduced BMD in whom DXA scanning is not indicated, options for reduced exposure to TD through event-based or intermittent dosing should be supported where appropriate for risk reduction (2B).
49. We recommend that in those aged ≥ 50 and/or with risk factors for osteoporosis, fracture risk should be calculated annually using the QFracture® (preferred) or FRAX® online assessment calculators (1A).

50. We recommend that that people at high risk (risk score greater than 10%) should be offered a DXA scan to confirm osteoporosis (1A).
51. We recommend that people at intermediate risk whose fracture risk is close to but under 10% who have risk factors that may be underestimated by FRAX®, such as people taking high doses of oral corticosteroids, should be offered a DXA scan (1A)
52. We recommend that people with osteoporosis who are at high risk for fractures should be switched to TAF-FTC (1B).
53. We recommend that people at low risk (risk score less than 10%) should not be a DXA scan, but given lifestyle advice and fracture risk checked annually whilst on PrEP (1B).

Pregnancy

54. We recommend that if an individual becomes pregnant while on PrEP that they continue PrEP during pregnancy or breastfeeding if there is an ongoing risk of HIV acquisition, after discussing the potential risks of TD-FTC. (2B)

Good practice points

- PrEP should be offered as part of a package of care which includes comprehensive sexual and reproductive healthcare services.
- The need for STI testing or toxicity monitoring should not be a barrier to PrEP resupply. Supply should never be conditional on testing or monitoring.
- Remain alert to acute HIV infection amongst people at risk of HIV, particularly in the presence of any symptoms, which are often non-specific in nature and counsel and manage accordingly.
- Assessment of pregnancy status in those not using reliable contraception should be conducted if indicated.
- Bone health:
  - Routine monitoring of BMD is not recommended in individuals taking TD for PrEP with no other risk factors for reduced BMD.
  - Supplementation with vitamin D and calcium may be considered, particularly if additional risks for osteopenia or osteoporosis, although there is no evidence currently to support this.
  - In those with risk factors for reduced BMD the FRAX tool could be undertaken, to indicate the need for a DEXA scan and potential treatment for reduced BMD.

Recommendations for Starting and Stopping TD-FTC and TAF-FTC PrEP: NB: There have been no clinical trials of double dose (two pills) lead-in other than for sexual exposures in MSM and TGW, but high quality pharmacokinetic/pharmacodynamic (PK) studies support with equal weight a double-dose (two pills) lead-in as compared to multi-day single dose lead-in for all exposures including injecting drug use.

55. We recommend that, if the risk of HIV acquisition is through receptive anal sex, oral PrEP can be started with a double dose (two pills) 2-24 hours before risk and safely stopped with a single dose daily for two days after last risk (**TD-FTC** [1A], **TAF-FTC** [1B])

56. We recommend that, if the risk of HIV acquisition is through insertive vaginal/neovaginal sex/anal sex, oral PrEP can be started with a double dose (two pills) 2-24 hours before risk and safely stopped with a single dose daily for two days after last risk

TD-FTC: Insertive anal [1A]. Insertive neovaginal/vaginal [1B]. **TAF-FTC:** Insertive vaginal/neovaginal/anal (1B)

57. We recommend that, if the risk of HIV acquisition is through receptive vaginal/neovaginal sex, PrEP can be started with a double dose (two pills) 2-24 hours before risk and safely stopped with a single dose daily for seven days after last risk.

(Receptive vaginal [1C], neovaginal [1D])

58. We recommend that, if the risk of HIV acquisition is through injecting drug use, oral PrEP can be started with a double dose (two pills) 2-24 hours before and safely stopped with single dose daily for seven days after last risk. [1C]

Good practice points

- We suggest that it is important to stress that for receptive vaginal/neovaginal sex and injecting drug use, users need to continue TD-FTC PrEP for seven days after exposure. Fewer than seven daily doses following a double dose start are likely to be incrementally less effective with reducing dose frequency. When daily dosing is continuous (ie when 4 or more doses have been taken in the week prior to an exposure), 4 doses per week in subsequent weeks are likely to provide good protection for all types of risk exposure.

We suggest that people who experience moderate-severe gastrointestinal side effects following the double dose (two pills), can take the dose as two separate tablets 6-12 hours apart.

Recommendations for PrEP and PEPSE For PrEP users who have drug to hand (See Table 3)

Sexual risk through condomless anal sex/insertive vaginal sex:

59. We recommend that if the risk of HIV acquisition is through condomless anal sex (insertive and receptive) / vaginal or neovaginal sex (insertive), and if seven days or less have elapsed since the last oral PrEP dose, PrEP should be resumed as prescribed (1B).
60. We recommend that, if more than seven days have elapsed since the last oral PrEP dose, PrEP should be restarted with a double dose of PrEP as soon as possible (preferably in the first 24h (1B) after exposure and no later than 72 hours (2C]), and continued daily while seeking advice from clinical services on possible intensification of PEPSE.

Sexual risk through condomless receptive vaginal /neovaginal sex

61. We recommend that, if the risk of HIV acquisition is through condomless receptive vaginal/neovaginal sex, and if three days or less have elapsed since the last oral PrEP dose, PrEP should be resumed with a double dose. (Vaginal [1B], Neovaginal [2C]).
62. We recommend that, if more than three days have elapsed since the last PrEP dose, PrEP should be restarted with a double dose of oral PrEP as soon as possible (preferably in the first 24h after exposure (Vaginal [1B]/Neovaginal [2C]) and no later than 72 hours (2C) and continued daily while seeking advice from clinical services on possible intensification of PEPSE.

Blood borne risk for people who inject drugs

63. We recommend that, if the risk of HIV acquisition is through injecting drug use and if four days or less have elapsed since the last oral PrEP dose, PrEP should be resumed with a double dose. (1D).
64. We recommend that, if more than four days have elapsed since the last oral PrEP dose, PrEP should be restarted with double dose of PrEP as soon as possible (preferably in the first 24h after exposure and no later than 72 hours) and continued daily while seeking advice from clinical services on possible intensification of PrEP (1D)

Missed post coital dose for event-based PrEP

65. We recommend that, for event-based oral PrEP users who are late with, or missed, the first post-coital dose, the first post-coital dose can still be taken up to 48 hours after sex, provided at least one tablet was taken before sex (1B); the second post-coital dose should be taken 24 hours after the first to complete the course.
66. We recommend that if more than 48 hours have elapsed after last risk, the first dose should be taken and advice should be sought from clinical services (1B)

Good practice points

- We suggest that PrEP users should routinely be given advice about what to do in the event of an HIV risk.
- We suggest that it is important that PrEP users understand that PrEP and PEP only reduce the risk of HIV acquisition when drug is taken as close as possible to the risk episode, and that the benefit of starting beyond 24 hours reduces substantially when there is no drug present at the time of risk.
- We suggest that PEP should be considered if there has been significant risk exposure within the last 72 hours at the point of initiating PrEP. If there are two or more risk episodes more than 72 hours before initiation, PrEP should be initiated with HIV testing as recommended in 6.2.2
- We suggest that PrEP users should be informed about how to access PEP advice in a timely manner

Recommendations for buying generic PrEP online

67. We recommend that clinicians should ensure full PrEP support, including renal monitoring, to patients who are taking oral PrEP they have sourced online. (1D)
68. We recommend that therapeutic drug monitoring is **not** required for those taking self-sourced oral PrEP (1B).

Good practice points

We suggest that:

- Clinicians should signpost individuals to IWantPrEPnow, PrEPster or https://www.prep.global/get-prep if they are unable or unwilling to access PrEP on the NHS. These site offers support and advice and the ability to source generic drug as safely as possible.
- The discussion of self-sourcing PrEP online needs to be fully informed including risks and benefits described in Sections 4 & 8, and advice given in line with these guidelines.
- Self-sourcing PrEP users buying TD-FTC or TAF-FTC online should be made aware that the product should originate from a manufacturer listed by the US FDA and that it is advisable to order in advance in case of delays in delivery.
- Self-sourcing users buying TAF-FTC should be made aware that this formulation of oral PrEP only has RCT evidence in cisgender men and transgender women who have sex with men.
- Clinicians should ensure that people buying TD-FTC or TAF-FTC are taking medication that is labelled as containing both tenofovir and emtricitabine and are taking PrEP correctly.
- Self-sourcing PrEP users should be advised to have regular STI (including HCV for those at risk) and HIV tests and renal monitoring in line with the monitoring schedule recommended in this guideline.

Recommendations for new therapies not yet commissioned

69. We recommend that long-acting injectable cabotegravir (CAB-LA) should be offered under compassionate release to those at risk of HIV, but have contraindications to oral PrEP options (1A)
70. We recommend that long-acting injectable cabotegravir is strongly supported as an alternative to a daily PrEP pill (1A)
71. We recommend that an oral lead-in for cabotegravir as PrEP is optional for people worried about side effects.
72. We recommend if an oral lead-is used, the first injection of CAB-LA should be given on the final day of oral dosing, or within 3 days of the final dose (1B
73. We recommend that people are advised that protective levels of cabotegravir are achieved 7 days following first injection (1A)
74. We recommend that people are advised that protective levels of cabotegravir are maintained for 8 weeks after the last injection (1A)

75. We recommend that people on CAB-LA have HIV antibody-antigen and HIV viral load testing every 8 weeks (1A).
76. We recommend that when CAB-LA is discontinued and risk of HIV continues, an alternative PrEP agent is initiated, starting at 8 weeks and continuing to at least 52 weeks after the last CAB-LA injection (1B)
77. We recommend that routine renal, liver and lipid monitoring are not required for those on injectable cabotegravir for PrEP (1A).
78. We recommend that people are advised that injection site reactions are the most commonly experienced side-effect of CAB-LA, and that these are most likely following the first injection and decrease over time. (1A).
79. We recommend that people considering CAB-LA are advised that they may experience a slighter greater increase in weight gain over time than with oral TD-FTC (1A).
80. We recommend that CAB-LA be avoided in people taking certain anticonvulsants (e.g. carbamazepine and phenytoin) and anti-mycobacterials such as rifampicin and rifabutin as drug-drug interactions with these medications significantly reduces cabotegravir plasma concentrations to sub-therapeutic levels.
81. We recommend that a monthly 25 mg dapivirine ring provides a modest, but significant reduction in HIV incidence for women in whom alternative forms of PrEP are unacceptable or unsuitable(9, 10) (1A)

Good practice points

We suggest that, where individuals are already established on new PrEP therapies on arrival in the UK, clinicians should make every effort to prescribe the method the participant prefers. Oral PrEP is available in all the countries in which CAB-LA and the dapivirine ring can be accessed, and there are good reasons why individuals have opted for one of these other methods.

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Chapter 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. We also aim to provide guidance to address the inequities of knowledge, uptake and access to PrEP for groups and communities who would benefit from PrEP but remain underserved. We have included guidance and recommendations for the use of injectable cabotegravir PrEP in advance of this being licensed for use in the UK.

The guidelines include:

- Guidance on PrEP equity and access (chapter 3)
- Efficacy and safety of PrEP (chapter 4)
- Suitability and risk assessment for PrEP (chapter 5)
- Baseline and ongoing testing, clinical management and monitoring (chapters 6 and 7)
- Starting/stopping PrEP, dosing and indications for post-exposure prophylaxis (PEP) (chapter 8)
- Self-sourcing / buying generic PrEP online (chapter 9)
- New PrEP therapies (chapter 10)

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.

Inclusivity

We recognise the importance of these guidelines being inclusive and relevant to all, regardless of sexual orientation 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' refer to cisgender, transgender or gender-queer men who have sex with men and 'heterosexual men and women' refers to cisgender, transgender or gender-queer men and women who have heterosexual sex. Non-binary people and clinicians supporting non-binary people should use the advice which best aligns with their individual needs. Where sections are specifically relevant to transgender people, we identify this using the terms transgender people, transgender men or transgender women.

Language

We recognise that language matters and acknowledge the importance of using non-stigmatising, person-centred language when discussing sexual health and HIV and have written the guidelines in line with the recommendations of the People First Charter. Further information can be found here: https://peoplefirstcharter.org

Chapter 2: Methods

2.1 Search strategy

All members of the writing 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 virtual meetings of the writing group and a meeting of community activists and organisations who commented on a draft of the guidelines in June 2023. The draft guidelines have been reviewed by the BASHH Clinical Effectiveness Group (CEG), who have ultimate editorial responsibility for the guidelines, in line with the methodology described in the CEG Framework for Guideline development published on the CEG webpage on the BASHH website. 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, STIs, adverse events, risk behaviours or risk compensation (condom use, number of sexual partners), adherence

The literature review search was from 1 January 2016 to April 2021. Medline, Embase and Cochrane Library databases were searched. Only papers in English were included. We did not exclude animal studies as this made very little difference to the search results. In addition, although the formal literature review was not repeated, subsequent evidence published between April 2021 and January 2024 that the writing group felt was relevant has been included.

Conference abstracts from CROI, IAS, BHIVA, HIV Research for Prevention (HIV4P), EACS and HIV Glasgow were searched from January 2019 to April 2021.

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.

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 (GPPs). GPPs are recommendations based on the clinical judgement and experience of the working group and feedback from community and public consultation. GPPs emphasise an area of important clinical practice for which there is not, or 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 and feedback

The guideline writing group included representation from Terrence Higgins Trust, Prepster, National AIDS Trust and African Advocacy Forum. In order to widen the stakeholder involvement, a meeting of community activists and organisations was held in June 2023, when feedback was sought on the content of the draft guidelines and recommendations prior to wider public consultation. We acknowledge and thank all the individuals and community organisations for their helpful contributions.

2.4 Generic preparations of tenofovir disoproxil

The guideline writing group recognises that although clinical trials of oral PrEP trials have used tenofovir disoproxil fumarate (TDF), other salts of tenofovir disoproxil (including maleate, succinate and phosphate) in generic formulations are now prescribed. We have therefore used the acronym TDF-FTC where Truvada was used in a trial and TD-FTC to denote all other (generic) forms of tenofovir disoproxil and emtricitabine. We use the acronym TAF-FTC to describe the use of tenofovir alafenamide fumarate (Descovy) as PrEP.

We use TD-XTC when referring to combinations where tenofovir disoproxil salts are combined with emtricitabine (FTC) or lamivudine (3TC).

2.5 Terminology used to describe:

PrEP dosing frequency:

There is no internationally agreed terminology for dosing options for PrEP. Regular dosing options discussed in these guidelines include daily dosing (taken continuously every day), and intermittent dosing (four doses per week which may be referred to as 'Ts and Ss', meaning taken on a Tuesday, Thursday, Saturday and Sunday). Event-based dosing (sometimes called Event-driven (ED) or On-demand (OD) dosing) has previously referred to dosing based on the IPERGAY trial dosing regimen. This involves taking two tablets 2 to 24 hours before risk and one tablet 24 hours and 48 hours following the initial double dose, also known as '2:1:1' dosing. This guideline also includes a new event-based option of two tablets 2 to 24 hours before risk and one tablet daily for 7 days following the initial double dose. We refer to this as 2:7 dosing.

Although the IPERGAY regimen allows for an Event-based regimen including **one** tablet 2 to 24 hours before risk and one tablet 24 hours and 48 hours following the initial double dose, if an Event-based course has been completed within the preceding 6 days – effectively '1:1:1' dosing, this terminology is not commonly used.

Condomless sex:

Condomless sex as referred to in this guideline includes penile, vaginal, neovaginal or anal sex without using either a male or female condoms.

Chapter 3. PrEP Equity

Recommendations for PrEP Equity
1. We recommend ensuring the fair distribution of provision and support for PrEP (PrEP equity) by addressing all factors that affect access to and uptake of PrEP and related healthcare (Grade 1C).
2. We recommend that all health providers, including policy makers, commissioners and community partners should identify and address how health service organisation and delivery can play a role in addressing persistent PrEP inequity. (1D)
Good practice points
We suggest that, with clear governance connections to specialist level 3 GUM services, PrEP provision should be expanded, with evaluation, to settings outside of specialist sexual health services including but not limited to, online services, in community pharmacies, drug and alcohol services, in primary care and in community settings likely to be accessed by people who would benefit from PrEP.
We suggest that sexual and reproductive health promotion information should include information and advice about PrEP that is co-designed with communities who would benefit from PrEP and be targeted at those groups who have poorer access to PrEP.
We suggest that organisations who work with communities who would benefit from PrEP and/or who deliver outreach work should ensure that information on PrEP is integrated into their work.
We suggest that anyone who offers information/support to potential PrEP users, or designs or delivers services should consider: • Who attends (and *who does not attend*) your clinic or service? • What is the physical and social environment when they arrive at your clinic or service? • What demands (resources, knowledge, behaviour, etc) are asked of them within the clinic or service? • What support do they need in understanding and using PrEP within their sexual and social lives? • How might the physical and social settings in which they live affect their PrEP access and use?

Key Evidence Summary for PrEP Equity

3.1 Inequity in PrEP awareness and access

PrEP uptake has been highest amongst gay, bisexual and other men who have sex with men (GBMSM) across the UK since its provision through NHS services (and in PrEP trials)(1, 2). PrEP has significant impact on reducing new HIV infections in this group(3). Poor and uneven awareness and uptake of PrEP in the UK – and internationally - has been reported amongst racially minoritized,(4, 5) trans and non-binary communities, heterosexual women(6) and men, as well as younger gay and bisexual men(1, 7, 8). Access and uptake is significantly constrained by health and socio-economic disparities and geographic difference.

