British Association for Sexual Health and HIV/British HIV Association guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2025

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With many thanks to Dr Catherine Nieman Sims for her endless support and hard work as BHIVA guidelines coordinator.

Dedication

These guidelines are dedicated to our late colleagues Dr Nick Medland and Dr Mags Portman. They made valuable contributions to the field and both are sorely missed.

Contents

Executive summary

The UK has committed to end transmission of human immunodeficiency virus (HIV) by 2030 [1] and there have been, in recent years, 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, transgender and non-binary people and people who inject drugs often have poorer knowledge of, reduced access to and lower 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 to all those at risk and to areas of and communities within the UK with low as well as high overall HIV prevalence.

In developing the 2025 PrEP guidelines we have purposefully included a new section on PrEP equity. We have also written a new section 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.

Sections 5 to 8 are intended to offer practical guidance in risk assessment, baseline and ongoing management and monitoring while on PrEP, starting and stopping 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 availability of long-acting injectable cabotegravir [4,5] in the near future, we have added a final section (section 10) to support the use of new therapies. The term 'PrEP' as used in the guidelines includes all currently available forms of HIV pre-exposure prophylaxis, including oral tablets, injectable PrEP and the intravaginal ring.

References

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2. UK Health Security Agency. HIV annual data. 2024. https://www.gov.uk/government/statistics/hiv-annual-data-tables (accessed 7th April 2025).
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5. Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. *Lancet* 2022; 399: 1779–1789.

Summary of recommendations

Recommendations for section 3 PrEP equity and access

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 (Grade 1D).
GPPs
• PrEP provision should be commissioned outside of specialist sexual health services including within, but not limited to, community pharmacies, drug and alcohol services, primary care and community settings likely to be accessed by people who would benefit from PrEP, as well as online services. There should be clear governance connections and locally defined referral criteria to specialist level 3 genitourinary medicine services.
• Sexual and reproductive health promotion information should include information and advice about PrEP that is co-designed with communities that would benefit from PrEP and should be targeted at those groups with poorer access to PrEP.
• Organisations working with communities that would benefit from PrEP and/or that deliver outreach work should ensure that information on PrEP is integrated into their work.
• 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 is required of PrEP users (e.g. resources, knowledge and behaviour) 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 section 4 PrEP efficacy and safety

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 GBMSM who are at elevated risk of HIV-acquisition through condomless sex (Grade 1A); • HIV-negative individuals having condomless sex with HIV-positive partners whose plasma viral load is not <200 copies/mL on antiretroviral therapy (ART) (Grade 1A); • Heterosexual men and women at greater risk of HIV acquisition* (see section 5) (Grade 1B). • Transgender women (Grade 1B) and transgender men and non-binary people (Grade 1D) at greater risk of HIV acquisition*; • People who inject drugs and who might share injecting equipment (Grade 1B); • People who, regardless of gender or sexual orientation, are likely to have condomless sex with people at risk of HIV (Grade 2B).
4. We recommend that young people (aged 15–22 years) should be offered PrEP in accordance with their risk (Grade 1A) and that those aged under 18 years should be offered TAF-FTC as PrEP (Grade 1B).

5. We recommend that young people on PrEP should be offered additional support and monitoring to optimise adherence (Grade 1B).
6. We recommend that PrEP using TD alone can be offered to heterosexual men and women if FTC is contraindicated (Grade 1A).
7. We suggest 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 (Grade 2C).
GPPs
• 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.
• Specific reassurance should be given to transgender people that there are no expected drug–drug interactions between PrEP and GAHT.

*Defined as where HIV risk is likely to be in excess of that of the background UK population and where benefit outweighs clinical risk of PrEP [1-3].

Recommendations for section 5 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 (Grade 2B); • People at risk of HIV*(Grade 1A–2C depending on group, see Table 1); • People who, regardless of gender or sexual orientation, are likely to have condomless anal or vaginal sex with people at risk of HIV* (Grade 2B); • People who inject drugs who might share injecting equipment (Grade 1A). PrEP is suitable for the populations, and in the presence of the indicators, shown in Table 1. *Defined as where HIV risk is likely to be in excess of that of the background UK population and where benefit outweighs clinical risk of PrEP (see section 4) [1-3].
When should PrEP be prescribed?
9. We recommend that PrEP should be prescribed for people for whom it is suitable as soon as HIV risk is identified as benefit is immediate and toxicity is uncommon and delayed (Grade 1A).
GPPs
PrEP offer
• PrEP suitability should be considered in people identifying or identified as being at risk of HIV infection. For example, all attendees to sexual and reproductive health services, wherever HIV testing is performed, or where an individual presents for regular or emergency contraception or STI testing.
Reviewing risk–benefit of PrEP
• Regular review of the risks and benefits of PrEP should be undertaken as these can change over time.
Assessment of PrEP suitability

- 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 PEP 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.

Table 1. Populations or indicators associated with suitability for PrEP

PrEP is suitable for the following:
Populations • GBMSM (Grade 1A) [7,8] • Black African men and women (Grade 1A) [7,8] • Transgender women (Grade 1A) [7,8] • Recent migrants (Grade 1D) [10] • People who inject drugs (Grade 1A) [7,8] • People who report sex work or transactional sex (Grade 1A for GBMSM and transgender women, Grade 2C for female sex workers [7,8,11]
Behavioural and personal indicators • Condomless anal or vaginal sex with one of the groups listed above (Grade 2D) • Condomless anal or vaginal sex where a sexual partner may have undiagnosed or untreated HIV infection (Grade 1A) [12,13] • Chemsex or group sex (Grade 1B for GBMSM) • Injecting drug use using shared equipment (Grade 1A) [7,8] • Travel to countries with high HIV prevalence where sex with people from those countries is likely (Grade 2D)
Other clinical markers • Other STI (Grade 1C) [9] • Hepatitis C virus (HCV) infection (Grade 1C) [9] • PEP use (Grade 1C) [14]
Injecting drug use • Injecting in an unsafe setting, sharing injecting equipment or limited access to needle and syringe programmes or opiate substitution treatment (Grade 1A) • Sexual risk in people who use drugs (Grade 1A)
Reduced sexual health autonomy • Drug and alcohol use (Grade 2D) • Safeguarding, consent and vulnerability issues (Grade 2D) • Inability to negotiate and/or use condoms (or employ other HIV prevention methods) with sexual partners (Grade 2D) • Coercive and/or violent power dynamics in relationships (e.g. intimate partner/domestic violence) (Grade 2D) • Precarious housing or homelessness and/or other factors that may affect material circumstances (Grade 2D)

- Risk of sexual exploitation and trafficking (Grade 2D)

** 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 PEP use after sexual exposure in GBMSM [14]), reported/likely sexual behaviour and drug use and vulnerability factors affecting sexual autonomy.

Recommendations for section 6 Baseline testing and clinical management

HIV testing
10. We recommend that baseline HIV testing with a combined antigen/antibody serology test is undertaken prior to commencing PrEP (Grade 1A).
11. We recommend that PrEP can be initiated while awaiting the result of a laboratory HIV antigen/antibody test unless there are symptoms suggestive of HIV seroconversion (Grade 1A); in individuals at ongoing high risk who have not had a laboratory HIV test in the last 45 days, a blood-based point-of-care test (POCT) may be indicated (Grade 1A).
12. We recommend that people 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 (Grade 1C). Atypical testing results should be discussed with a regional expert (Grade 1C).
STI and blood-borne virus testing
13. We recommend that testing for STIs should be undertaken at baseline (Grade 1B).
14. We recommend that testing for HBV should be undertaken at baseline according to local screening protocols (Grade 1A).
15. If there is no evidence of current or previous infection or immunity, we recommend that HBV vaccination should be offered (Grade 1A).
16. Oral PrEP may be started pending results of hepatitis B surface antigen (HBsAg) testing, but results should be reviewed at the earliest possible time as TD-FTC and TAF-FTC are active against HBV (Grade 1A).
17. We recommend that individuals with HBV infection should be referred for assessment including need for HBV treatment according to national guidelines (Grade 1A).
18. We suggest that for individuals with HBV but not requiring treatment for HBV, daily oral PrEP would be the preferred option, but event-based oral PrEP can also be offered (Grade 2C).
19. We recommend that individuals with chronic HBV should be counselled that there is a potential risk of HBV reactivation if PrEP is stopped, and that following PrEP discontinuation they will require monitoring with HBV DNA and liver function tests for 12 months if not on other HBV treatment (Grade 1C).
20. We recommend that testing for HCV should be undertaken at baseline in GBMSM and other at-risk groups; if positive, the individual should be referred to specialist services for further investigation and consideration of early direct-acting antiviral (DAA) treatment (Grade 1B).
Renal function (see Flowchart 1)
21. We recommend that serum creatinine level and eGFR should be determined at baseline (Grade 1A). 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, and PrEP can be commenced while waiting for the results (Grade 1A).
22. We suggest that eGFR for individuals starting TD-FTC should be ≥60 mL/min/1.73 m^2 (Grade 2A).
23. We recommend that if eGFR ≥90mL/min/1.73 m^2 at baseline and the person is aged <40 years, with no risks for renal disease, then annual eGFR testing should be conducted (Grade 1A).