There is also evidence that the principal current barrier to access and uptake of PrEP is a lack of capacity and availability of appointments for PrEP services; especially online appointments and particularly for those wanting to start PrEP for the first time(9). This is a

major factor influencing individual decisions to self-source and self-fund PrEP, which is not an option available to those impacted by socio-economic disparities. There are limited data on awareness of and access to PrEP by those who take part in practices that are highly stigmatized and often criminalised, such as sex work and injecting drug use(10). These groups are known to be disproportionately affected by higher rates of HIV infection, later HIV diagnoses and poorer health outcomes(11). Addressing PrEP equity is therefore critical, not only for reasons of justice, but because it is essential to ensure the effectiveness of PrEP as an HIV prevention intervention at the population level.

Key groups currently underrepresented in NHS PrEP users

- Black African & Black Caribbean communities
- Queer communities of colour (including Black, Brown, Latinx and other groups)
- Migrant communities
- Trans and/or non-binary people
- People who inject drugs
- People who sell sex
- Young gay and bisexual men
- Heterosexual women who may be at risk of HIV and who are not included above.
- Men who have sex with men, but who don't identify as gay or bisexual

Geographical barriers may compound the issues affecting people from these groups who live in rural or semi-urban locations.

3.2 Working towards equity within the PrEP care continuum

Addressing PrEP equity requires attention to both individual and structural factors(12). Consider issues of equity at each stage of the PrEP care continuum: *Settings – Access – Awareness – Knowledge – Uptake – Retention.* Providers should review and address barriers to PrEP equity under these headings and the questions posed in *Appendix 1.*

1. Settings: Identify and address barriers within PrEP-related settings. This includes the physical space; the experience of new users and marginalized communities; collection of data on exclusion and lack of connections with other services.

2. Access: Consider and address accessibility, travel, affordability, service adequacy and privacy at all stages of the PrEP journey.

3. Awareness: Include marginalized communities who may benefit from PrEP but may not be aware of it by taking an inclusive approach to the provision of PrEP information and healthcare.

4. Knowledge: Expand PrEP knowledge and literacy by encouraging and enabling dialogue within and across groups, communities and institutions so that health-related

information can be adapted and incorporated into social norms of community health practices.

5. Uptake (Candidacy) Work to ensure awareness of PrEP candidacy and related barriers and facilitators in all practitioners and potential PrEP users.

6. Retention (Adherence & Support): Develop targeted strategies to support PrEP initiation and sustained use that work for marginalized groups with higher rates of discontinuation such as those with lower socio-economic status, substance use and younger people.

3.2.1 Settings

Settings where people learn about, access and use PrEP can create and/or exacerbate a range of physical and social barriers for potential PrEP users. Structural inequalities add to these barriers and disproportionately affect those from marginalized communities. For example, individuals with insecure immigration status and other migrants may not understand that NHS sexual health services are free for everyone. Such individuals may also be concerned that a health provider is obliged to report the individual, thereby risking being deported or imprisoned. Cultures and stigmas about PrEP exist both within health settings and within communities.

3.2.2 Access

Equity of access to PrEP is about more than addressing physical access to health services, it also applies to accessing knowledge and requires consideration of the wider physical and digital infrastructure, along with clinic organisation.

- *Accessibility* is access to services that make PrEP available (whether tailored to specific communities or general services) which are appropriately resourced. This includes in a location within reasonable distance of patients, means of access (such as online/phone/drop-in) as well as availability (enough capacity to address need).
- *Affordability* means balancing the effort spent in accessing and using services within the existing time and resource constraints affecting potential PrEP users.
- *Adequacy* means access to the health workers who are equipped to consider and address the needs of all individuals who might benefit from PrEP.

Examination of PrEP implementation programmes(12, 13), pilots(14-16) and research with communities(17-19) suggest that offering multiple ways of accessing a PrEP service can increase equity. Online booking systems may provide more flexibility and privacy for a young adult living at home with their family. Telephone booking systems, available in English only and with multiple steps to navigate, can dissuade people who do not speak English fluently, or who do not have sufficient telephone credit to wait on hold, to access a service. Open access walk-in services may be required for those who are unable to

navigate either telephone or online systems and outreach services may also be required for some population groups.

Physical distance and/or limited financial resources can limit access to sexual health services in rural areas. Working in partnership with primary care services or local community organisations may enable some of the PrEP pathway e.g. STI screening and renal monitoring to be delivered in a setting other than the PrEP provider. Local pharmacy collection services can also help to address geographical isolation (9).

3.2.3 Awareness & Knowledge

PrEP Awareness

Awareness of PrEP is influenced by age, sex, gender, sexual orientation, proximity to HIV, race and geography(20). It is also affected by social norms within communities where PrEP is, or is not, discussed and used, and wider community networks(5, 21). In marginalized communities who may benefit from PrEP but may not be aware of it, health services should work with existing community stakeholders to identify and address community-specific barriers and needs(22) by providing accurate information about PrEP and employing appropriate inclusive language, messaging and delivery tailored to specific communities.
Awareness of PrEP through clinical services requires attention to the context within which the information is provided, including:

- having an inclusive approach to the provision of healthcare to marginalized communities(23), and
- integrating PrEP information and provision into existing generic services.(24)

PrEP Knowledge

PrEP knowledge goes beyond awareness and the provision of information. PrEP literacy(25, 26) encompasses the ability and skills of individuals and communities that means they:

- Are equipped and willing to engage with PrEP.
- Have access to and understand PrEP information.
- Have capacity to apply learned PrEP information within their sexual and social lives.
- Have capacity to engage with others about PrEP information and related sexual behaviours.

Case Study 1 – Creating PrEP awareness pathways

Josef is a 27-year-old who migrated to the UK from Slovakia 18 months ago. He is having regular condomless anal intercourse with men he meets online. His only healthcare encounter was at a GP registration appointment where he informed them he was having sex with men, but there was no conversation about PEP or PrEP. He has accessed regular HIV testing online. He is aware of PEP and PrEP but had been scared to access it in Slovakia, did not know how to access it the UK and assumed he would have to pay for it. Recently a sexual partner informed him he was HIV positive without a suppressed HIV viral load and advised Josef to go to a sexual health clinic to get PEP. He is provided

with accessible information about PEP and PrEP and commenced on PEP with a view to continuing on PrEP afterwards. He is signposted to PrEP support and other related sexual health resources. Josef's case highlights the difficulties migrants may have in accessing PrEP due to lack of UK-specific PrEP knowledge and difficulty navigating healthcare in unfamiliar settings.

Case study 2–Supporting PrEP knowledge & literacy through community partners
Mohamed is a 45-year-old Black African man, originally from Sudan. He attends a sexual health service with pain on passing urine. When asked, he reports he has been married to a woman for 8 years and has no casual sexual partners. He is treated for non-specific urethritis on the day and subsequently diagnosed with chlamydia. He is HIV negative but is uncontactable for partner notification. He presents eight months later with recurrent symptoms and on further probing about partners he reports he is married and has no casual partners. However, he reports multiple other sexual partners, both in the UK and Sudan, that he refers to as "his wives." This initiates a discussion about his risk and that of his partners and his eligibility for PrEP. He expresses concern about "how it may look to his wives." He is followed up with the health adviser team and engages with a community organisation to support his decision making and education about PrEP. He is subsequently commenced on PrEP.

3.2.4 Uptake (Candidacy):

Candidacy is the process through which individuals identify themselves as candidates for particular interventions.(27) Awareness and knowledge may not be enough to convince people or health practitioners of their candidacy for PrEP. For example, a study in trans women reported 82% PrEP awareness, but only 27% of participants had ever taken it.(18, 28)

Risk Assessment. People not seeing themselves as candidates for PrEP may be attributed to poor understandings of their personal risk of HIV or inaccurate risk assessment. This could include not recognizing their sexual partner's risk as a result of concurrent relationships or participation in high-risk sexual transmission networks. Individuals might not consider themselves to be a candidate for PrEP because:

- It is not commonly talked about within their peer groups.
- It is not seen as something that would be acceptable to their peers and/or sexual partners.
- It is for a specific population of which they are not a part.
- They do not believe they fulfil clinical eligibility criteria or PrEP is not something that will suit their life circumstances (due to mobility, homelessness, drug use, etc).
- They have concerns that PrEP will interfere with other medication e.g. gender affirming hormone therapy.

Risk assessment by the practitioner

Not all health practitioners will consider patients as potential PrEP users. This may be because:

- The person does not appear to be a member of populations already using and/or seen to benefit most from PrEP.
- They may not describe their risk of HIV in a way that fits in with existing clinical ideas about PrEP eligibility.
- They may be judged not to be able to adhere to PrEP because of their lifestyle or social circumstances.

Case Study 3 – Recognizing PrEP Candidacy

Sandra is a 32-year-old heterosexual woman of mixed Black African and White British heritage who attends a sexual health service with symptoms of recurrent vaginal thrush and requests a repeat supply of her oral contraception. During her consultation she refers only to her husband and does not mention other sexual partners. No reference is made to PrEP by Sandra and no conversation about PrEP is initiated by the clinician. Sandra may not be aware of PrEP and /or does not think PrEP applies to her situation. The clinician assumes that Sandra is of low risk due to her mentioning only one partner. Later, during an HIV awareness event delivered by a community organisation it is found that Sandra's husband travels to his native country, Senegal, for business multiple times a year and she is concerned that he may have sexual partners in Senegal. He also becomes angry when Sandra tries to explore her concerns. PrEP is explained to Sandra, and she decided to commence PrEP at her local sexual health service. Her first consultation was a missed opportunity which may or may not have been avoided by improving knowledge and skills through experience and training for the clinician. Offering a diversity of tailored pathways to access PrEP to marginalised communities mitigated the barriers to access for this patient.

3.2.5 Retention (Adherence & Support)

Adherence and support in sustaining PrEP use may be seen as 'more challenging' for PrEP users from marginalized communities and may affect PrEP prescribing practices.(29) In a study of PrEP users, discontinuation of PrEP remained high amongst those with lower socio-economic status, substance use and in younger people.(8)

Programmes successfully working with people using recreational drugs who are unlikely to attend sexual health services have found that support outside of a formal clinical setting can help to initiate and retain PrEP users(14, 15). Key elements which may apply to other groups include:

- Flexible initiation and follow-up locations outside clinics (e.g. community settings).
- Access to prescriptions and/or drug storage in pharmacy and/or community settings.

- Provision for short-term prescriptions to mitigate lost or stolen medication.
- Remote physician review and good patient-provider relationships.

Case study 4 – Supporting Adherence

Steven is a 24-year-old male sex worker who has sex with men and is on daily PrEP. When he first commenced PrEP he found no difficulty in keeping up with a once daily routine. However, his housing has become unstable, and his long-term relationship has ended. During PrEP follow up it becomes clear that he is only sporadically taking PrEP and frequently missing more than 3 doses per week or taking extended breaks from PrEP. He is becoming anxious as he was having condomless anal sex more than once a week and knows he is putting himself at increased risk. The clinical team offer additional support such as telephone check ins and referral to a psychologist. He is also signposted to a PrEP adherence app (preptrack.co.uk) and linked into online support spaces such as http://www.prepster.co.uk. All these interventions provide Stephen with better confidence and a plan to manage PrEP adherence in relation to his new circumstances.

3.3 New PrEP Technologies

Case Study 5 – Alternative Dosing Options for Women

Patience is a 28-year-old Zambian woman who successfully initiated daily PrEP in 2017 following her regular partner's HIV diagnosis. She discontinued PrEP after 9 months when his HIV viral load became undetectable. She is now in a new relationship with a Zimbabwean partner she sees intermittently and whom she knows has other partners. He strongly disapproves of her taking daily PrEP when he is not around. She attends a sexual health clinic for HIV testing and initially declines PrEP for this reason. She is advised of the option of taking a double dose of PrEP followed by daily dosing and taking PrEP for 7 days after their last condomless sex before stopping PrEP. She feels that she will be able to 'Quick start' PrEP in this way when her partner visits at short notice and decides to re-initiate PrEP on this basis.

New formulations of PrEP including injectable PrEP will progress through licensing and approval processes in the UK and elsewhere and may be being used by individuals visiting the UK, or arriving to live, work or study in the UK, having been prescribed before arriving.

These formulations may serve to increase access and adherence to PrEP, especially amongst those populations who are least likely to use oral PrEP, but also have the potential to increase inequity. All aspects of PrEP equity should be considered in the provision of new formulations, for example the adherence benefits of injectable PrEP versus the potential access and affordability issues involved in 2-monthly clinic visits for injections.

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Chapter 4: Efficacy and Safety

4.1 Efficacy of PrEP

Recommendations for PrEP Efficacy
3. We recommend that PrEP should be offered to people, regardless of their gender or sexual orientation, who would benefit from a reduction in HIV risk* This includes: • HIV-negative gay, bisexual and other men who have sex with men who are at elevated risk of HIV-acquisition through condomless sex (1A) • HIV-negative individuals having condomless sex with HIV positive partners whose plasma viral load is not <200 copies/ml on ART (1A) • Heterosexual men and women at greater risk of HIV acquisition*. See Section 5. (1B) • Trans women (1B), trans men and nonbinary people (1D) at greater risk of HIV acquisition* • People who inject drugs and who might share injecting equipment (1B) • People who, regardless of gender or sexual orientation, are likely to have condomless sex with people at risk of HIV (2B) *defined as where HIV risk is likely to be in excess of the background UK population and where benefit outweighs clinical risk of PrEP (see Chapter 4)(1-3)
4. We recommend that young people (aged 15-22) should be offered PrEP in accordance with their reported risk (1B) and that those aged under 18 years should be offered TAF-FTC as PrEP (1B) 5. We recommend that young people on PrEP should be offered additional support and monitoring to optimise adherence (1B) 6. We recommend that PrEP using TD alone can be offered to heterosexual men and women if FTC is contraindicated (1A) 7. We recommend that TD alone should not be offered as PrEP to GBMSM. This is based on lack of evidence, rather than evidence of lack of effect (2C)
Good practice points
• We suggest that, as bone formation continues into the early 20s, TAF-FTC PrEP when commenced before the age of 18 years should be continued until the individual is aged 20 years. • We suggest that specific reassurance should be given to trans people that there are no expected drug–drug interactions between PrEP and gender affirming hormone therapy (GAHT).

Footnote:
Condomless sex as referred to in this guideline includes penile, vaginal, neovaginal or anal sex without using either a male or female condoms. Condomless oral sex alone carries a very low (though non-zero) risk of HIV transmission and is not routinely regarded as an indication for PrEP.

*defined as where HIV risk is in excess of the background UK population and where benefit outweighs clinical risk of PrEP

Evidence Summary for PrEP efficacy

Gay, bisexual and other men who have sex with men (GBMSM):

- PrEP efficacy in GBMSM has been well studied in PrEP clinical trials and there is high quality RCT evidence demonstrating PrEP efficacy (TDF-FTC) in this population; with both daily (the PROUD study)(1) and on demand (the IPERGAY study)(2) dosing.
- In the iPrEX daily TDF-FTC Open Label Extension study, of whom 1,533 participants were GBMSM, there were no HIV seroconversions in those taking ≥4 pills per week(3).
- There is one RCT comparing daily TAF-FTC with TDF-FTC (the DISCOVER trial, 98.6% GBMSM)(4) which demonstrated that TAF-FTC was non-inferior to TDF-FTC for HIV prevention.
- Open label extension (OLE) projects, phase two pilots and post-marketing data have further demonstrated effectiveness of both daily and on demand TDF-FTC as PrEP in GBMSM(3, 5-8)
- There has been one trial of TDF monotherapy as PrEP in GBMSM - the CDC MSM Safety Trial(9). This study demonstrated safety, but was not powered for efficacy assessment, and TDF monotherapy is not recommended as PrEP for GBMSM.
- One RCT of long acting injectable cabotegravir (CAB-LA) has shown it to be superior to daily oral TDF-FTC in preventing HIV acquisition men who have sex with men(10)

Heterosexual populations:

- Efficacy of PrEP (TDF-FTC and TDF alone) in heterosexual populations has been demonstrated in randomised controlled trials in sub-Saharan Africa.
- Partners PrEP(11) and TDF-2(12) were phase 3 RCTs carried out in East Africa and Botswana among sero-different heterosexual couples and sexually active heterosexuals at high risk of HIV; reporting efficacy of 75% and 62% respectively of daily TDF-FTC PrEP.
- Partners PrEP(11) included a daily TDF only PrEP arm which had comparable overall efficacy (67%).
- In Partners PrEP, the HIV-1 protective effects of TDF and TDF–FTC were not statistically different according to sex(11).
- There have been no efficacy trials in heterosexual men and women in high income countries, nor of event-based regimens in heterosexual populations.
- For heterosexual men, the results of trials in GBMSM and transgender women have been extrapolated to inform guidance on PrEP efficacy for insertive vaginal sex, including event-based dosing (see table 1 on page 71)
- One RCT of long acting injectable cabotegravir has shown it to be superior to daily oral TDF-FTC at preventing HIV infection in women (13)

Transgender people

- Both trans men and trans women are at increased risk of HIV infection and are identified as a key group who would benefit from PrEP.
- Gender affirming care is important to foster appropriate uptake and use of PrEP, and includes use of preferred pronouns and names, respecting diversity in gender identities and expressions and generally creating safe spaces for trans people.
- Trans women formed a minority of oral PrEP RCT participants(4, 14), and there are no data for trans men.
- In a subgroup analysis of iPrEx, daily oral TDF-FTC had lower effectiveness in trans women compared to MSM, primarily due to lower adherence(14). There were, however, no seroconversions in trans women with drug concentrations compatible with four or more TDF-FTC tablets per week(14).
- In the DISCOVER trial (daily TAF-FTC vs TDF-FTC), none of the 74 trans women acquired HIV during the study. The majority of the trans women participating in the trial were taking feminising gender affirming hormone therapy (GAHT): 71% TAF-FTC arm, 72% TDF/FTC arm(4).
- One RCT of long acting injectable cabotegravir has shown it to be superior to daily oral TDF/FTC in a RCT which included transgender women(10). Of 570 (12.5%) transgender women in the trial, 2 acquired HIV in the CAB-LA arm (of 13 overall) and there was no evidence of a difference in efficacy compared to MSM participants(10).
- Several small studies demonstrate no effect of PrEP (TDF-FTC) on concentrations of feminising GAHT levels (estradiol)(15, 16).
- The University of Liverpool (www.hiv-druginteractions.org) have also examined interactions between ARVs and oestrogen and anti-androgen preparations used in male-to-female gender affirming therapy (GAHT), indicating no clinically significant interactions are expected.
- However, the possibility of drug–drug interactions between PrEP and gender affirming hormone therapy (GAHT) remains a concern for some trans people and reassurances should be given that there are no expected interactions.
- Some small studies have suggested that the use of gender-affirming hormones may reduce the concentrations of TDF and FTC among trans women on PrEP by 12–27%(17, 18)
- The 2022 WHO implementation guidance for PrEP stated that while lower PrEP concentration is unlikely to affect the efficacy of daily oral PrEP, the efficacy of event based dosing (ED)-PrEP efficacy in people assigned male at birth who are taking estradiol-based hormones “is unclear”(19).
- Other studies have found that trans men and trans women had comparable TFV-DP concentrations with daily TDF-FTC PrEP compared to cisgender men (20). And that TDF levels remained in the protective range in transgender participants and similar PrEP efficacy should be expected in trans gender people compared to cis gender people particularly for daily dosing(15-17).