24. We suggest that if eGFR is ≥90 mL/min/1.73 m^2 at baseline and the person is ≥40 years or has risks for renal disease, then eGFR should be repeated at 6 months (Grade 2B).
25. We suggest that if eGFR is between 70 and 89 mL/min/1.73 m^2 at baseline, risks for renal disease should be assessed, reduced exposure to oral PrEP should be considered (e.g. with event-based or intermittent dosing of oral PrEP) and eGFR repeated at 3 months; where renal function is stable, monitoring can continue every 6–12 months (Grade 2B).
26. We suggest that if eGFR is 60–69 mL/min/1.73 m^2 at baseline, eGFR should be repeated in 2–4 weeks, having stopped any creatine/protein supplements, risks for renal disease should be assessed and reducing exposure to oral PrEP should be considered with event-based or intermittent dosing (Grade 2B). Where renal function is stable, monitoring can continue every 6 months.
27. We recommend that individuals with an eGFR between 30 and 60 mL/min/1.73 m^2 at baseline should have the full assessment recommended in Flowchart 1 and are recommended TAF-FTC PrEP (Grade 1A).
Bone function
28. We recommend that oral PrEP recipients should be informed of the risk of reduction in BMD of approximately 1.5–2% at the hip and spine following 48 weeks of TDF-FTC PrEP (Grade 1B) but that there is no evidence of an increased risk of fractures while taking PrEP (Grade 1A).
29. We recommend that all oral PrEP recipients should be assessed for markers of increased absolute fracture risk, including previous fracture(s) at the wrist, spine or hip, smoking, high alcohol intake, menopause and high-dose oral or systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for ≥3 months), or other causes of secondary osteoporosis (Grade 1D).
30. We recommend that those aged under 18 years should be offered TAF-FTC as PrEP (Grade 1B).
31. We recommend that in those aged ≥50 years and/or with risk factors for osteoporosis, fracture risk should be calculated using the QFracture® or FRAX® online assessment calculators (Grade 1B). Those at high risk (risk score >10%) should be offered a DXA scan [1] (Grade 1C).
32. We suggest that in people with markers of increased fracture risk and/or with confirmed osteoporosis on DXA scanning (see GPPs below) who require continuous daily oral PrEP, alternatives to TD-FTC PrEP (currently TAF-FTC only) should be advised (Grade 2B).
33. We suggest 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 (Grade 2C).
Pregnancy
34. We suggest that if an individual is pregnant when starting PrEP and there is an ongoing risk of HIV acquisition, PrEP should be continued during pregnancy and breastfeeding, after discussing the potential risks of TD-FTC (Grade 2B).
GPPs
• PrEP should be offered as part of a package of care including condom provision, regular HIV and STI testing and monitoring of renal function.
• People who could benefit from PrEP should be informed of the evidence for the effectiveness and safety of PrEP.
• 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.
• The possibility of reduced renal function with TD-FTC should be discussed with individuals who have pre-existing chronic renal disease or risk factors for renal disease (diabetes, hypertension, >40 years of age or eGFR <90 mL/min/1.73 m^2).

• 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 20 years of age.
• Routine monitoring of BMD is not recommended in individuals taking PrEP with no other risk factors for reduced BMD.
• 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.
• People at low risk (risk score <10%) should not be offered a DXA scan, but given lifestyle advice and fracture risk checked annually while on PrEP.
• Vitamin D and calcium supplementation should be recommended to PrEP recipients of all ages with risk factors for reduced BMD, particularly those under the age of 25 years.
• PrEP initiation in the presence of a negative blood POCT and absence of symptoms of acute HIV infection should not be delayed while awaiting laboratory or confirmatory results.
• Access to PrEP among people at high risk of HIV infection is not delayed; wherever possible aim to initiate on the day of testing. At the time of PrEP initiation, all tests should be undertaken, results reviewed as soon as possible and PrEP prescription modified accordingly once results become available.
• We suggest that clinicians remain alert to acute HIV infection among 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 for pregnancy should be conducted in women and other people who can get pregnant who are not using reliable contraception, if indicated.
• Adverse events should be reported through the yellow card scheme (https://yellowcard.mhra.gov.uk/).

Recommendations for section 7 On-going clinical management and monitoring

HIV testing
35. We recommend that HIV testing should be undertaken every 3–6 months for people taking PrEP with a laboratory combined HIV antigen/antibody test (Grade 1A) or a blood-based POCT (Grade 1B).
36. Following the discontinuation of PrEP, we recommend retesting for HIV 45 days after the last risk (Grade 1B).
37. In the presence of indeterminate HIV test results, for people having reported use of intermittent PrEP or PEP, we recommend serology with samples being sent to the reference laboratory at the UKHSA for detailed analysis, including western blotting and HIV DNA testing. We recommend continuation of PrEP until results of additional HIV testing is known. In complex cases we recommend referral to the UKHSA/IDRIS clinic for expert review (imperial.idris@nhs.net) (Grade 1B).
38. We recommend baseline resistance testing for people with confirmed primary HIV infection, to look for evidence of resistance-associated mutations to tenofovir or FTC along with other transmitted mutations (Grade 1B).
STI and blood-borne virus testing and management
39. We recommend 3-monthly STI screening (chlamydia, gonorrhoea and syphilis) for people taking PrEP who have new or multiple sexual partners (Grade 1A).
40. We recommend that GBMSM and others at ongoing risk should be screened using HBV serology annually if they have not been vaccinated (Grade 1B).
41. We recommend that referral to specialist care should be made for follow-up care and management of active HBV infection and assessment of the need for HBV treatment

(Grade 1A).
42. Where oral PrEP is stopped in individuals with chronic HBV who are not on treatment for HBV, we recommend regular testing with HBV DNA and aminotransferases for 12 months following discontinuation of PrEP (Grade 1C).
43. We recommend that GBMSM and others at ongoing risk should be screened for HCV in line with hepatitis testing guidelines [1,2]; if positive, the individual should be referred to specialist services for further investigation and consideration of early DAA treatment (Grade 1B).
Testing and management of renal function (see Flowchart 1)
44. We recommend ongoing monitoring of renal function with serum creatinine and eGFR (Grade 1A).
45. We recommend that if eGFR remains ≥90 mL/min/1.73 m^2 and the person is aged <40 years with no risks for renal disease, eGFR should be assessed annually (Grade 1A).
46. We suggest that if an individual experiences 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 (Grade 2B).
47. We suggest that where a significant drop in eGFR is experienced, it is confirmed with the CKD-EPI 2021 equation to calculate creatinine clearance (Grade 2B).
48. We suggest that if a significant drop in eGFR is not confirmed with the CKD-EPI 2021 equation, eGFR is repeated at 3 months and renal monitoring continued every 6–12 months (Grade 2B).
49. We suggest that if eGFR is between 70 and 89 mL/min/1.73 m^2 while taking PrEP, risks for renal disease should be assessed, reduced exposure to TD with event-based or TTSS dosing considered, and eGFR repeated at 3 months. Where renal function is stable, monitoring can continue every 6–12 months (Grade 2B).
50. We suggest that if eGFR is 60–69 mL/min/1.73 m^2 while taking PrEP, eGFR should be repeated in 2–4 weeks, having stopped any creatine/protein supplements, to assess the risk of renal disease and reducing exposure to TDF should be considered with event-based or TTSS dosing. Where renal function is stable, monitoring can continue every 6 months (Grade 2B).
51. We recommend that if eGFR is <60 mL/min/1.73 m^2, the risks and benefits of continuing PrEP should be assessed on a case-by-case basis. Local MDT advice should be sought to determine the need for further investigations and frequency of monitoring (Grade 1C)
52. Individuals with an eGFR <60 mL/min/1.73 m^2 should be recommended TAF-containing PrEP (Grade 1A)
53. We recommend that that if eGFR <60 mL/min/1.73 m^2, the risks and benefits of continuing PrEP should be assessed on a case-by-case basis. Specialist renal input should be obtained to determine further investigations and frequency of monitoring (Grade 1C)
Changing PrEP and weight gain
54. We recommend that individuals switching from TD-FTC (or CAB-LA) to TAF-FTC PrEP should be advised of the possible risk of modest weight gain compared to TD-FTC, due to the suppressive effect of TD on weight (Grade 1B).
Testing and management of bone function
55. We suggest that for individuals with markers of increased fracture risk and/or with confirmed osteoporosis on DXA scanning (see GPPs below) who are taking continuous daily PrEP, alternatives to TD-containing PrEP (currently TAF-FTC only) should be advised (Grade 2B).
56. We suggest 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 (Grade 2B).
57. We recommend that in those aged ≥50 years and/or with risk factors for osteoporosis, fracture risk should be calculated annually using the QFracture® or FRAX® online assessment