People who inject drugs (PWID):

- There is limited evidence for the efficacy of PrEP in PWID.
- The Bangkok Tenofovir Study (BTS), a phase 3, placebo controlled RCT, provides the best available evidence of the effectiveness of daily TDF-FTC PrEP in PWID(21).
- The BTS demonstrated a 49% reduction in HIV incidence, with efficacy strongly linked to adherence. It is however difficult to distinguish the impact of PrEP on parenteral HIV transmission from s N Niceexual transmission in PWID(21).

Young People:

- There are limited studies designed to explore the efficacy of TDF-FTC in young people with most data being from small demonstration studies with no control group (22-26).
- Studies have demonstrated the feasibility and acceptability of PrEP in young MSM and young MSM of colour,(24, 25) although in this group, self-reported adherence and corresponding plasma drug concentrations were low. Longer term adherence is also a concern in young people with results demonstrating decreased use of TDF-FTC over time(22-26).
- One study of 451 sexually active adolescent girls and young women aged 16 – 22 in South Africa and Zimbabwe demonstrated high levels of oral PrEP (95%) uptake with 55% persisting on PrEP at 12 months(22). Adherence dropped during the trial with dried blood spot testing demonstrating detectable TFV-DP levels in 84% at one month, 57% at 6 months and 31% at 12 months. One large Australian study reported that with 2 years of first supply, 49% of under 30's had discontinued PrEP compared to 32% of over 40s(27).

For a more detailed evidence review of PrEP efficacy. Please see Appendix 2

4.2 Safety of PrEP

This section summarises the evidence for the safety of PrEP. For recommendations on baseline testing, clinical management and ongoing monitoring see Chapters 6 and 7.

Evidence Summary for PrEP Safety

4.2.1 Impact of PrEP on renal function

- Randomised controlled trials (RCTs) have shown very good renal safety data for daily and on-demand oral TDF-FTC as PrEP in MSM and trans women(1, 2, 28, 29). Further, RCTs in sub-Saharan Africa have shown good renal safety data for daily oral TDF-FTC as PrEP in men and women(11, 30, 31).

- Whilst TDF-FTC containing PrEP regimens have been associated with small rises in serum creatinine, the vast majority of changes to renal function are mild, non-progressive and reversible reductions in creatinine clearance (CrCl).
- The majority of trial participants on TDF-FTC experienced an early (first 4-12 weeks) minor decline in creatinine clearance, followed by stabilisation and no further decline. Risk factors for kidney disease (or worsening kidney disease) with TD-FTC include lower baseline eGFR, ≥40 years of age, type 2 diabetes, hypertension and recreational drug use.
- Individuals using TAF-containing PrEP regimens are less likely to suffer renal adverse events. In the DISCOVER trial, participants taking TAF-FTC had very few study drug related renal adverse events and there were no discontinuations related to renal tubulopathy(32).
- Two RCTs (in men who have sex with men, transgender and cisgender women) demonstrated good renal safety for long acting injectable cabotegravir PrEP. In both HPTN083 and HPTN084 there were no significant differences in renal adverse events between the CAB-LA group and the TDF-FTC group (10, 13).

Impact of creatine supplements on serum creatinine levels:

Creatine supplements can increase levels of serum creatinine and affect interpretation of renal function testing. The effects of creatine supplementation are thought to be short lived, as the creatinine half-life is approximately 4 hours(33, 34).

4.2.2 PrEP safety in pregnancy, breastfeeding or in those taking hormonal contraception

- The available evidence suggests that PrEP does not affect the effectiveness of hormone-based contraception methods in preventing pregnancy. In HIV-negative women taking PrEP in the Partners PrEP study, there was no evidence that PrEP affected hormonal contraceptive effectiveness (including the oral contraceptive pill, DMPA or hormonal implants)(35).
- Contraception consultations in sexual and reproductive health services should be seen as an opportunity to discuss PrEP with women and other people needing contraception who may be at increased risk of HIV acquisition through condomless sex.
- The available evidence from three RCTs and two observational studies suggests that PrEP is safe in HIV negative pregnant women(36, 37) and this is consistent with findings from studies of pregnant women living with HIV or HBV and treated with TDF(38). PrEP may be one option to prevent HIV seronegative partners from acquiring HIV infection in a serodifferent relationship during attempts to conceive if the HIV positive partner is not on suppressive ART. Overall, the benefits of preventing HIV acquisition in pregnancy greatly outweigh any potential negative consequences for the mother or infant.
- The available evidence suggests that PrEP is safe for the infant when women are breast feeding(39, 40). There is extensive experience of TDF-FTC use in women with HIV who

are breastfeeding. These data confirm very low median concentrations of both FTC and TDF secreted in breast milk(39, 40).

- There is no evidence that PrEP affects the fertility of women or men.

4.2.3 Impact of PrEP on bone mineral density

- There are small, but statistically significant reductions in the mean bone mineral density of less than 2% as measured by mean percentage reduction in z-score over time measured by dual-energy X-ray absorptiometry (DXA) scanning at the hip and lumbar spine (LS) observed in study populations with varied demographics exposed to oral PrEP including TDF and TDF/FTC in comparison to placebo(41-44).
- The magnitude of bone loss on daily TDF PrEP is inversely related to adherence as measured by plasma levels of TDF and the rate of loss appears to reduce over time(41).
- There is no published evidence on bone mineral density changes in those taking on-demand TDF PrEP.
- Recovery of bone mass to levels at or near those prior to PrEP has been shown following discontinuation after a relatively short duration of taking TDF PrEP (48 weeks)(44, 45).
- Although long term data are lacking, there is no evidence of an increased rate of fractures whilst on TDF containing PrEP or during currently available follow up observation(28, 36, 37).

Impact of PrEP on bone mineral density in younger and older people

- Peak bone mass is typically achieved by the mid-20s and predicts bone fractures in later life, with the period of maximal bone accrual occurring before the age of 18 years. Consequently, uncertainty remains regarding the use of TDF PrEP in some adolescent and young adult individuals.
- Small studies of bone mineral density in adolescent and young MSM (aged between 15 and 22) taking TDF PrEP have demonstrated declines in z scores BMD at the spine, hip and whole body, with greatest declines seen in those aged 15 – 19 compared to those aged 20-22(24, 25). Z scores at spine, hip and whole body stayed below baseline after PrEP discontinuation in the younger age group, but not the older age group. However, by week 48 after discontinuing PrEP, there was no difference in hip BMD Z scores between age groups.
- Consistent with these findings, in the small group of individuals 18-25 years (n=25) in the DISCOVER bone sub study, reductions in BMD on TDF were numerically greater in those ≤25 than over 25 years (-2.2% vs -0.9% hip, -2.3 vs -1.0 % spine at 48w) and greater at 48w than at 96w(4)
- Factors recognised to be associated with reduced bone mass include vitamin D insufficiency, low dietary calcium, low bodyweight, and possibly amphetamine and inhaled nitrite use(42), and may be disproportionately represented in PrEP users.

- There is very little evidence regarding bone changes with TDF PrEP in older individuals, or on the effects of TDF PrEP in combination with hormonal contraception including DMPA or NET-EN, or with progestogens used in gender affirming hormone therapy(41).

Impact of non-TDF containing PrEP regimens on bone mineral density

- Bone density changes have more recently been investigated in studies of agents other than TDF. In the BMD substudy of the DISCOVER trial of daily TAF-FTC vs TDF-FTC, increases in average bone mineral density at both the spine and hip were seen in the group taking TAF and decreases in average BMD were seen in the TDF arm; mean BMD at hip and spine increased by 0.2-1.0% at 48W and 96W in an approximately linear fashion in the TAF/FTC arm and reduced by -1.0 to -1.4% in the TDF-FTC arm ($p<0.0001$ for difference in ANOVA model at both sites and both time points)(4, 46).
- In an analysis of the categorical change in BMD at 96 weeks, the proportion of participants with >3% increase in BMD at the spine was significantly greater in the TAF than TDF arm and similarly for those with >5% increase in BMD. At the hip, a >3% increase was seen in a significantly greater proportion of the TAF than TDF arm(46).
- In men under the age of 25 (n=25) in the DISCOVER bone substudy(4), numerically greater increases in bone density on TAF-FTC were observed in those aged ≤25 than 25 and over at both the hip (1.2% vs 0.6%) and the spine (1.4% vs 0.9%) at 96 weeks but there was some recovery of bone loss in the TDF group as compared to 48 weeks and the difference between arms at 96 weeks was not significant in ANOVA analysis. HPTN 069, a comparison of Maraviroc (MVC) or MVC-FTC with MVC-TDF or TDF-FTC in MSM, TGW and cisgender women showed a significantly greater bone loss at 48 weeks in the TDF-containing group at the hip, but not at the lumbar spine(4, 46, 47)
- Long acting injectable cabotegravir PrEP does not have a bone safety signal. In data presented at CROI 2023 from HPTN 083 in GBMSM and trans women, BMD gain was seen in those on CAB-LA PrEP over 2 years study follow up, while those on TDF-FTC PrEP had BMD loss(48) .

4.2.4 Interventions to protect bone health

- TDF may induce a state of functional vitamin D deficiency. In 48 matched pairs of daily TDF recipients (68% vitamin D deficient at baseline, median age 33), supplementation with vitamin D 4000 IU/day from week 24 significantly reduced the bone turnover marker procollagen-I N-terminal propeptide (P1NP) by week 48, but did not affect levels of C-telopeptide, PTH, or 25-OH vitamin D3(49).

- In a study of 100 Thai males aged 15-24, (39% of vitamin D deficient), at 24 weeks the addition of vitamin D/calcium supplementation resulted in a greater proportion having a >3% increase in lumbar spine bone mineral density (LSBMD) by DXA compared to

baseline (67.6% vs. 42.9% respectively; p = 0.03), despite incomplete adherence both to PrEP (52%) and vitamin D/calcium (66%)(50)

- A Canadian survey of 161 current or prospective PrEP users, 31% reported adequate dietary calcium intake but over 90% were willing to take supplementation(51).

- NICE Guidance on Assessment of Fragility Fracture, last updated 2017 and due full review in 2025, should be used to guide assessment(52).

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Chapter 5. PrEP Suitability and Risk Assessment

Recommendations for PrEP Suitability and Risk Assessment
Who should be offered PrEP? 8. We recommend that PrEP should be offered to people, regardless of their gender or sexual orientation who would benefit from a reduction in HIV risk* including: • people who request PrEP (2B) • people at risk of HIV*(1A/1B depending on group) • people who, regardless of gender or sexual orientation, are likely to have condomless anal or vaginal sex with people at risk of HIV* (2B) • people who inject drugs who might share injecting equipment (1A) *defined as where HIV risk is likely to be in excess of the background UK population and where benefit outweighs clinical risk of PrEP (see Chapter 4)(1-3)
When should PrEP be prescribed? 9. We recommend that PrEP should be prescribed for people in whom it is suitable as soon as HIV risk is identified as benefit is immediate and toxicity is uncommon and delayed. (1A)
Good practice points
PrEP offer: We suggest that PrEP should be considered in people identifying or identified as being at risk of HIV infection. For example, where HIV testing is performed, or an individual presents for regular or emergency contraception or STI testing
Reviewing PrEP risk/benefit: We suggest that there is ongoing consideration and review of risk and benefit as this can change over time
• **Assessment of PrEP suitability:** We suggest that assessment of HIV and STI risk and suitability for PrEP should be integrated into the broader sexual and reproductive health context. People who could benefit from PrEP will be encountered in community healthcare, general practice, and sexual and reproductive health services. HIV risk may become apparent in the context of care related to contraception, pregnancy or abortion, or in the emergency setting in the context of HIV testing or PEPSE provision. This particularly applies to women and other people who would benefit from a reduction in HIV risk but do not attend sexual health services. It also includes people in whom HIV or STI testing is stigmatised or who had not previously considered HIV risk.

Key Evidence Summary for PrEP Suitability and Risk Assessment

5.1 Risks and benefits of PrEP

The benefits of PrEP are rapid and substantial. Therefore, with only uncommon exceptions, PrEP should be initiated in people who request it or who identify or are identified as being at risk of HIV, as defined above. PrEP is a key part of transmission elimination strategies in the UK and globally(1, 4-6). PrEP is well-tolerated and current evidence suggests that any toxicities are delayed, uncommon, specific and reversible in the context of adequate monitoring (Chapters 4,6 & 7)(7, 8).

5.2 The move away from trial eligibility criteria

Focussing on eligibility criteria for clinical trials makes it difficult to fully identify the range of individuals who would benefit from PrEP, particularly those who are at risk due to their partners' sexual behaviour, or those who do not initially report risk. Eligibility criteria are often determined by clinical trial design and do not represent an evidence base for the limits of risk-benefit assessments. While defining these limits helps to identify people who would benefit from PrEP, caution should be exercised to ensure that people are not excluded. A wider range of population–level and individual level indicators are appropriate to ensure that PrEP reaches all those who could benefit (Table 1).

5.3 Population groups with the greatest demonstrated clinical benefit of PrEP

The decision to offer or initiate PrEP is informed by sexual and or drug use history and risks that have occurred in the preceding months or are likely to occur in the following months.

Evidence of PrEP benefit is greatest for men who have sex with men, and trans women who have sex with men who report receptive condomless anal sex and people who report condomless vaginal or anal sex with an HIV positive partner without viral suppression.

People in one or more of the following groups are also likely to benefit from PrEP: people who have sexualised drug use (chemsex), people who have condomless anal or vaginal sex with a partner of unknown HIV status where their partner or the person themselves is a man who has sex with men and or from a country with a high HIV prevalence, people who inject drugs who share injecting equipment or who have multiple risks including through sex (9)

5.4 When should PrEP be offered?

PrEP is suitable for most people who request it and, in almost all situations, offering and initiating PrEP to those who request it is appropriate. Exceptions include where individual risk is not higher than that of the background UK population or where clinical risk of PrEP outweighs benefit(7, 8) (Chapter 4). Wherever clinicians or other health workers are reviewing the risk of sexually transmitted infection (STI), including HIV, or discussing contraception with a patient, the suitability for PrEP should be considered. These situations include when an HIV test or other STI tests are offered or the results reviewed, when an STI is diagnosed or treated, when partner notification occurs, when PEPSE is initiated or reviewed and in many contraception and other sexual and reproductive health consultations. In people for whom transmission risk is difficult to ascertain and/or who have an elevated risk of PrEP toxicity, expert advice or MDT discussion may be appropriate to determine the appropriate advice to the individual.

People with anxiety about HIV transmission that seems greater than their objective risk may request PrEP. Longitudinal risk may be greater or less than initially reported and PrEP is very safe in the context of regular monitoring, particularly in the short term while longitudinal risk is being assessed. Although people who take PrEP gain significant relief of anxiety and psychological distress, recommendations on PrEP benefit should be based on

transmission risk. Referral for ongoing discussion and support or to psychological services, if relevant, should be considered for people whose anxiety is disproportionate to their reported risk of HIV acquisition.

PrEP is **not** indicated for people who **only** have sex with a person/people living with HIV on ART with viral load <200 copies/ml as the risk of HIV transmission is zero. It is important that PrEP information, education and individual discussions do not inadvertently undermine U=U messages and contribute to HIV stigma.