calculators (Grade 1B).
58. We recommend that people at high risk (risk score >10%) should be offered a DXA scan to confirm osteoporosis according to local guidance and referral pathways (Grade 1C).
59. 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 according to local guidance and referral pathways (Grade 1A).
60. We recommend that people with osteoporosis who are at high risk of fractures should be switched to TAF-FTC (Grade 1B).
61. We recommend that people at low risk (risk score <10%) should not be offered a DXA scan but given lifestyle advice and fracture risk checked every 3 years while on PrEP (Grade 1B).
Pregnancy
62. We suggest that individuals who becomes pregnant while on PrEP should continue PrEP during pregnancy or breastfeeding if there is an ongoing risk of HIV acquisition, after discussing the potential risks of TD-FTC (Grade 2B).
GPPs
• PrEP should be offered as part of a package of care that includes comprehensive sexual and reproductive healthcare services.
• PrEP should be supplied according to the testing and monitoring guidance outlined in these guidelines, but the need for STI testing or toxicity monitoring should not be a barrier to PrEP resupply. Supply should never be contingent on testing or monitoring [3].
• Healthcare professionals should remain alert to acute HIV infection among people at risk of HIV, particularly in the presence of any symptoms which are often non-specific in nature, and counsel and manage accordingly.
• Pregnancy status should be assessed in those not using reliable contraception if indicated.
• 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 there are 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 used to assess the need for a DXA scan and potential treatment for reduced BMD.

Recommendations for section 8.1 Starting and stopping TD-FTC and TAF-FTC PrEP

63. We recommend that continuous daily dosing of oral PrEP can be used by all individuals for all types of exposure (TD-FTC and TAF-FTC, Grade 1A).
64. 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 2 days after the last risk (includes 2:1:1 event-based dosing) (TD-FTC, Grade 1A; TAF-FTC, Grade 1B).
65. We recommend that, if the risk of HIV acquisition is through insertive vaginal/neovaginal/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 2 days after the last risk (includes 2:1:1 event-based dosing) (TD-FTC: insertive anal sex, Grade 1A; insertive vaginal/neovaginal sex, Grade 1B; TAF-FTC: insertive anal/vaginal/neovaginal sex, Grade 1B).
66. 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 7 days after the last risk (includes 2:7 event-based dosing)

(TD-FTC and TAF-FTC: receptive vaginal sex, Grade 1C; receptive neovaginal sex, Grade 1D).
67. 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 risk and safely stopped with single dose daily for 7 days after the last risk (includes 2:7 event-based dosing) (TD-FTC and TAF-FTC, Grade 1C).
GPPs
• Taking the initial dose of PrEP with food may reduce gastrointestinal side effects and increase total drug absorption (AUC) of TDF by approximately 40% and of TAF by 60%.
• It is important to stress that for event-based dosing for receptive vaginal/neovaginal sex and injecting drug use, users need to continue TD-FTC PrEP for 7 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 (i.e. when four or more doses have been taken in the week prior to an exposure), four doses per week in subsequent weeks are likely to provide good protection for all types of risk exposure. TTSS dosing may be an option for all users for all types of exposure, where reduced dosing is indicated for toxicity reasons and event-based dosing is not suitable.
• 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 within the 2- to 24-hour window period. The second tablet should be taken at least 2 hours before risk.

Recommendations for section 8.2 PEP in PrEP users

Sexual risk* through condomless anal sex/insertive vaginal sex
68. We recommend that if the risk of HIV acquisition is through condomless insertive or receptive anal sex or insertive vaginal or neovaginal sex, and if ≤7 days have elapsed since the last oral PrEP dose, PrEP should be resumed with a double dose as prescribed** (Grade 1B).
69. We recommend that if more than 7 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 24 hours (Grade 1B) after exposure and no later than 72 hours (Grade 2C), and continued daily while seeking advice from clinical services on possible intensification to PEP.
Sexual risk* through condomless receptive vaginal/neovaginal sex
70. We recommend that if the risk of HIV acquisition is through condomless receptive vaginal or neovaginal sex, and if ≤3 days have elapsed since the last oral PrEP dose, PrEP should be resumed with a double dose as prescribed (vaginal, Grade 1B; neovaginal, Grade 2C).
71. We recommend that if more than 3 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 24 hours after exposure (vaginal, Grade 1B; neovaginal, Grade 2C) and no later than 72 hours (Grade 2C), and continued daily while seeking advice from clinical services on possible intensification to PEP.
Blood-borne risk for people who inject drugs
72. We recommend that, if the risk of HIV acquisition is through injecting drug use and if ≤4 days have elapsed since the last oral PrEP dose, PrEP should be resumed with a double dose as prescribed (Grade 1D).

73. We recommend that, if more than 4 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 24 hours after exposure and no later than 72 hours, and continued daily while seeking advice from clinical services on possible intensification to PEP (Grade 1D).
Missed post-coital dose for event-based PrEP
74. We recommend that, for event-based (2:1:1) 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 (Grade 1B); the second post-coital dose should be taken 24 hours after the first to complete the course.
75. We recommend that if more than 48 hours have elapsed after the last risk or for 2:7 dosing, the first dose should be taken and daily dosing continued until advice is sought from clinical services (Grade 1B).
GPPs
• PrEP users should routinely be given advice about what to do in the event of an HIV risk, with or without PrEP medication available.
• It is important that PrEP users understand that PrEP and PEP only reduce the risk of HIV acquisition when medication 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.
• PEP should be considered if there has been significant risk exposure within the preceding 72 hours at the point of first initiating PrEP. If there are two or more risk episodes more than 72 hours before initiation, so PEP is not indicated, PrEP should be initiated with HIV testing as recommended in section 6.3.
• PrEP users should be informed about how to access PEP advice in a timely manner.

*Sexual risk: no condom, partner not on suppressive ART or PrEP.

**We recommend that when PrEP tablets are started or restarted after an exposure, the initial dosing regimen is used. This means that a double-dose start should be used in every case. We acknowledge that for people having insertive or receptive anal sex, or insertive vaginal or neovaginal sex, the prescribed starting dose if a PrEP tablet has been taken within the last 7 days would be a single tablet dose (as per the 'IPERGAY regimen'; see Table 2). The need for a double dose will depend on the type of exposure, the time elapsed since exposure (up to 72 hours) and the absolute number of doses taken in the preceding 7 days. Where a total of four or more tablets have been taken in the last 7 days, it is likely that levels will be protective with an additional single tablet but for consistency and given the lack of direct evidence in this area, we suggest that a double dose is used routinely.

Recommendations for section 9 Buying generic PrEP online

76. We recommend that clinicians should ensure full PrEP support, including renal monitoring, for individuals who are taking oral PrEP that they have sourced online (Grade 1D).
77. We recommend that therapeutic drug monitoring is **not** required for those taking self-sourced oral PrEP (Grade 1B).
For those self-managing their PrEP use
78. We recommend that HIV testing with a laboratory antigen/antibody test is undertaken prior to commencing oral PrEP, which can be provided through self-sampling (Grade 1A).
79. We recommend that 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 (Grade 1A) or a blood-based POCT (Grade 1B).
80. Self-testing for HIV (using saliva or blood samples) is not recommended for people at

initiation of PrEP and ongoing regular monitoring should be undertaken with blood-based combined HIV antigen/antibody self-sampling or clinic-based testing (Grade 1B).
GPPs
• Clinicians can signpost individuals to IWantPrEPnow or PrEPster if they are unable or unwilling to access PrEP on the NHS. These sites offer support and advice and the ability to source generic drugs as safely as possible.
• The discussion of self-sourcing PrEP online needs to be fully informed including the risks and benefits described in section 4 and section 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 Food and Drug Administration (FDA) and that it is advisable to order in advance in case of delays in delivery.
• Clinicians should recommend that people buying TD-FTC or TAF-FTC ensure that they 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 these guidelines.