Note

*Scottish population-level data showed that any recent bacterial STI (not solely rectal) in GBMBM was a predictor of HIV seroconversion.

Table 1: Indicators or factors associated with suitability for PrEP

Indicators/factors associated with PrEP suitability**
Population level indicators • Men who have sex with men (1A)(7, 8) • Black African men and women (1A)(7, 8) • Transgender women (1A)(7, 8) • Recent migrants (1D)(10) • People who inject drugs (1A)(7, 8) • People who report sex work or transactional sex (1A for MSM & TGW, FSW)(7, 8, 11)
Behavioural and personal indicators (2,D). • Condomless anal or vaginal/frontal sex with one of the groups listed above. • Condomless anal or vaginal/frontal sex where a sexual partner may have undiagnosed or untreated HIV infection(12, 13) (1A). • Chemsex or group sex (1B for GBMSM) • Injecting drug use using shared equipment (1A)(7, 8) • Travel to countries with high HIV prevalence where sex with people from those countries is likely**
Other clinical markers. • Other sexually transmitted infection (1C)(9). • HCV infection (1C)(9). • PEPSE use (1C) (14).
Injecting Drug use (1A): • Injecting in an unsafe setting, sharing injecting equipment or limited access to needle and syringe programmes (NSP) or opiate substitution treatment (OST). • Sexual risk in people who use drugs.
Reduced sexual health autonomy (2D) • Drug and alcohol use. • Safeguarding, consent and vulnerability issues.

- Inability to negotiate and/or use condoms (or employ other HIV prevention methods) with sexual partners.
- Coercive and/or violent power dynamics in relationships (e.g. intimate partner/domestic violence).
- Precarious housing or homelessness, and/or other factors that may affect material circumstances.
- Risk of sexual exploitation and trafficking.

** Factors known to be associated with HIV risk should prompt a consideration of PrEP and include population level indicators, clinical indicators (e.g. previous / current STIs and PEPSE use in GBMSM(14), reported sexual behaviour / likely sexual behaviour and drug use and vulnerability factors affecting sexual autonomy.

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Chapter 6: Baseline testing and clinical management

6.1 Baseline testing and management

Recommendations for baseline testing and management

HIV testing

10. We recommend that baseline HIV testing with a combined antigen/antibody serology test is undertaken prior to commencing PrEP (1A)
11. For individuals who have no history of a high-risk sexual exposure in the preceding 6 weeks, or for those in whom high risk exposure has not involved the use of PrEP or PEP, we recommend that PrEP can be safely initiated on the same day in the presence of a negative 3rd generation or higher or blood based POCT pending the results of laboratory HIV antigen/antibody test (1A)
12. We recommend HIV viral load testing should be considered where a high-risk exposure has happened in the preceding 6 weeks, PEP has been taken or PrEP has been inconsistently used and/or there are symptoms consistent with HIV seroconversion. (1B)
13. We recommend that patients with symptoms suggestive of seroconversion should be investigated with a combined HIV antigen/antibody test and HIV viral load and PrEP initiation be deferred until HIV infection has been excluded. Atypical testing results should be discussed with a regional expert. (1C)

STI and BBV testing

14. We recommend that testing for STIs should be undertaken at baseline. (1B)
15. We recommend that testing for hepatitis B should be undertaken at baseline (1A)
16. We recommend that testing for hepatitis C should be undertaken at baseline in GBMSM and other at-risk groups (1B)

Renal function

17. We recommend that serum creatinine and eGFR should be performed at baseline. Renal function should be checked on the same day or as close to PrEP initiation as possible and the results checked as soon as possible, but PrEP can be commenced while waiting for the results (1A)
18. We recommend that eGFR for individuals starting TD-FTC should be ≥60 ml/min/1.73m^2 (2A)
19. We recommend that if eGFR ≥ 90ml/min/1.73m^2 at baseline and the person is aged < 40 years, with no risks for renal disease, then annual eGFR testing should be conducted (1A) [***See flow chart on page 53]***
20. We recommend that if eGFR is ≥ 90 ml/min/1.73m^2 at baseline and the person is ≥ 40 years or has risks for renal disease then eGFR should be repeated at 6 months (2B) [***See flow chart on page 53]***
21. We recommend that if eGFR is between 70 – 89ml/min/1.73m^2 at baseline then risks for renal disease should be checked, reduced exposure to oral PrEP be considered (e.g. with event based or intermittent dosing) of oral PrEP and eGFR repeated at 3 months (2B) ***See flow chart on page 53***
22. We recommend that if eGFR is 60 - 69 ml/min/1.73m^2 at baseline then eGFR should be repeated in 2-4 weeks, having stopped any creatine/protein supplements, assessing risks for renal disease and consider reduced to exposure to oral PrEP with event based or intermittent dosing (2B) **See flow chart on page 53**
23. We recommend that individuals with an eGFR between 30 - 60 ml/min/1.73m^2 at baseline have the full assessment recommended in the ***flow chart on page 53*** and are recommended TAF-FTC PrEP (1A)

Bone function

24. We recommend that oral PrEP recipients should be informed of the risk of reduction in BMD of around 1.5–2% at the hip and spine following 48 weeks of TDF-FTC PrEP (1B) but that there is no evidence of an increased risk of fractures while taking PrEP (1A)

25. We recommend that all oral PrEP recipients should be assessed for markers of increased absolute fracture risk e.g. previous fracture(s) at wrist, spine or hip, smoking, high alcohol intake, menopause, high-dose oral or high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer), or other causes of secondary osteoporosis (1D)
26. We recommend that those aged under 18 should be offered TAF-FTC as PrEP (1B)
27. We recommend that in those aged ≥ 50 and/or with risk factors for osteoporosis, fracture risk should be calculated using the QFracture® (preferred) or FRAX® online assessment calculators. Those at high risk (risk score greater than 10%) should be offered a DXA scan(6) *
28. We recommend that in people with markers of increased fracture risk and/or with confirmed osteoporosis on DXA scanning (see GPP) who require continuous daily oral PrEP, alternatives to TD-FTC PrEP (currently TAF-FTC only) should be advised (2B)
29. We recommend that in those with risk factors for reduced BMD in whom DXA scanning is not indicated, options for reduced exposure to TD through event-based or interval dosing should be supported where appropriate for risk reduction (2C)

Pregnancy

30. We recommend that if an individual is pregnant when starting PrEP that they initiate PrEP during pregnancy and breastfeeding if there is an ongoing risk of HIV acquisition, after discussing the potential risks of TD-FTC. (2B)

*From NICE Clinical Guideline 146: Osteoporosis; ungraded recommendation

Good practice points

- We suggest that PrEP should be offered as part of a package of care including condom provision, regular HIV and STI testing and monitoring of renal function.
- We suggest that people who could benefit from PrEP should be informed of the evidence for effectiveness and safety of PrEP
- We suggest that a thorough medical history before initiating PrEP is essential to identify people at greater risk of adverse events who might require closer renal or bone monitoring including a medication history for concomitant nephrotoxic drugs
- We suggest that the possibility of reduced renal function with TD-FTC is discussed with individuals who have pre-existing chronic renal disease or risk factors (diabetes, hypertension, >40 years of age, eGFR <90 ml/min/1.73m^2)
- We suggest that routine monitoring of BMD is not recommended in individuals taking PrEP with no other risk factors for reduced BMD.
- We suggest that people at intermediate risk whose fracture risk is close to but under 10% who have risk factors that may be underestimated by FRAX®, such as people taking high doses of oral corticosteroids, should be offered a DXA scan.
- We suggest that people at low risk (risk score less than 10%) should not be offered a DXA scan, but given lifestyle advice and fracture risk checked annually whilst on PrEP
- We suggest that vitamin D and calcium supplementation is recommended to PrEP recipients of all ages with risk factors for reduced BMD, particularly those under the age of 25 years.
- We suggest that PrEP initiation in the presence of a negative blood POCT and absence of Acute HIV Infection (AHI) symptoms should not be delayed whilst awaiting laboratory or confirmatory results.
- We suggest that access to PrEP amongst people at high risk of HIV infection is not delayed; wherever possible aim to initiate on same day of testing. Take all tests at the time of PrEP initiation, review results as soon as possible and modify PrEP prescription accordingly once results become available.
- We suggest that clinicians remain alert to acute HIV infection amongst people at risk of HIV, particularly in the presence of any symptoms, which are often non-specific in nature, and counsel and manage accordingly.

- We suggest that assessment for pregnancy is conducted in women and other people who can get pregnant who are not using reliable contraception if indicated.
- We suggest that adverse events should be reported through the yellow card scheme (https://yellowcard.mhra.gov.uk/).

Summary of baseline testing

- Testing for STIs and blood borne viruses (HIV, HCV and HBV) should be undertaken at initiation of PrEP.
- Baseline HIV testing is mandatory prior to starting PrEP.
- Where indicated, individuals initiating PrEP should be vaccinated against hepatitis A, hepatitis B, HPV and mpox (if available).
- Assessment of renal function at baseline is essential for PrEP initiation.
- If an individual had a high-risk exposure to HIV within the 72 hours prior to PrEP initiation consider PEPSE prior to transitioning to PrEP.
- If transitioning from PEPSE to PrEP, HIV testing should be performed 6 weeks after starting PEPSE and, again, 6 weeks after starting PrEP.
- A history of condomless anal or vaginal sex within the HIV window period is not an exclusion criterion to starting PrEP, although starting PrEP should be deferred in those with signs or symptoms consistent with acute HIV infection.
- If acute HIV infection is suspected, delay starting PrEP until HIV infection can be reliably excluded.
- If HIV seroconversion on PrEP is suspected, we recommend that antiretroviral therapy is intensified.

6.2 Baseline testing and management overview

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

- If an individual has had a high-risk exposure to HIV within the previous 72 hours, it may be appropriate to consider a course of PEPSE prior to transitioning to PrEP (see Chapter 8).
- Testing for HIV should be performed in line with current PEPSE guidelines (2).
- However, if immediately transitioning to PrEP after a course of PEPSE, HIV testing should be performed 6 weeks after starting the course of PEPSE and again 6 weeks after starting PrEP.

6.2.2 HIV testing prior to PrEP initiation

- Baseline HIV testing is mandatory prior to starting PrEP as initiation in the context of undiagnosed HIV infection could lead to the development of antiretroviral drug resistance. In order to facilitate same-day PrEP initiation, service providers may

perform blood-based point-of-care tests (POCTs), although caution must be given to the possibility of both false-positive, and, in early infection, false-negative results.

- In the absence of symptoms of AHI (3) and in the presence of a negative HIV test or blood based POCT test and ongoing risk of HIV, PrEP can be started immediately to mitigate against the risk of infection.

- Oral POCT tests should not be used prior to PrEP prescription because of lower sensitivity, particularly during the window period. Starting PrEP should not follow self-reported HIV negative results alone.

- Where a high-risk exposure (e.g. condomless anal sex) has occurred within the previous 3 weeks, to exclude acute HIV infection, an HIV viral load could be considered in addition to sending a combined HIV antigen/antibody test prior to starting PrEP.

- A combined antigen/antibody HIV test result should be repeated 45 days after PrEP initiation in those where a risk occurred in the 6 weeks prior to initiating PrEP, although this does not have to be face-to-face. HIV testing should then be repeated at 90 days post-PrEP initiation.

- A person with a positive HIV test at baseline should be managed in accordance with current guidelines with referral to start antiretroviral therapy from an HIV specialist unit(4).

6.2.3 Acute HIV infection

- PrEP is indicated for individuals at risk of HIV acquisition and clinicians should therefore be very sensitive to the possible risk of acute HIV infection (AHI) and take an appropriate symptom history, noting that only a proportion (40–90%) with AHI will be symptomatic.
- The symptoms most strongly associated with AHI are fever and rash(3). Other symptoms include headache, malaise, arthralgia and sore throat. However, symptoms of AHI may be non-specific 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 or vaginal 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 3 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.

- If an individual taking PrEP is diagnosed with HIV, intensification of ART by the addition of a third agent is recommended with immediate referral to HIV clinical care. Management will be in accordance with BHIVA guidelines(4).

6.2.4. Atypical and indeterminate HIV test results

- Atypical HIV testing results include: (1) unchanging antibody reactivity on two or more consecutive samples that do not fit with a pattern usually associated with confirmed positivity; and (2) discrepant reactivity that changes over time, while remaining on PrEP or for a period of time after stopping PrEP.

- There is evidence that PrEP(5) or early ART initiation(6) in acute infection can cause blunting of the HIV-1 antibody response, with both non-reactive or atypical and non-progressive HIV serology and Fiebig profiles seen, in a setting where viral load is likely to be undetectable.

- Atypical testing cases should be discussed with a regional expert and investigated further for possible seroconversion. Cases can be referred to the UKHSA/IDRIS clinic for review and advice (imperial.IDRIS@nhs.net).

- If a seroconversion event is suspected on PrEP, the writing group recommends that current best practice is to intensify ART while investigations are ongoing.

- If an atypical result is first detected when off PrEP, then it is advised that no further PrEP is prescribed until an expert consensus is reached regarding the individual's HIV status.

- Laboratory request forms submitted with samples for further virological investigation (including HIV viral load testing or combined antibody/antigen testing, Western Blot and HIV DNA testing) should contain information on whether the patient has been taking either PEPSE or PrEP, and if so, when and for what duration, to allow for better interpretation of atypical results. Complex cases should be referred to the UKHSA/IDRIS clinic for review (imperial.IDRIS@nhs.net).

6.2.5 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 combined antigen/antibody HIV test. Atypical findings should be managed as detailed above.

- People with confirmed HIV infection, should be managed in line with existing BHIVA HIV treatment guidelines and clinicians should intensify ART while awaiting review with a specialist in HIV medicine.

6.2.6 STI and viral hepatitis testing prior to starting PrEP

STI testing

- STI testing is recommended at baseline in accordance with national recommendations and guidelines. This includes nucleic acid amplification tests (NAAT) for gonococcal and chlamydial infection at sites of exposure (genital, rectal, pharyngeal) and syphilis serology.

- As part of a comprehensive risk reduction strategy, 3-monthly STI testing (chlamydia, gonorrhoea and syphilis) is recommended for people taking PrEP who have new or multiple sexual partners.

- Less frequent testing for STIs may be appropriate for those who, for example, have a single partner who is HIV positive and is not virally suppressed or those with less frequent partner change.

- The recommendation for 3-monthly testing for STIs should not be a barrier to the provision of a 6-month supply of PrEP.

6.2.7 Assessment of viral hepatitis status when prescribing PrEP

Hepatitis B

- Testing for hepatitis B using surface antigen as well as anti-Hep B core antibody testing should be undertaken at baseline. If there is no evidence of current or previous infection or immunity then HBV vaccination should be offered as per current guidelines(7).

- The iPrEx study(8) demonstrated it was possible to use TDF-FTC in patients with chronic HBV and, importantly, demonstrated the ability to stop PrEP safely in patients without cirrhosis and without the occurrence of significant hepatic flares, although regular monitoring after stopping TD-based PrEP is important to detect relapse and manage HBV (including treatment, when eligible).

- PrEP may be started pending results of HBsAg, but results should be reviewed at the soonest possible time as both TD 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.

- TD-FTC may be used simultaneously as treatment for chronic active HBV infection and as PrEP.

- In the event of identifying HBsAg positive result, TD-based daily or event-based oral PrEP can be safely offered to people (9).

- Referral to hepatology specialist or primary care, depending on local pathways, should be made for follow up care and management of active HBV infection.

Hepatitis C

- High background prevalence of HCV has been reported in HIV-negative GBMSM before starting PrEP in both clinical trials and PrEP demonstration projects(10, 11)
- Screening for hepatitis C should be undertaken at baseline in GBMSM and other at-risk groups as recommended in national guidelines (7).
- People with previously undiagnosed HCV should be referred to specialist services for assessment and consideration of directly acting antiviral (DAA) treatment.
- No data on HCV prevalence is available for heterosexual people on PrEP, however, the incidence is unlikely to be increased in the absence of specific risk factors such as intravenous drug use.

Hepatitis A

- Screening and vaccination for hepatitis A should be undertaken in line with national guidelines and targeted at those at greater risk (men who have sex with men, people who inject drugs and those infected with hepatitis B or C)(7).

6.2.8 Assessment and management of renal function at baseline

- TD containing PrEP has a minimal and reversible impact on renal function. PrEP trials have shown modest declines in renal function with administration of daily TDF-FTC which, although statistically significant, are rarely of clinical significance and the incidence of serious renal events was very low and mostly reversible(12-16). Patients with TAF containing PrEP regimens are less likely to suffer renal adverse events(17). For further information detailing the evidence for impact of PrEP on renal function see Chapter 4.2.1 on page 32 and Appendix 1.
- It is necessary to assess the risk of chronic kidney disease (CKD) at baseline. Factors that may indicate an individual is at higher risk of CKD include being aged 40 years

or above, being on concomitant medication associated with renal impairment, or the presence of comorbidities such as hypertension and diabetes(18, 19).

- 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 TD-FTC.
- Serum creatinine and eGFR should be performed at baseline. PrEP may be started immediately, but results should be reviewed as soon as possible.
- A number of studies have demonstrated that the 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(18). The most effective way to calculate eGFR is therefore using the CKD-EPI equation (See Appendix 3).
- Routine urinalysis for proteinuria is not recommended during follow-up in those with normal renal function at baseline and no risks for renal disease, as detection of proteinuria has a very low positive predictive value (PPV) for creatinine elevation (0.7%)(12). In addition, testing for specific renal proximal tubular dysfunction seen with TDF, using detailed markers of tubular proteinuria, is also not recommended as part of routine monitoring as it does not predict a clinically relevant eGFR decline(20).

For details on how to manage eGFR results at baseline ***see Flowchart 1 on page 56***

6.2.9 Assessment of bone mineral density

- Small, but statistically significant reductions in the mean bone mineral density have been demonstrated in individuals taking TDF containing PrEP. The magnitude of the bone loss is inversely related to adherence. Recovery of bone mass has been shown following discontinuation of PrEP and there is, to date, no evidence of increased risk of fractures with TDF containing PrEP.
- For detail on how to assess and manage bone mineral density at baseline ***see Flowchart 2 on page 58***

6.2.10 Assessment of pregnancy

- Assessment of pregnancy should be undertaken at baseline. After discussing the potential risks and benefits of taking PrEP, recommend continuation of PrEP during pregnancy (or breastfeeding) for those with an ongoing risk for HIV and report information regarding PrEP use during pregnancy to the Antiretroviral Pregnancy Registry.

6.2.11 Prescribing PrEP

- We recommend that TD-FTC is used for PrEP for MSM, trans women, trans men and heterosexual men and women. For heterosexual men and women only, TD

alone may be considered. Note that event-based dosing is not recommended for any group with TD alone.

- We recommend TAF-FTC for those with poor renal function (eGFR < 60ml/min/1.73m^2), those with proven osteoporosis and those aged under 18 years.
- When first starting PrEP (and when re-starting), dispensing a 90-day supply of medication is usually recommended. Follow-up should be planned for 4 weeks later (either face to face or by telephone) to review adherence and any side effects.
- For individuals with low risk of toxicity and good adherence to PrEP who have completed initial follow up visits, the routine supply of 180 days of oral PrEP medication is recommended. Routinely providing 180 days' supply has significant benefits in terms of convenience and service capacity.

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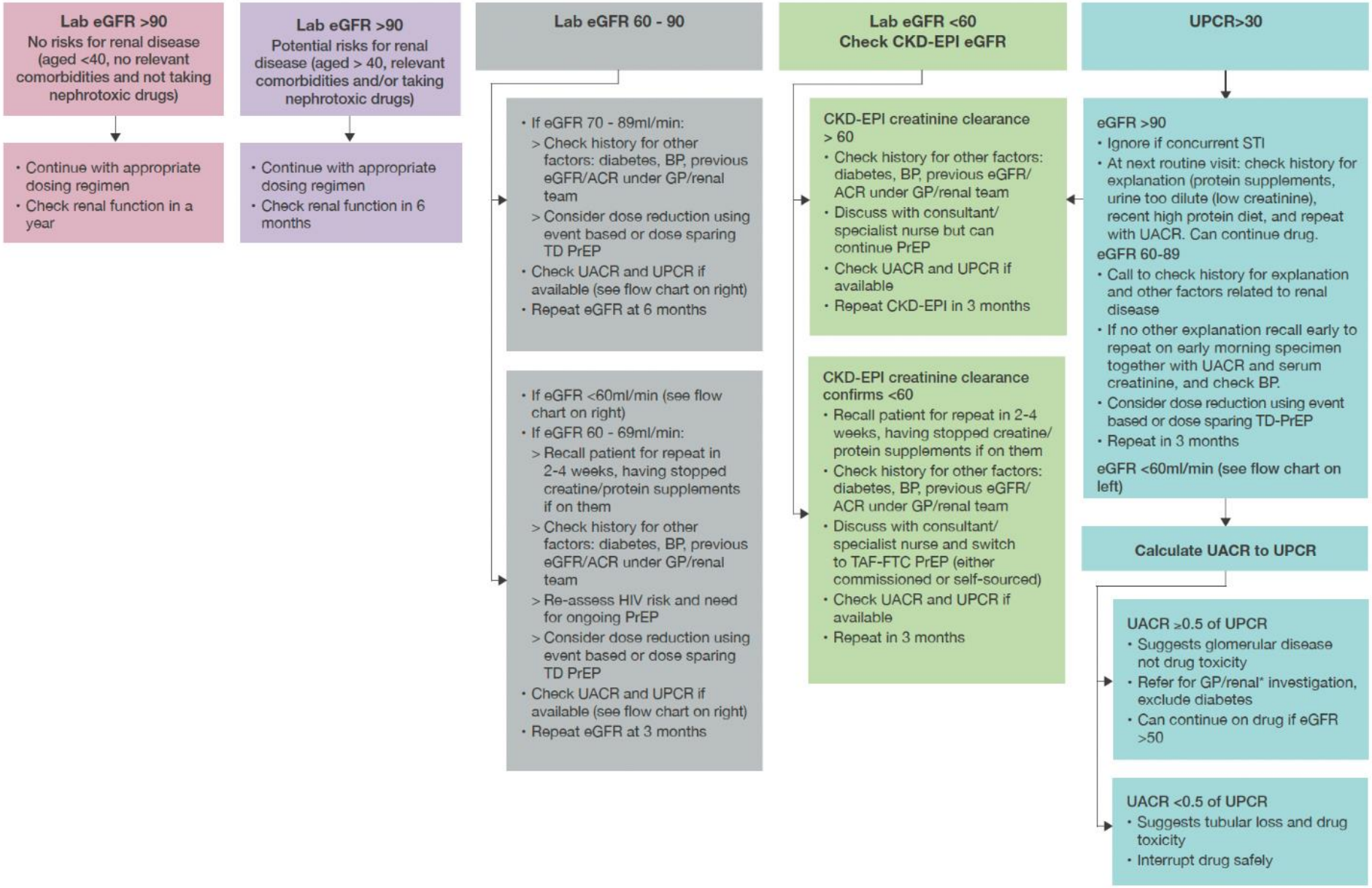
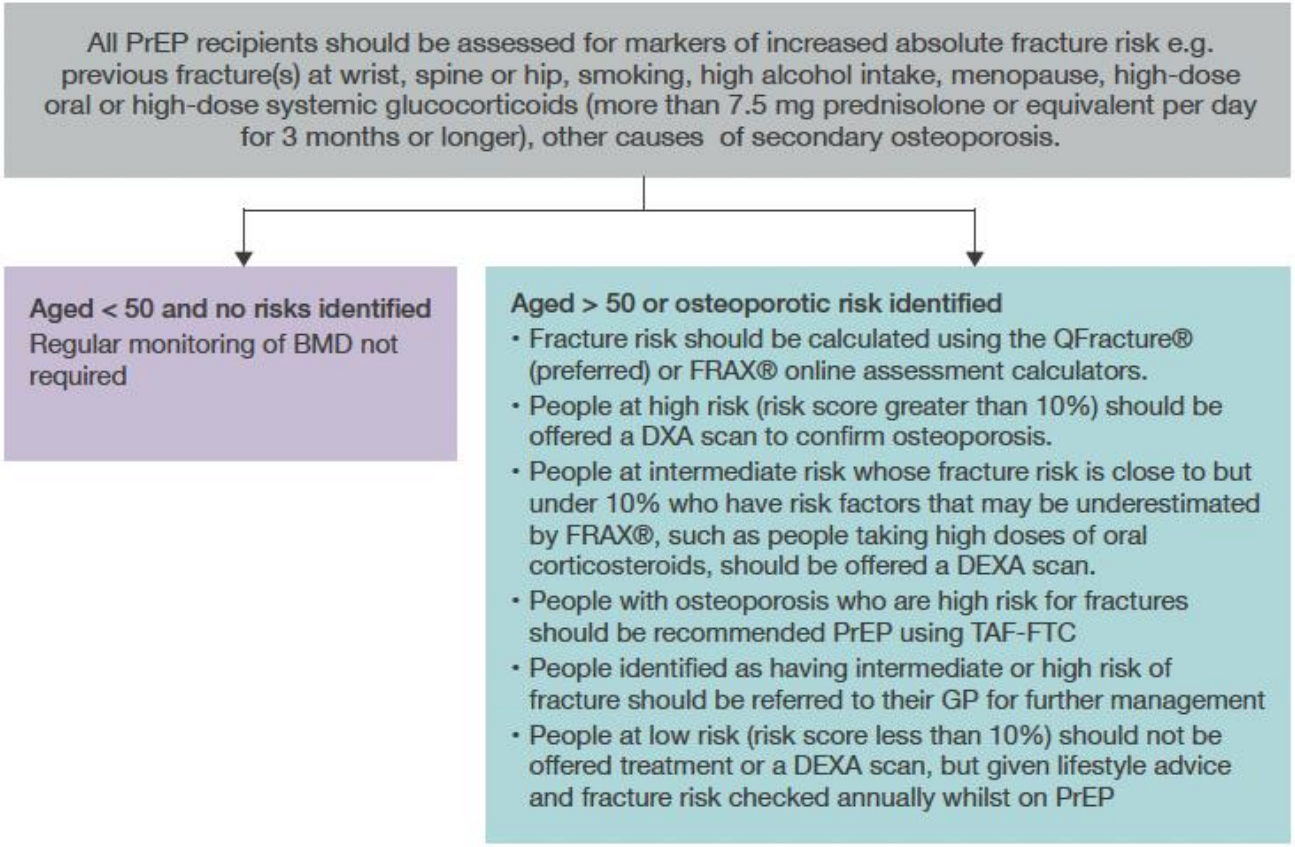
Flowchart 1: Managing renal function at baseline



Flowchart 2: Managing bone mineral density assessment at baseline



NICE guidelines: managing osteoporosis and frature risk
https://cks.nice.org.uk/topics/osteoporosis-prevention-of-fragility-fractures/

CHAPTER 7: On-going clinical management and monitoring

Recommendations for on-going clinical management and monitoring

HIV Testing

31. We recommend HIV testing should be undertaken every 3 - 6 months for people taking PrEP with a laboratory combined HIV antigen/antibody test (1A) or a blood based POCT (1B).
32. We recommend 3-monthly testing for bacterial STIs (chlamydia, gonorrhoea and syphilis) for people taking PrEP who have new or multiple sexual partners and regular HCV testing in those at ongoing risk in line with hepatitis testing guidelines(7, 8) (1B)
33. We recommended that following the discontinuation of PrEP, retest for HIV at day 45 (1B)
34. In the presence of indeterminate HIV test results, for people having reported use of intermittent PrEP or PEP, we recommend serology and samples to be sent to the reference laboratory at the UK Health Security Agency for detailed analysis, including Western Blot and HIV DNA testing. We recommend continuation of PrEP until additional results of HIV testing is complete. In complex cases we recommend referral to the UKHSA/IDRIS clinic for expert review (Imperial.IDRIS@nhs.net) (1B)
35. 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)

Testing and management of renal function (*See flow chart on page 59)*

36. We recommend that ongoing monitoring of renal function is assessed with serum creatinine and eGFR (1A)
37. We recommend that if eGFR remains ≥ 90ml/min/1.73m^2 and the person is aged < 40 years, with no risks for renal disease then annual eGFR should be conducted (1A)
38. We recommend that if an individual has a significant drop in eGFR (defined as a confirmed reduction of 15ml/min or 25% in eGFR from baseline), more frequent renal monitoring is required (2B)
39. We recommend that where a significant drop in eGFR is experienced, it is confirmed with the CKD-EPI equation to calculate creatinine clearance (2B)
40. We recommend that if a significant drop in eGFR is not confirmed with CKD-EPI that eGFR is repeated at 3 months and ongoing renal monitoring continued as per the flow chart on page 60 (2B)
41. We recommend that if eGFR is between 70 – 89ml/min/1.73m^2 whilst taking PrEP, then risks for renal disease should be checked, reduced exposure to TD with EBD or intermittent dosing considered, and eGFR repeated at 3 months (2B)
42. We recommend that if eGFR is 60-69 ml/min/1.73m^2 whilst taking PrEP then eGFR should be repeated in 2-4 weeks, having stopped any creatine/protein supplements, assessing risks for renal disease and consider reducing exposure to TDF with EBD or intermittent dosing (2B)
43. We recommend that if eGFR < 60 ml/min/1.73m^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 **See flow chart on page 61**
44. We recommend that individuals with an eGFR < 60 ml/min/1.73m^2 be recommended TAF containing PrEP (1A) **See flow chart on page 61**
45. We recommend that that if eGFR < 60 ml/min/1.73m^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) **See flow chart on page 61**

TAF-FTC PrEP and weight gain

46. We recommend that individuals taking TAF-FTC PrEP should be advised of the risk of modest weight gain compared to TD-FTC (1B).

Testing and management of bone function

47. We recommend that those with markers of increased fracture risk and/or with confirmed osteoporosis on DXA scanning (see GPP) who are taking continuous daily PrEP, alternatives to TD-PrEP (currently TAF-FTC only) should be advised (2B).
48. We recommend that in those with risk factors for reduced BMD in whom DXA scanning is not indicated, options for reduced exposure to TD through event-based or intermittent dosing should be supported where appropriate for risk reduction (2B).
49. We recommend that in those aged ≥ 50 and/or with risk factors for osteoporosis, fracture risk should be calculated annually using the QFracture® (preferred) or FRAX® online assessment calculators (1A).
50. We recommend that that people at high risk (risk score greater than 10%) should be offered a DXA scan to confirm osteoporosis (1A).
51. We recommend that people at intermediate risk whose fracture risk is close to but under 10% who have risk factors that may be underestimated by FRAX®, such as people taking high doses of oral corticosteroids, should be offered a DXA scan (1A)
52. We recommend that people with osteoporosis who are at high risk for fractures should be switched to TAF-FTC (1B).
53. We recommend that people at low risk (risk score less than 10%) should not be a DXA scan, but given lifestyle advice and fracture risk checked annually whilst on PrEP (1B).

Pregnancy

54. We recommend that if an individual becomes pregnant while on PrEP that they continue PrEP during pregnancy or breastfeeding if there is an ongoing risk of HIV acquisition, after discussing the potential risks of TD-FTC. (2B)

Good practice points

- PrEP should be offered as part of a package of care which includes comprehensive sexual and reproductive healthcare services.
- The need for STI testing or toxicity monitoring should not be a barrier to PrEP resupply. Supply should never be conditional on testing or monitoring.
- Remain alert to acute HIV infection amongst people at risk of HIV, particularly in the presence of any symptoms, which are often non-specific in nature and counsel and manage accordingly.
- Assessment of pregnancy status in those not using reliable contraception should be conducted if indicated.
- Bone health:
  - Routine monitoring of BMD is not recommended in individuals taking TD for PrEP with no other risk factors for reduced BMD.
  - Supplementation with vitamin D and calcium may be considered, particularly if additional risks for osteopenia or osteoporosis, although there is no evidence currently to support this.
    - In those with risk factors for reduced BMD the FRAX tool could be undertaken, to indicate the need for a DEXA scan and potential treatment for reduced BMD.

Overview

Follow up testing and monitoring of individuals receiving PrEP should focus on excluding HIV, screening for and treating sexually transmitted infections and monitoring for renal safety.

7.1 HIV testing

- Regular HIV testing with a laboratory combined HIV antigen/antibody test or a blood based POCT is required to both confirm an individual is HIV negative and to ensure early detection and management of any incident HIV infections.
- Those who have new or multiple partners should have an HIV test every 3 months.
- Less frequent HIV testing may be appropriate for those who are assessed to be at lower risk of HIV acquisition, for example those who have less frequent partner change i.e., 3 - 6 monthly. However, there is no clear evidence to support an HIV testing frequency of less than 3 monthly.
- For investigation and management of atypical and indeterminate HIV test results or possible HIV seroconversion during follow up please see section 6.2.4 on page 49 including how to access specialist advice.

7.2 STI testing

- High rates of bacterial STIs have been observed among PrEP users, especially GBMSM. However, not all people on PrEP have the same risk for sexually transmitted infections. In an Australian study of nearly 3,000 PrEP users (98.5% of whom were GBMSM) high rates of STIs were seen, but mostly concentrated in a subset of participants. In this study 25% of participants accounted for 76% of the STIs(1).

- As part of a comprehensive risk reduction strategy, 3-monthly STI screening (chlamydia, gonorrhoea, and syphilis) is recommended for people taking PrEP who have new or multiple sexual partners. Less frequent testing for STIs may be appropriate for those who, for example, have a single partner who is HIV positive and is not virally suppressed or those with less frequent partner change.

- Sexually transmissible enteric infections (STEIs) are associated with high-risk and dense sexual networks in MSM(2-4). This includes MSM using PrEP and clinicians should consider STEIs as the cause of any gastroenteric symptoms among MSM PrEP users and arrange suitable testing and treatment.

- Several cross-sectional community and clinic-based surveys suggest that up to 10% of MSM using HIV PrEP may also be taking antibiotics as pre- and post-exposure prophylaxis for sexually transmitted infections(5). This follows trials such as the USA based Doxy-PEP study in GBMSM and trans women which observed a 62–66% lower frequency of bacterial STIs in the active arm (200 mg of doxycycline taken within 72 h after condomless sex) compared to the ‘standard of care’ arm(6). It is recommended

that clinicians routinely ask PrEP users if they are using antibiotics in this way and provide appropriate advice on potential risks and benefits(7), based on current BASHH guidance.

7.3 Hepatitis C testing

- GBMSM and others with ongoing risk should be screened for hepatitis C annually.
- 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 DAA treatment.
- For anti-HCV positive individuals who have previously cleared HCV, HCV testing would specifically need to be with HCV RNA or HCV-cAg testing.