Recommendations for section 10 New therapies

81. We recommend that CAB-LA should be offered under compassionate release to those at risk of HIV, but who have contraindications to oral PrEP options (Grade 1A).
82. We recommend that CAB-LA is strongly supported as an alternative to a daily PrEP pill (Grade 1A).
83. We suggest that an oral lead-in for CAB-LA as PrEP is optional for people worried about side effects (Grade 2B).
84. We recommend that 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 (Grade 1B).
85. We recommend that people are advised that protective levels of CAB-LA are achieved 7 days following the first injection (Grade 1A).
86. We recommend that the second CAB-LA injection is given a month after the first (Grade 1A).
87. We recommend that people are advised that protective levels of CAB-LA are maintained for 2 months after the second and subsequent injections (Grade 1A).
88. We recommend that people on CAB-LA have both HIV antigen/antibody and HIV viral load testing every 8 weeks (Grade 1A).
89. We recommend that when CAB-LA is discontinued and risk of HIV continues, an alternative PrEP agent is initiated, starting at 2 months and continuing to at least 12 months after the last CAB-LA injection or as long as risk continues (Grade 1B).
90. We recommend that routine renal, liver and lipid monitoring are not required for those on CAB-LA for PrEP (Grade 1A).
91. 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 (Grade 1A).
92. We recommend that CAB-LA should be avoided in people taking certain anticonvulsants (e.g. carbamazepine and phenytoin) and anti-mycobacterial agents such as rifampicin and rifabutin as drug–drug interactions with these medications significantly reduce

cabotegravir plasma concentrations to subtherapeutic levels (Grade 1C).
93. We recommend that a monthly 25 mg dapivirine ring provides a modest, but significant, reduction in HIV incidence in women for whom alternative forms of PrEP are unacceptable or unsuitable [1,2] (Grade 1A).
GPPs
• People considering switching from TD-FTC to CAB-LA should be advised of the risk of modest weight gain due to removal of the weight gain suppressive effect of TD-FTC. Individuals initiating CAB-LA who are PrEP naïve, or switching from non-TD-FTC-based PrEP (such as TAF-FTC), should expect similar weight trajectories to the general population.
• Where individuals are already established on new PrEP therapies on arrival in the UK, clinicians should endeavour 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.

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 human immunodeficiency virus (HIV) acquisition. We also aim to provide guidance to address the inequities of knowledge and uptake of and access to PrEP for groups and communities that would benefit from PrEP but remain underserved. The guideline development process was underpinned by a specific focus on access to and equity of PrEP provision, recognising that clinical guidelines can inform but not define standards or parameters for service delivery or commissioning.

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

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

1.1 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 'gay, bisexual and other men who have sex with men' (GBMSM) refers 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 that 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'.

1.2 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.

2 Methods

2.1 Search strategy

- All members of the writing group underwent training in the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. A comprehensive literature review of PrEP and HIV prevention was conducted using the PICO (Population, Intervention, Comparison, Outcome) question shown below.

- PICO questions were set as:
  - POPULATION: HIV negative;
  - INTERVENTION: PrEP;
  - COMPARISON: no specific comparators were applied to avoid limiting the search;
  - OUTCOMES: HIV infection, sexually transmitted infections (STIs), adverse events, risk behaviours or risk compensation (condom use or number of sexual partners), adherence.

- The formal literature search was from 1 January 2016 to April 2021. Medline, Embase and the 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. Abstracts from the following conferences were also searched: Conference on Retroviruses and Opportunistic Infections (CROI), International AIDS Society (IAS), British HIV Association (BHIVA), HIV Research for Prevention (HIV4P), European AIDS Clinical Society (EACS) and HIV Glasgow.
- In addition, although the formal literature review was not repeated, evidence published between April 2021 and January 2025 that the writing group felt was relevant has been included in these guidelines.

2.2 GRADE system

- The strength of evidence is graded as 1 or 2.