7.4 Renal monitoring

TD containing PrEP has a minimal and reversible impact on renal function. PrEP trials have shown modest declines in renal function with administration of daily TDF-FTC(8) which, although statistically significant, are rarely of clinical significance and the incidence of serious renal events was very low and mostly reversible(8-12).

For information on how to monitor renal function and manage reductions in eGFR see Flowchart 3 on page 65. It should be noted that a significant change in renal function is defined by the NHS England Specialist Commissioning HIV Clinical Reference Group PrEP working group as a reduction in eGFR of 15ml/min in the past 12 months or 25% reduction in eGFR in the past 12 months.

For an evidence review of PrEP and renal function see Chapter 4.2.1 on page 32 and Appendix 2

7.5 Bone mineral density

Small, but statistically significant reductions in the mean bone mineral density have been demonstrated in individuals taking TDF containing PrEP. The magnitude of the bone loss is inversely related to adherence. Recovery of bones mass has been shown following discontinuation of PrEP and there is, to date, no evidence of an increased risk of fractures in people taking TDF containing PrEP.

For information on how to monitor bone mineral density see Flowchart 4 on page 67

- For an evidence review of PrEP and bone mineral density see section 4.2.3 on page 33 and Appendix 2

7.6 TAF-FTC PrEP, lipids and weight gain

- In the DISCOVER trial(13), which compared daily TDF-FTC and TAF-FTC for PrEP in MSM and transgender women, there was greater weight gain among participants who took TAF-FTC compared to those taking TDF-FTC (median weight gain 1.7kg vs 0.5kg, p<0.0001). Study participants who received TDF-FTC had decreases in lipid levels after both 48 and 96 weeks, yet individuals who received TAF-FTC had stable lipid levels through 96 weeks.

7.7 Pregnancy and conception

PrEP may be one option to prevent HIV seronegative partners from acquiring HIV infection in a serodifferent relationship during attempts to conceive if the HIV positive partner is not on suppressive ART. Regular assessment of pregnancy status should be undertaken in women and other people who could become pregnant who are not on reliable contraception. If an individual becomes pregnant while on PrEP, we suggest a discussion of the known risks and benefits of taking TD-FTC or TAF-FTC during pregnancy. After discussing the potential risks, 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.

Flow chart 3: Managing drops in renal function whilst on PrEP

Confirmed reduction of 15ml/min or 25% in eGFR from baseline (Significant reduction)

Check CKD-EPI eGFR

CKD-EPI eGFR <60ml/min
- Recall pt for repeat in 2-4 weeks, having stopped creatine/protein supplements if on them
- Check history for other factors: diabetes, BP, previous eGFR/ACR under GP/renal team
- Discuss with consultant/specialist nurse and switch to TAF-FTC PrEP (either commissioned or self-sourced)
- Check UACR and UPCR if available

CKD-EPI eGFR: 60 - 69ml/min:
- Recall pt for repeat in 2-4 wks, having stopped creatine/protein supplements if on them
- Check history for other factors: diabetes, BP, previous eGFR/ACR under GP/renal team
- Re-assess HIV risk and need for ongoing PrEP
- Consider dose reduction to event based or dose sparing TD PrEP
- Check UACR and UPCR if available (see flow chart below)
- Repeat at 3months

CKD-EPI eGFR: 70 - 89ml/min:
- Check history for other factors: diabetes, BP, previous eGFR/ACR under GP/renal team
- Consider dose reduction to event based or dose sparing TD PrEP
- Re-assess HIV risk and need for ongoing PrEP
- Check UACR and UPCR if available (see flow chart below)
- Repeat at 3 months

CKD-EPI eGFR >90ml/min
- Check history for other factors: diabetes, BP, previous eGFR/ACR under GP/renal team
- Continue with current dosing
- Repeat in 3 months

UPCR>30

CKD-EPI eGFR >90 on PrEP
- Ignore if concurrent STI
- At next routine visit: check history for explanation (protein supplements, urine too dilute (low creatinine), recent high protein diet, and repeat with UACR. Can continue drug.

CKD-EPI eGFR 60-89 on PrEP
- Call to check history for explanation and other factors related to renal disease
- If no other explanation recall early to repeat on early morning specimen together with UACR and serum creatinine, and check BP. Can continue drug.

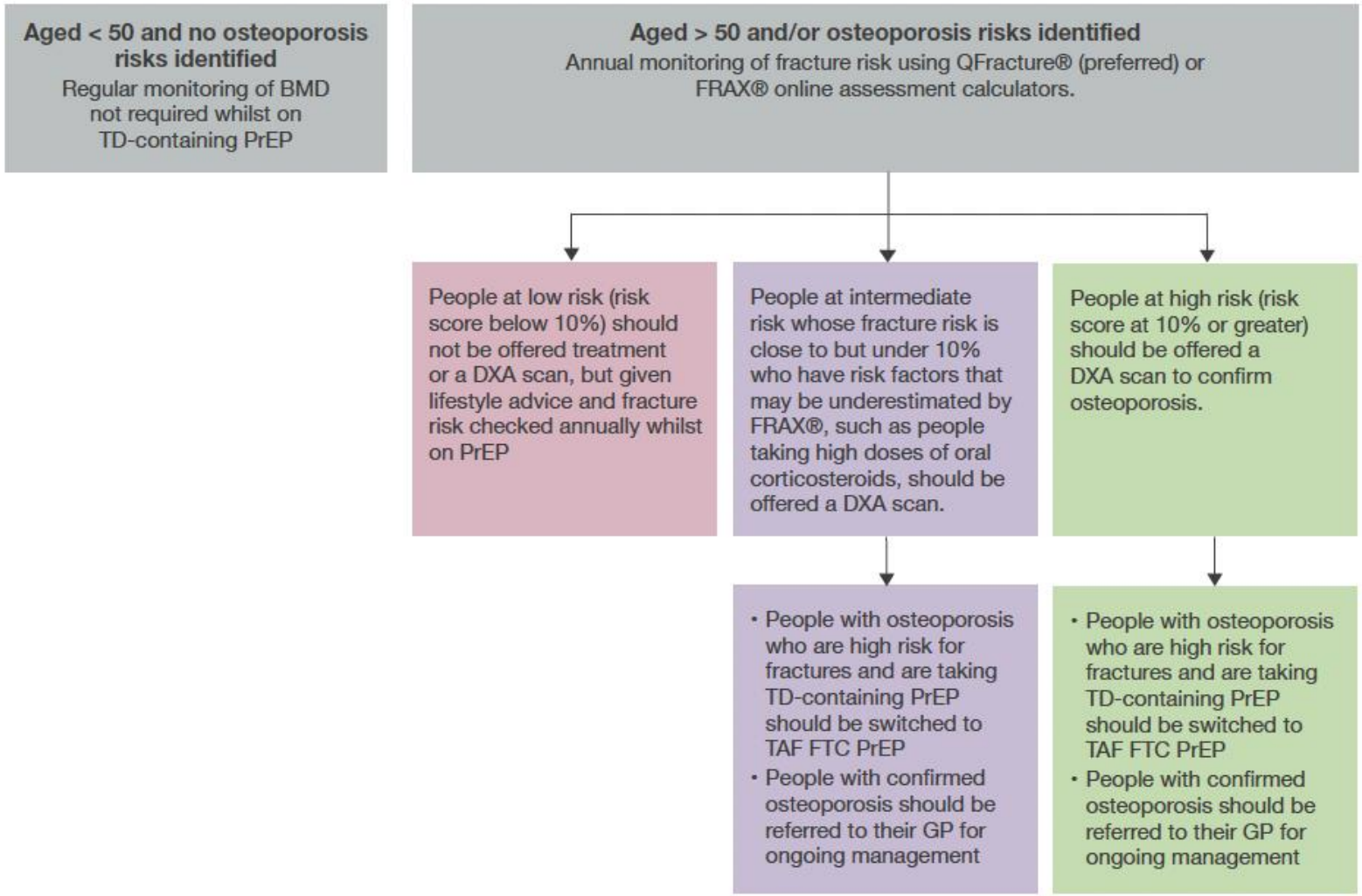
CKD-EPI eGFR <60ml/min (See box on right)

Calculate UACR to UPCR

UACR ≥0.5 of UPCR
- Suggests glomerular disease not drug toxicity
- Refer for GP/renal* investigation, exclude diabetes
- Can continue on drug if eGFR >50
- Switch to TAF -FTC PrEP (either commissioned or self-sourced)

UACR <0.5 of UPCR
- Suggests tubular loss and drug toxicity
- Interrupt drug safely

Flowchart 4: Managing bone mineral density – ongoing monitoring



NICE guidelines: managing osteoporosis and fracture risk
https://cks.nice.org.uk/topics/osteoporosis-prevention-of-fragility-fractures/

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Chapter 8: Starting/stopping, PK, dosing, indications for PEPSE

8.1 Starting and stopping TD-FTC and TAF-FTC PrEP

Recommendations for Starting and Stopping TD-FTC and TAF-FTC PrEP:

NB: There have been no clinical trials of double dose (two pills) lead-in other than for sexual exposures in MSM and TGW, but high quality pharmacokinetic/pharmacodynamic (PK) studies support with equal weight a double-dose (two pills) lead-in as compared to multi-day single dose lead-in for all exposures including injecting drug use.

55. We recommend that, if the risk of HIV acquisition is through receptive anal sex, oral PrEP can be started with a double dose (two pills) 2-24 hours before risk and safely stopped with a single dose daily for two days after last risk (**TD-FTC** [1A], **TAF-FTC** [1B])

56. We recommend that, if the risk of HIV acquisition is through insertive vaginal/neovaginal sex/anal sex, oral PrEP can be started with a double dose (two pills) 2-24 hours before risk and safely stopped with a single dose daily for two days after last risk

TD-FTC: Insertive anal [1A]. Insertive neovaginal/vaginal [1B]. **TAF-FTC:** Insertive vaginal/neovaginal/anal (1B)

57. We recommend that, if the risk of HIV acquisition is through receptive vaginal/neovaginal sex, PrEP can be started with a double dose (two pills) 2-24 hours before risk and safely stopped with a single dose daily for seven days after last risk.
(Receptive vaginal [1C], neovaginal [1D])

58. We recommend that, if the risk of HIV acquisition is through injecting drug use, oral PrEP can be started with a double dose (two pills) 2-24 hours before and safely stopped with single dose daily for seven days after last risk. [1C]

Good practice points

- We suggest that it is important to stress that for receptive vaginal/neovaginal sex and injecting drug use, users need to continue TD-FTC PrEP for seven days after exposure. Fewer than seven daily doses following a double dose start are likely to be incrementally less effective with reducing dose frequency. When daily dosing is continuous (ie when 4 or more doses have been taken in the week prior to an exposure), 4 doses per week in subsequent weeks are likely to provide good protection for all types of risk exposure.

We suggest that people who experience moderate-severe gastrointestinal side effects following the double dose (two pills), can take the dose as two separate tablets 6-12 hours apart.

Key Evidence Summary for Starting and Stopping TDF-FTC or TAF-FTC PrEP

- Starting and stopping PrEP in the context of insertive and receptive anal sex has been evaluated in a single RCT in GBMSM and trans women(IPERGAY)(1), starting with a double dose of TDF-FTC taken 2–24 hours before sex (followed by a single tablet 24 hours and 48 hours after double dose). This regimen showed a relative risk reduction of 86% in HIV acquisition compared with placebo. The only infections seen in the group taking TDF-FTC were amongst those who had discontinued drug, suggesting the biological efficacy is close to 100%. This level of protection is further supported by the open-label cohort study Prevenir(2), pharmacokinetic studies(3) including one with ex-

vivo tissue challenge(4), animal challenge data(5) and supported by observational data from routine use in Europe since 2016.

- Two large RCTs show that daily TDF-FTC is effective for insertive vaginal sex in heterosexual men(6, 7). Although lead-in times for insertive vaginal sex have not been assessed in placebo controlled clinical trials, extrapolation from other studies and a pharmacokinetic (PK)/pharmacodynamic (PD) study evaluated a double dose start of TDF-FTC and TAF-FTC and found both sufficient to reduce HIV transmission across foreskin tissue and PBMCs (Peripheral Blood Mononuclear Cells) in ex-vivo challenge (8). This, and the fact that the IPERGAY (9) study reported no HIV infections in men whose risk was from insertive (anal) sex only, can be extrapolated to support the recommendation that event-based TD-FTC can be taken by cis-gender men for insertive vaginal sex.
- The time to clinical protection for receptive vaginal sex has been extrapolated from PK/PD studies of TDF-FTC as all the RCTs assessed daily regimens. Cottrell et al conducted a high-quality clinical study providing evidence that three days of daily TDF-FTC achieves steady state EC90 drug levels in the female genital tract (FGT) in 99% of the population(4). Following a double dose (two pills) start, protective levels of TDF-FTC in the FGT were achieved in 99% of women 2 hours after dosing (vs 81% in rectal tissues). The data supports with equal weight a double-dose (two pills) lead-in or one pill a day for three days before receptive vaginal sex as the recommended dosing regimen for PrEP. For receptive neovaginal sex it is necessary to extrapolate from the evidence for colorectal and FGT tissues and on this basis, the same recommendation applies. Although a number of published randomised clinical trials of PrEP have included a significant population of trans women and there is no evidence of lower efficacy in this population, the number in whom risk included receptive neovaginal sex is not known. PK studies including neovaginal exposure are underway.
- The Cottrell PK/PD model also supported a double dose start two hours prior to sex for the FGT and colorectal tissues, achieving EC90 in 98% and 81% of the population in FGT and colorectal tissues respectively(4). After a double dose start, administered 2 or 24 before coitus, followed by single doses 24 and 48 hours later (2;1;1, Event Based Dosing (EBD) or 'IPERGAY regimen'), target exposure was maintained for 240 hours after exposure in rectal tissues, but only 85% of FGT samples had protective levels at 120 hours because of the rapid clearance of FTC-TP, and this is why a longer duration of daily pills (7 days) after the last risk may be required to maintain effective protection in the FGT. This observation is consistent with other pharmacological studies(10), but inconsistent with the Partners PrEP RCT in which the observed effectiveness for TDF alone compared to placebo was similar to TDF-FTC in female participants at risk of acquiring HIV (hazard ratio vs placebo of 0.29 (95% CI, 0.13–0.63) for TDF alone and 0.34 for TDF-FTC (95% CI, 0.16–0.72)(11). As TDF alone does not reach EC90 in FGT this observation suggests that the level of drug in PBMC is at least equally important in preventing an established infection. However, as the extent to which protection depends upon PBMC drug levels as opposed to levels in FGT (and other) tissues remains unclear, current recommendations are to continue daily dosing for a full seven days after receptive vaginal & neovaginal exposure, following a double-dose start.

- Several mathematical models using drug level adherence mapped to clinical effectiveness derived from the RCTs support the observation from the pharmacological studies that cisgender women require more days of drug for protection(12, 13). However, only one of three RCTs that enrolled women was able to demonstrate clinical effectiveness(11) due to low adherence overall resulting in wide confidence intervals for some estimates in the models(13-15). An alternative modelling study (Zhang 2023) based on all available clinical trials of daily TD-FTC in women and exploring the wide range of reported clinical average efficacy, also strongly suggests that the lower (or no) efficacy of PrEP reported in heterosexual cis women is a function of low adherence rather than tissue drug concentrations(16). If PBMC drug levels are the relevant marker of protection, then 3-4 doses per week will offer similar levels of protection for receptive vaginal sex as for other sexual exposures. The extent to which effectiveness in clinical trials was dependent on drug pharmacokinetics as opposed to adherence is incompletely understood, but recent evidence suggests that adherence is the main driver of the observed difference in efficacy in heterosexual women.
- When protection depends on PBMC alone, as is the case for blood-borne risk, then it is useful to consider the number of doses required to achieve 16fmol/M of TFV-DP, the accepted benchmark for 90% protection(10, 17). Interestingly, the time to steady state is shorter in HIV negative populations compared to people living with HIV and can be achieved in 5 days. Once achieved effective levels are maintained for at least another seven days in PBMC, with active metabolites still detected 14 days after the last dose(17). Modelling drug levels in PBMC based on the Cottrell model and studies in women and applied to blood-borne risk in PWID suggested that for both TD-FTC and TAF-FTC(18), a single dose would provide protection within 0.5 hours and lasting for at least 84 hours for at least 99% of the population. Two regular doses per week maintained protection in 100% of the population. For PWID, we make the same dosing recommendations as for sexual exposure, although it may be the case that fewer doses will offer protection.
- Drug levels of TFV-DP following a double dose of TAF are 7.5-fold higher in PBMC than TDF(8), and 2-fold higher in foreskin tissue. Several studies have confirmed that TFV-DP is lower in rectal tissues after TAF compared to TDF(19, 20); in spite of this clinical equivalence was demonstrated in the randomised controlled Phase 3 clinical trial DISCOVER comparing daily TAF-FTC to TDF-FTC(21). There was a lower number of infections in the TAF-FTC group, but this was not statistically significant (seven compared to 15). Based on current evidence, we recommend the same lead in period for TAF-FTC as for TDF-FTC.
- Thurman et al evaluated a single dose and 14 days of TAF-FTC and confirmed that FTC reaches highly effective levels within 4h in genital tissues and PBMC and is the main driver of potency in the FGT(19). TFV-DP levels in PBMC are also higher with TAF-FTC and maintained for longer than for TD-FTC(18). The results from two ongoing clinical trials in women comparing daily TDF-FTC to TAF-FTC are awaited, but TAF-FTC promises to be at least as effective as TDF-FTC.

Table 2: Summary table of starting and stopping TD-FTC and TAF-FTC PrEP:

	TD-FTC 200/245mg or TAF-FTC 200/25mg fixed dose combinations	
	Time to start of protection	**Safely stopping**
Receptive anal	Double dose (2 pills) 2-24 hours before risk	Continue single dose daily for 2 days after last risk
Insertive vaginal/neovaginal /anal	Double dose (2 pills) 2-24 hours before risk	Continue single dose daily for 2 days after last risk
Receptive vaginal/neovaginal	Double dose (2 pills) 2-24 hours before risk	Continue single dose daily for 7 days after last risk
People who inject drugs	Double dose (2 pills) 2-24 hours before risk	Continue single dose daily for 7 days after last risk

8.2 Indications for PEPSE in PrEP users

PrEP users need to understand how to use their PrEP as PEPSE if there is insufficient drug in the tissues at the time of exposure to HIV, as they have two of the three drugs used as PEPSE to hand.

Recommendations for PrEP and PEPSE For PrEP users who have drug to hand (See Table 3)

Sexual risk through condomless anal sex/insertive vaginal sex:

59. We recommend that if the risk of HIV acquisition is through condomless anal sex (insertive and receptive) / vaginal or neovaginal sex (insertive), and if seven days or less have elapsed since the last oral PrEP dose, PrEP should be resumed as prescribed (1B).
60. We recommend that, if more than seven days have elapsed since the last oral PrEP dose, PrEP should be restarted with a double dose of PrEP as soon as possible (preferably in the first 24h (1B) after exposure and no later than 72 hours (2C]), and continued daily while seeking advice from clinical services on possible intensification of PEPSE.

Sexual risk through condomless receptive vaginal /neovaginal sex

61. We recommend that, if the risk of HIV acquisition is through condomless receptive vaginal/neovaginal sex, and if three days or less have elapsed since the last oral PrEP dose, PrEP should be resumed with a double dose. (Vaginal [1B], Neovaginal [2C]).
62. We recommend that, if more than three days have elapsed since the last PrEP dose, PrEP should be restarted with a double dose of oral PrEP as soon as possible (preferably in the first 24h after exposure (Vaginal [1B]/Neovaginal [2C]) and no later than 72 hours (2C) and continued daily while seeking advice from clinical services on possible intensification of PEPSE.

Blood borne risk for people who inject drugs

63. We recommend that, if the risk of HIV acquisition is through injecting drug use and if four days or less have elapsed since the last oral PrEP dose, PrEP should be resumed with a double dose. (1D).
64. We recommend that, if more than four days have elapsed since the last oral PrEP dose, PrEP should be restarted with double dose of PrEP as soon as possible (preferably in the first 24h after exposure and no later than 72 hours) and continued daily while seeking advice from clinical services on possible intensification of PrEP (1D)

Missed post coital dose for event-based PrEP

65. We recommend that, for event-based oral PrEP users who are late with, or missed, the first post-coital dose, the first post-coital dose can still be taken up to 48 hours after sex, provided at least one tablet was taken before sex (1B); the second post-coital dose should be taken 24 hours after the first to complete the course.
66. We recommend that if more than 48 hours have elapsed after last risk, the first dose should be taken and advice should be sought from clinical services (1B)

Good practice points

- We suggest that PrEP users should routinely be given advice about what to do in the event of an HIV risk.
- We suggest that it is important that PrEP users understand that PrEP and PEP only reduce the risk of HIV acquisition when drug is taken as close as possible to the risk episode, and that the benefit of starting beyond 24 hours reduces substantially when there is no drug present at the time of risk.
- We suggest that PEP should be considered if there has been significant risk exposure within the last 72 hours at the point of initiating PrEP. If there are two or more risk episodes more than 72 hours before initiation, PrEP should be initiated with HIV testing as recommended in 6.2.2
- We suggest that PrEP users should be informed about how to access PEP advice in a timely manner

Key Evidence Summary for PEPSE in PrEP users

- There is consistent evidence from animal challenge studies supporting the effectiveness of short course antiretroviral prophylaxis (1 or 2 timepoints only) that is started prior to challenge or within 24 hours (5, 22-25). Starting PEPSE beyond 24 hours has been evaluated in two animal challenge experiments using the SHIV challenge models ((22, 25)). In Otten's study protection was seen in 4/4 starting at 36 hours and 2/3 starting at 72 hours, but 1/4 controls were not infected making interpretation difficult. The most recent animal challenge studies have been carefully designed to mirror sexual exposure with compartment challenge, and to map drug levels to those seen in clinical studies. There are limitations, but they provide proof of concept that shorter courses of PEPSE, even when only TDF-FTC is deployed, are highly effective if administered in the first 24 hours after exposure (15, 24, 25). Bekerman evaluated TAF-FTC-Bictegravir 100mg taken 48 and 72h after challenge and 3 out of 6 animals were protected (1B) (25).
- The earliest estimate for completion of the viral cycle is 28 hours (26) and this explains why PEPSE is most effective when started within 24 hours (1B). Within a few days HIV viral replication in $CD4^+$ T cells becomes exponential with expansion to GALT, lymph nodes and spleen and beyond. Fiebig estimated the window period to detection of HIV RNA to be 5d. Konrad et al used HIV RNA results from seroconversion panels to quantify the length of the eclipse and concluded this was an average of 8-10 days depending on the size of inoculum (27) which they estimated to confer low/medium/high risk exposure.
- In the clinical setting, simply resuming PrEP as prescribed is possible when effective levels are present. For colorectal tissues and PBMC, effective drug levels associated with 90% reduction in risk, as defined by Anderson et al in 2012(28), are maintained for at least 7 days in both compartments once achieved (28, 29). Although PBMC are not impacted by gender, effective levels are only maintained for 2-3 days in the FGT, and therefore it is reasonable to assume there is inadequate protection for the FGT at the portal of entry if the last pill was taken more than 3 days prior to exposure.
- Effective levels also depend on how much TDF-FTC was taken prior to the last dose, and for how long. The 90% effective drug level of 16 fmol/M for TFV-DP in PBMCs was established using a pharmacological study (STRAND) and a case-control analysis of iPrEX by Anderson, Glidden et al in 2012(28). In HPTN 066 and STRAND dosing was observed for regimens of one (HPTN066 only), two, four or seven tablets a week(10). The concentration achieved was proportional to the dose with four or seven a week exceeding the threshold of 16 fmol/M for TFV-DP in PBMC considered to be 90% effective and two a week somewhat below this in both studies (9 and 11 fmol/M respectively). Other studies confirm the compartment differences with effective drug levels persisting for longer in colorectal tissues and less time in FGT.
- TFV-DP is dose-proportional so higher doses, and more frequent doses (eg daily) result in higher drug concentration in tissues. Provided at least two tablets a week were taken, drug levels will be boosted to adequate protection with the next single dose in PBMC and colorectal tissues, but a double dose (two tablets) is advised to boost levels in the FGT.

- Differences in study design, time of sampling, time from sampling to analysis and other laboratory factors explain the variation in results but the observations of drug proportionality and compartmental variation are consistent. A double dose (two tablets) will result in higher concentrations of TFV-DP in tissues and PBMC within 24h, and is more likely to achieve effective levels in this timeframe than a single dose. Furthermore, the concentration of these two drugs in the FGT (FTC-TP) and colorectal tissues (TFV-DP) make them an excellent choice for PrEP and PEPSE.

Table 3: Summary Table for PrEP users who have drug to hand

Sexual risk (no condom, partner not on ART or PrEP)	**Gap between last PrEP dose before exposure and resumption of PrEP**	**Recommendation after exposure**	**Level of evidence**
Insertive/receptive anal sex or insertive vaginal sex	≤ 7d	Resume PrEP with a double dose as prescribed	1B: PK/PD, RCT
	> 7d	Take double dose of PrEP as soon as possible in the 24 hours after exposure, continue daily, seek urgent advice from clinical services for intensification of PEPSE	1B: animal challenge; PK/PD
Receptive vaginal sex	≤ 3d	Resume PrEP with a double dose as prescribed	1B: PK/PD
	> 3d	Take double dose of PrEP as soon as possible in the 24 hours after exposure, continue daily, seek urgent advice from clinical services for intensification of PEPSE	1B: animal challenge; PK/PD
Receptive neovaginal sex	≤ 3d	Resume PrEP with a double dose as prescribed	2C
	> 3d	Take double dose of PrEP as soon as possible in the 24h after exposure, continue daily, seek urgent advice from clinical services for intensification of PEPSE	2C

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Chapter 9 Buying generic PrEP online

Recommendations for buying generic PrEP online
67. We recommend that clinicians should ensure full PrEP support, including renal monitoring, to patients who are taking oral PrEP they have sourced online. (1D)
68. We recommend that therapeutic drug monitoring is **not** required for those taking self-sourced oral PrEP (1B).
Good practice points
We suggest that: • Clinicians should signpost individuals to IWantPrEPnow, PrEPster or https://www.prep.global/get-prep if they are unable or unwilling to access PrEP on the NHS. These site offers support and advice and the ability to source generic drug as safely as possible. • The discussion of self-sourcing PrEP online needs to be fully informed including risks and benefits described in Sections 4 & 8, and advice given in line with these guidelines. • Self-sourcing PrEP users buying TD-FTC or TAF-FTC online should be made aware that the product should originate from a manufacturer listed by the US FDA and that it is advisable to order in advance in case of delays in delivery. • Self-sourcing users buying TAF-FTC should be made aware that this formulation of oral PrEP only has RCT evidence in cisgender men and transgender women who have sex with men. • Clinicians should ensure that people buying TD-FTC or TAF-FTC are taking medication that is labelled as containing both tenofovir and emtricitabine and are taking PrEP correctly. • Self-sourcing PrEP users should be advised to have regular STI (including HCV for those at risk) and HIV tests and renal monitoring in line with the monitoring schedule recommended in this guideline.

Key evidence summary for buying generic PrEP online

While data from annual PrEP User Surveys(1) conducted by PrEPster, iwantPrEPnow and UKHSA suggests a downward trend in this practice, buying generic PrEP online is still the preferred or only option for some people. There is also evidence to suggest that, with clinical support, self-sourcing of PrEP can be done safely(2).

9.1. Reasons for buying PrEP online:

Despite PrEP being routinely available in all four nations of the UK, some people still prefer to self-source drug online(2). Some people prefer the flexibility of self-managing check-ups as and when needed. Those who are geographically isolated or feel highly burdened by 3-monthly check-ups or are affected by other barriers to access as outlined in Chapter 3, may opt to self-source in order to avoid the (perceived or actual) rigidity of regular clinic visits and check-ups, or because of issues relating to stigma or risk of disclosure. It is also possible that lack of access to appointments for initiating or continuing PrEP at NHS sexual health services(3) is driving demand for generic PrEP online. However, this option is only available to those with resources to support self-sourcing.

Some people will prefer to test online/self-sample only – and may choose to do so more or less frequently than the current guidelines recommend. Recommendations on the frequency of renal monitoring and STI testing in this guideline are based on the best available evidence for the population, including those who self-source PrEP. More or less frequent monitoring and testing may be appropriate for some people, but using PrEP without any renal monitoring or STI testing is not recommended. It should be noted, for those self-managing their PrEP use that;

- We recommend HIV testing with a laboratory antigen/antibody test is undertaken prior to commencing oral PrEP, which can be provided through self-sampling. (1A)

- We recommend HIV testing should be undertaken every 3 months for people taking PrEP who have new or multiple sexual partners with a laboratory combined HIV antigen/antibody test (1A) or a blood based POCT. (1B)

- Self-testing for HIV (using saliva or blood samples) is not recommended for people at initiation of PrEP, but ongoing regular monitoring can be undertaken with a blood based HIV POCT or self-test or combined HIV antigen/antibody self-sampling or clinic based testing.

Self-sourcing PrEP users should be encouraged to access renal monitoring testing either from a sexual health service, their GP or from an online PrEP service where available.

For some people, self-sourcing may be the only option for those requiring different types or formulations of PrEP. It is likely to remain an option for those who do not meet NHS eligibility criteria for TAF-FTC but prefer to take it or for those who are eligible for TAF-FTC but who struggle, for whatever reason, to access it.

9.2 Authenticity of tenofovir-emtricitabine bought online

There are several manufacturers of generic TD-FTC and TAF-FTC that import into the UK. These generic manufacturers have their own quality control processes in place and meet production standards that are considered satisfactory by the WHO and the FDA. There is no evidence that PrEP bought online from the major suppliers into the UK is substandard (contain less or variable amounts of active ingredients), nor has there ever been evidence of counterfeit PrEP in circulation.

Therapeutic drug monitoring (TDM) data from 293 online generic PrEP users at 56 Dean Street found pharmacokinetic (PK) levels for both tenofovir and emtricitabine equivalent to that of branded drug Truvada(4, 5). Community organisation PrEPster, in a collaboration with a University College London (UCL) laboratory tested all variants of PrEP available from six of the leading PrEP suppliers and found PK levels to be equivalent to Truvada(4). The same data is not available for TAF-FTC, but supplies are sourced from the same manufacturers by the same suppliers.

9.3 Importing medicines bought online

In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) advises that it is legal to buy up to 3 months of medicines from outside the UK for personal use. There is no requirement for a certificate or authorisation, but MHRA strongly advises that the medicines are kept in their original packaging and are transported in accordance with storage conditions specified by the manufacturer. This not only helps identify the medicines, but also helps ensure the product's stability. The MHRA provides guidance on safely buying medicines online: https://www.gov.uk/government/news/know-what-youre-buying

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

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Chapter 10: New therapies

NB: Guidance on CAB-LA in this chapter was written in advance of NICE and SMC UK regulatory approvals being granted.

Recommendations for new therapies not yet commissioned
69. We recommend that long-acting injectable cabotegravir (CAB-LA) should be offered under compassionate release to those at risk of HIV, but have contraindications to oral PrEP options (1A) 70. We recommend that long-acting injectable cabotegravir is strongly supported as an alternative to a daily PrEP pill (1A) 71. We recommend that an oral lead-in for cabotegravir as PrEP is optional for people worried about side effects. 72. We recommend if an oral lead-is used, the first injection of CAB-LA should be given on the final day of oral dosing, or within 3 days of the final dose (1B 73. We recommend that people are advised that protective levels of cabotegravir are achieved 7 days following first injection (1A) 74. We recommend that people are advised that protective levels of cabotegravir are maintained for 8 weeks after the last injection (1A) 75. We recommend that people on CAB-LA have HIV antibody-antigen and HIV viral load testing every 8 weeks (1A). 76. We recommend that when CAB-LA is discontinued and risk of HIV continues, an alternative PrEP agent is initiated, starting at 8 weeks and continuing to at least 52 weeks after the last CAB-LA injection (1B) 77. We recommend that routine renal, liver and lipid monitoring are not required for those on injectable cabotegravir for PrEP (1A). 78. We recommend that people are advised that injection site reactions are the most commonly experienced side-effect of CAB-LA, and that these are most likely following the first injection and decrease over time. (1A). 79. We recommend that people considering CAB-LA are advised that they may experience a slighter greater increase in weight gain over time than with oral TD-FTC (1A). 80. We recommend that CAB-LA be avoided in people taking certain anticonvulsants (e.g. carbamazepine and phenytoin) and anti-mycobacterials such as rifampicin and rifabutin as drug-drug interactions with these medications significantly reduces cabotegravir plasma concentrations to sub-therapeutic levels. 81. We recommend that a monthly 25 mg dapivirine ring provides a modest, but significant reduction in HIV incidence for women in whom alternative forms of PrEP are unacceptable or unsuitable(9, 10) (1A)
Good practice points
We suggest that, where individuals are already established on new PrEP therapies on arrival in the UK, clinicians should make every effort to prescribe the method the participant prefers. Oral PrEP is

available in all the countries in which CAB-LA and the dapivirine ring can be accessed, and there are good reasons why individuals have opted for one of these other methods.

Key Evidence Summary for New PrEP therapies

See Table 4 on page 93 for a summary of the major trials and open label observational studies demonstrating efficacy and effectiveness of new PrEP therapies

10.1 Injectable long-acting cabotegravir

Injectable cabotegravir (Apretude) for PrEP was licensed by the European Medicines Agency in September 2023(3). Applications for NICE and SMC authorisation in the United Kingdom are anticipated for approval if granted in late 2024/early 2025.

10.1.1 Efficacy of CAB-LA

GBMSM and transgender women

- Long-acting cabotegravir (CAB-LA) was superior to oral TDF/FTC PrEP in a published randomised controlled trials in GBMSM and transgender women (HTPN 083) (4, 5).
- After a final ascertainment of HIV status, there were 13 vs 39 (HR 0.34; 95% CI 0.18-0.62; P<0.001)(4) incident HIV infections in the CAB-LA and in the TDF/FTC groups respectively. In those who acquired HIV infection in the active TDF/FTC group, none had protective levels of drug in plasma.

Heterosexual women

- Long-acting cabotegravir (CAB-LA) was also superior to oral TDF/FTC PrEP in a randomised controlled trials in heterosexual cis women at high risk of HIV in SSA (HTPN 084) (4, 5).
- After a final ascertainment of HIV status, there were 4 vs 36 (HR 0.12; 95% CI 0.05-0.31; p<0.0001)(5) incident HIV infections in the cabotegravir and in the active TDF/FTC groups respectively.

Young people

- A subpopulation of 55 female adolescents recruited from 3 African countries in HTPN-084, age range 12-17 years old, mean 16 years, found CAB-LA acceptable and in 92% preferable to oral PrEP (6).

Potential impact of HIV-1 sub-subtype A6: In people living with HIV, HIV-1 subtype A6 has been found to be a risk factor for virological failure in studies of long-acting CAB/rilpivirine (7, 8). The impact of A6 on efficacy of CAB-LA for PrEP is as yet unknown. However, the increasing prevalence of subtype A6 in Poland and Ukraine(9), and in displaced

populations, may require consideration if CAB -LA is to be used for prevention in populations where subtype A6 is high or confirmed(10)).

9.1.2 Time to protection for CAB-LA

- Plasma cabotegravir concentrations above the in vitro protein-adjusted 90% maximal inhibitory concentration (PA-IC90) provided protection in 97% of male macaques challenged intrarectally and 4x PA-IC 90 provided protection for 90% of female macaques challenged intravaginally with simian HIV (11, 12).
- In Phase 1 trials of healthy human adults, cabotegravir 600mg IM median plasma target levels (>4x PA-IC90) were achieved within three days (first measurement taken at 3 days) after ultrasound guided gluteal injection and reached maximum plasma concentrations with median Tmax at seven days. The target level of >4x PA-IC90 was maintained for eight weeks in 100% of participants (13).
- The CAB-LA tail is approximately one year (12-23% of individuals have detectable levels at 52-60 weeks after injection (13-15), but around 80% have no detectable levels at 24 weeks). Levels of protection for HIV acquisition (>4x PA-IC90) consistently last up to eight weeks since the last injection.
- In a phase I/II study of cabotegravir (with rilpivirine) for treatment of HIV in 23 adolescents aged 12-17, plasma levels were comparable to those observed in RCT of adult patients (16).

10.1.3 Safety for CAB-LA

- **Monitoring**: Based on the clinical trials (17), renal, liver and lipid monitoring are not required for those on injectable cabotegravir.
- **Adverse events:** In HTPN 083 (GBMSM and transwomen), injection site reactions were more common in the CAB-LA arm, reported by 1724 (81.4%) participants compared to 652 (31.3%) in the placebo injection arm and mostly following the first injection. Reactions were mainly mild or moderate and decreased in frequency over time, and of 10,666 reactions in the CAB-LA arm, 6486 (60.8%) were pain and 2530 (23.7%) were tenderness. There were 50 (2.4%) participants on the active arm who permanently discontinued injections due to an injection reaction(4).
- In the HTPN 084 trial, injection site reactions were less commonly reported, with only 38% of participants in the cabotegravir arm reported injection site reactions, vs 10.8% in the placebo injection arm, and no-one discontinued for this reason. Most injection site reactions were reported at the first injection and diminished over time(5).
- There were no differences in grade 2 or 3 adverse events relating to creatinine clearance in HPTN 083 or HPTN 084 for CAB-LA vs TDF-FTC. (HPTN 083 grade 2 AEs 69.6% vs 73.1% and grade 3 AEs 7% vs 8.3% for CAB-LA vs TDF-FTC, respectively, HPTN-084 grade 2 AEs 72.2% vs 74.3% and grade 3 AEs 6.8% vs 7.8%)(4, 5). WHO recommends that renal monitoring is not required for CAB-LA(18).
- There were no differences in grade 3 AEs events of raised AST or ALT in HPTN 083 or HPTN 084. (HPTN-083 ALT 1% vs 1.4% and AST 2.3% vs 3% for CAB-LA vs TDF-FTC,

respectively. HPTN 084 ALT 0.7% vs 0.9% and AST 0.9% vs 0.8% for CAB-LA vs TDF-FTC, respectively)(4, 5). CAB-LA is not active against hepatitis B or hepatitis C.

- **Weight gain:** There is a small, but statistically significant difference in annualised weight gain between CAB-LA and TDF-FTC in HPTN 083 and HTPN 084(4, 5). In HPTN083 (GBMSM, trans women), differences in weight change were largely driven by weight loss in the TDF-FTC group in year 1, thereafter, the weight changes were similar (approximately 1 kg per year in both groups). In HPTN 084 (cis women SSA), 25% of participants were obese (BMI ≥30 kg/m²) at baseline with a mean weight gain of 2 kg/year and no difference by trial arm.
- **Hepatitis status:** Testing for HBV and HCV is indicated with referral for those with positive test results. CAB-LA is not active against HBV and in people who are HBsAg positive TDF-based oral PrEP should be offered as the preferred PrEP option.
- **Pregnancy:** Pregnancy was a contraindication to recruitment into HPTN084 with a requirement to use long-acting contraceptive, however 138 pregnancies were recorded during the study including 63 in the CAB-LA group. No known adverse outcomes were recorded related to CAB-LA(5).
- **Young People:** Safety data is limited in people under 18. In HPTN 084, 52 participants completed up to week 33 injections and three participants stopped CAB-LA for unrelated drug AEs (16).
- **Metabolism**: CAB-LA metabolism is by UGT1A1. Possible drug interactions due to induction of uridine diphosphate glucuronosyl transferase (UGT) 1A1 and 1A9 should be considered when prescribing CAB-LA. These include anticonvulsants and antimycobacterials such as Rifampicin (see Table 6 in the summary of product characteristics)(19). The co-administration of oral antacid products with oral cabotegravir during an oral lead-in period has a theoretical risk of reducing cabotegravir absorption through chelation. The manufacturer advises that Antacid products containing polyvalent cations are to be administered at least 2 hours before or 4 hours after oral cabotegravir(20).
- **Breakthrough HIV infection**: CAB-LA is highly effective at preventing HIV infection. However a total of 5 incident and 15 prevalent infections were observed in the cabotagravir arms of HTPN 083 and 084 combined, of which 6 (all in HTPN 083) were regarded as possible pharmacological failures having evidence of on time CAB-LA injections with adequate CAB-LA levels (21). Long-Acting Early Viral Inhibition (LEVI) Syndrome has been described on CAB-LA PrEP where HIV viral suppression & delayed/diminished Ab expression persisted for months, even after CAB-LA injections were discontinued. Testing with a sensitive RNA assay (30-copy LLOD) detected most infections before INSTI resistance emerged(22, 23)(24)
- **Resistance**: In HPTN 083,(24) INSTI resistance was detected in one of the four baseline infection and four of the nine incident infections (vs NRTI resistance in six incident infections in the TDF/FTC arm). No resistance was detected during the CAB-LA tail. Phenotyping for three of the five INSTI resistance cases were showed one case susceptible to DTG, one case susceptible to BIC and 1 partially susceptible to BIC. Two cases were resistant to CAB, EVG, RAL.

10.1.4 Monitoring on injectable cabotegravir

- FDA and CDC guidance is to conduct an RNA viral load test together with an HIV antigen/antibody test every 8 weeks. This is based on the 62-day delay in diagnosis observed in HPTN083(4)(24) when HIV RNA testing was not conducted in real-time. Incident infections in adherent users of long-acting cabotegravir were very infrequent in the clinical trials, but RNA testing (plus HIV antigen/antibody test) on the day of the switch is recommended. Other tests recommended when starting oral PrEP in the UK (see chapter 6) should also be conducted, although there is no evidence from clinical trials to suggest that ongoing routine renal or hepatic monitoring is indicated.

- CAB-LA users who have only had one injection, or whose due injection was over 8 weeks late, need special consideration regarding the possibility of continuing long-acting cabotegravir in the UK. In HPTN 083 and 084, participants who were 8 or more weeks late for an injection restarted with a 4-week interval between the first two injections before moving to an 8-week interval. A 12-week interval between the first two injections and a 16-week interval for the third and later injections was tolerated in the trial. However, FDA guidance(25) is more conservative and recommends restarting for users who are 4 or more weeks late (allowing a gap of up to 8 weeks between the first two injections, or up to 12 weeks for the third and later). This is the approach recommended in the UK, including RNA testing in addition to an HIV antigen/antibody test at each visit to minimise the risk of delay in diagnosis and consequent integrase inhibitor resistance mutations.

- Detectable HIV RNA whilst on CAB-LA should be urgently recalled for history of adherence, discussion of risk and consideration for ARV intensification. Repeat HIV fourth Ag/Ab testing, HIV RNA and resistance testing (including INSTI resistance) should be undertaken and any concerns of HIV confirmation testing is discussed with imperial.IDRIS@nhs.net. Consider intensification to TDF-FTC or TAF-FTC NRTI backbone and boosted PI and following BHIVA HIV treatment guidelines.

10.2 Dapivirine ring

- The Dapivirine ring is inserted vaginally, has a 24h lead in and releases DPV locally over a month with no systemic release. The dapivirine ring resulted in modest protection (27% and 35% reduction in HIV incidence) when compared to a placebo ring in two randomised controlled trials (1, 2). Although there was evidence of some use in over 80% in both trials, it is likely that consistent correct use was much lower(1). The half-life of dapivirine in vaginal fluids is much shorter than the metabolites of TD-XTC, so continued use after sex without a condom is required for adequate drug levels.
- None of the grade 3 or 4, or serious adverse events reported in RCTs were considered related to study product (dapivirine ring or placebo). In the ASPIRE trial (1), the majority of grade 2 events considered to be related by the clinician were urogenital tract symptoms or signs, although not all affected participants were in the active group. There were no differences in incident sexually transmitted infections between the two groups in this trial.

- Continuing dapivirine ring after breakthrough HIV infection was not associated with resistance in the study arm participants, suggesting that any resistance noted was transmitted and not selected by the dapivirine ring.

10.3 Access to new therapies in UK

- Access to Investigational long acting Cabotegravir for HIV prevention is available outside of the United States. The manufacturer (ViiV) will facilitate access to CAB-LA through a compassionate release scheme. Requests by the treating physician can be made via their website, https://viiv-cu-portal.idea-point.com/. Registration and online request forms are completed.
- The Population Council has taken on responsibility for the International Partnership for Microbicides (https://www.ipmglobal.org/contact-us) and is the point of contact should an individual wish to continue to use the dapivirine ring. This would require applying for a permission to import the ring.

10.4 Switching from dapivirine ring or injectable cabotegravir to oral TD-XTC temporarily or permanently:

- Women using the dapivirine ring who have adhered to the 1-monthly or 3-monthly visit regimen can switch to oral PrEP as soon as the ring is removed, or in anticipation of removal to ensure continuous protection. A fourth generation HIV ELISA test should be taken on the day of the switch, together with any other tests recommended when starting oral PrEP in the UK (see chapter 6).
- Men, women and trans gender populations using long-acting cabotegravir who are established on the 8-weekly regimen can switch to oral PrEP eight weeks after the last injection. In light of the long pharmacokinetic tail for cabotegravir quarterly HIV testing is advisable for 12 months after the last injection, regardless of risk.

10.5 Lenacapavir

Lenacapavir is a potent long acting capsid inhibitor licensed for the treatment of HIV and approved as both oral tablets and solution for subcutaneous injection. Two Phase 3 clinical trials of the use of Lenacapavir as PrEP (PURPOSE 1 and 2), were registered in 2021 and are underway at the time of writing, both are using Lenacapavir as a subcutaneous injection given every 26 weeks (6 months). PURPOSE 1(26) compares subcutaneous Lenacapavir vs TAF-FTC or TDF-FTC in adolescent girls and young women in South Africa and Uganda, and PURPOSE 2(27) compares subcutaneous Lenacapavir vs TDF-FTC in cisgender men, transgender women, transgender men, and gender non-binary individuals who have sex with partners assigned male at birth. Both trials are scheduled to run until 2027. PURPOSE 5 will be recruiting in the UK in 2024.

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Table 4. Efficacy and Effectiveness of new PrEP therapies

Study	Design	Location	Participants (N)	Study population	Participants age/gender/ ethnicity	Primary mode of HIV acquisition	PrEP dosing and comparison	Adherence	Overall effectiveness of PrEP (95% CI) by mITT†	Study quality and risk of bias
RCTs										
ASPIRE(1) (MTN-020)	RCT 1:1	Malawi, South Africa, Uganda, Zimbabwe.	2629	Cis-women	Median age: 26years (IQR: 22-31). African Women 100%	Vaginal	Monthly Dapivirine ring v placebo	Overall rate of retention 85%, no significant difference between the two arms. PK: 82% plasma samples >95pg/ml; 84% returned rings in sub-study <23.5mg and correlation with plasma samples although the range included discordant values including high residual when plasma levels >95 mg/ml.	71/1313 v 97/1313 infections 27% (95% CI 1-46; p=046) Post-hoc analysis >21 years 56% (95% CI 31-71; p<0.001)	Overall rating: Some concerns but not at high risk of bias At least one HIV result was available for 99% participants, with 93% and 88% attending the month 12 and 24 visits respectively. 143 in the intervention group terminated the study early, slightly more than the 129 in the placebo group largely explained by the larger number who declined to participate in the intervention group. Rings were not returned in the first calendar year so no data for this period. No difference in NNRTI resistance mutations: 8/68 (12%) in dapivirine group compared to 10/96 (10%) in placebo
The Ring(2) (IPM-027)	RCT 2:1	South Africa, Uganda.	1959	Cis-women	Mean age: 26years (range 18-45). Black African 99% Other 1%	Vaginal	Monthly Dapivirine ring v placebo	PK: 84% of plasma samples ≥95pg/ml 83% rings ≤ 23.5 mg with at least 73% of participants at all visits fulfilling both criteria	77/1300 v 56/650 infections 31% (95% CI 1-51%; p=0.04) Pre-specified analyses: >21 years 37% (95% CI 3-59%; p=0.43)	Overall rating: Some concerns but not at high risk of bias 97% rings dispensed were returned. No difference overall in NNRTI resistance mutations: 14/77 (18%) in dapivirine group compared to 9/56 (16%) in placebo, but E138A was more frequent in dapivirine group than placebo (12% v 2%)
HPTN 083(3)	RCT 1:1	USA, Latin America, Asia, Africa	4566	Cis-MSM & Transgendered women	Median age: 26 years MSM 87.4% Transgender women 12.5% Unspecified 0.1% Of 1698 US participants,	Rectal	CAB (OLI+LA) & TDF-FTC placebo vs CAB-LA placebo & TDF-FTC	Participant retention 86.5% at 1 year, oral tablet lead in phase 96.6% adherence TDF-FTC subgroup (390), 74.2% tenofovir concentrations >40 ng per mL; 86.0% tenofovir concentrations >0.3ng per mL	13 vs 39 infections Hazard ratio 0.34 (95% CI 0.18-0.62; p<0.001) ***Post hoc*** Removal of baseline infection CAB group HIV incidence 0.37 (95% CI 0.19-0.65) Hazard ratio 0.37 (95% CI 0.19-0.65	Overall rating: No concerns, at low risk of bias. Randomised, with allocation concealment, baseline demographics equal in both arms, analysis using ITT. Outcomes available for ~98% of those randomised

					49.8% identified as black					
HPTN 084(4)	RCT 1:1	Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zimbabwe	3224	Cis-women	Median age: 25 years (IQR 22-30)	Vaginal	CAB LA & TDF-FTC placebo vs CAB LA placebo & TDF-FTC	TDF-FTC subgroup (362), 48% tenofovir concentrations >40 ng per mL.* 64.0% tenofovir conentrations >0.3ng per mL *consistent with daily use	4 vs 36 infections HIV incidence CAB LA 0.2 (95% CI 0.006 – 0.52) vs TDF/FTC 1.85 (95% CI 1.3 – 2.57) Hazard ratio 0.12 (95% CI 0.05-0.31 p<0.0001)	Overall rating: No concerns, at low risk of bias. Randomised, with allocation concealment, baseline demographics equal in both arms, analysis using ITT. At least one HIV result post randomisation available for 98% of those randomised
OLE studies										
HOPE (MTN-025)(5)	OLE	Malawi, South Africa, Uganda, Zimbabwe	1456	Cis-women (ASPIRE extension)	Median age: 31 years (IQR: 27-37). African women 100%	Vaginal	Monthly Dapivirine ring offered	PK: 89% had more than 0.9mg released, indicating at least some use	1342 (92%) uptake at baseline; >79% at each visit with 73% uptake at every visit HIV incidence 2.7 per 100pyrs (95% CI: 1.9-3.8) v counterfactual 4.4 (95% CI: 3.2-5.8)	OLE studies are at inherent increased risk of bias, ROB tool not applicable to these studies. Note that women were older in HOPE, inevitably, and had prior experience of using the ring when they chose to participate. 4.4/100pyrs predicted by simulations based on the placebo group of preceding ASPIRE trial
DREAM IPM032(6)	OLE	South Africa Uganda	931	Cis-women (The Ring extension)	Mean age: 30 years (range 20-50) Black 98.9%	Vaginal	Monthly Dapivirine ring (3 monthly visits for most of the follow-up)		HIV incidence 1.8 per 100pyrs (95% CI: 3.7-5.8)	OLE studies are at inherent increased risk of bias, ROB tool not applicable to these studies. As with HOPE, women were older and had experience of the ring. They were more likely to be married and 76.1% of partners knew about the ring, compared to 54.4% in The Ring trial.

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