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

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

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

- The quality of evidence is graded from A to D.

- **Grade A** evidence is high-quality evidence 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 is moderate-quality evidence from randomised trials that suffer 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 (GPPs)

- The writing group has also included GPPs, in addition to graded recommendations. GPPs are recommendations based on the clinical judgement and experience of the writing group and feedback from the community and public consultation. GPPs emphasise an area of important clinical practice for which there is not, nor is there likely to be, any significant research evidence. They address an aspect of treatment or 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 Writing group, stakeholder involvement and feedback

- The recommendations are the result of a series of virtual meetings of the writing group and a meeting of community activists and organisations in June 2023 at which comments on a draft of the guidelines were received. The draft guidelines have been reviewed by the BASHH Clinical Effectiveness Group (CEG); members of the group have ultimate editorial responsibility for the guidelines, in line with the methodology described in the CEG Framework for Guideline development published on the BASHH website: https://www.bashh.org/professionals/bashh_groups/39/clinical_effectiveness_group/public/. The writing group also reviewed and incorporated input from the public consultation process.

- The writing group included representation from Terrence Higgins Trust, The Love Tank, National AIDS Trust and Africa Advocacy Foundation. 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. Formal public consultation on the draft guidelines was undertaken from 27th September 2024 to 26th November 2024. All comments received were reviewed and addressed. We acknowledge and thank all individuals and community organisations for their helpful contributions.

2.4 Terminology

2.4.1 PrEP

- The term 'PrEP' as used in the guidelines includes all currently available forms of HIV pre-exposure prophylaxis, including oral tablets, injectable PrEP and the intravaginal ring. The level of detail included on individual preparations depends upon the current and anticipated level of use in the UK.

- Routine availability in the UK depends on a number of regulatory and structural factors including Medicines and Healthcare products Regulatory Agency (MHRA), National Institute for Health and Care Excellence (NICE) and Scottish Medicines Consortium (SMC) approval, national and regional commissioning and procurement arrangements for NHS provision and/or cost and availability of self-sourced medication.

- However, uncertainty about the criteria for availability of cabotegravir PrEP in England and Wales persisted through and beyond the guideline consultation period and significant new evidence was presented after the extended literature review period for the guidelines (January 2024). Cabotegravir for PrEP was approved for use in the UK by the MHRA in May 2024 [1,2] and the SMC approved cabotegravir PrEP in February 2025 [3]. At the conclusion of the guidelines process routine availability remained unclear; for this reason cabotegravir use is addressed in an individual section but indications and use of cabotegravir are not included in every section of the guidelines.

2.4.2 Generic preparations of tenofovir disoproxil

- The writing group recognises that although clinical trials of oral PrEP have used tenofovir disoproxil fumarate (TDF), other salts of tenofovir disoproxil (including maleate, succinate and phosphate) in generic formulations are now widely 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 (FTC). We use the acronym TAF-FTC to describe the use of tenofovir alafenamide fumarate and emtricitabine (Descovy) as PrEP, and TD-XTC when referring to combinations in which tenofovir disoproxil salts are combined with FTC or lamivudine (3TC). TFV-DP refers to tenofovir diphosphate, the active cellular metabolite of both TD-XTC and TAF-FTC measured in pharmacokinetic (PK) and pharmacodynamic (PD) studies and FTC-TP refers to emtricitabine triphosphate, the phosphorylated cellular anabolite of FTC.

2.4.3 PrEP dosing options

- 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);
  - **TTSS**, which refers to taking four oral doses of PrEP per week i.e. one tablet on a Tuesday, Thursday, Saturday and Sunday;
  - **Event-based dosing** (sometimes called event-driven or on-demand dosing), which has previously referred to dosing based on the IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les Gays) trial dosing regimen. This involves taking two tablets 2 to 24 hours before risk and one tablet 24 and 48 hours following the initial double dose, and is also known as '2:1:1' dosing;
  - **A new option: 2:7 dosing**. In these guidelines we also include 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.

- If an event-based course has been completed within the preceding 7 days (effectively '1:1:1' dosing), the IPERGAY regimen allows for an event-based regimen including **one** tablet 2 to 24 hours before risk and one tablet 24 and 48 hours following the initial double dose; however, this terminology is not commonly used.

- The concept of recommending initiating or restarting oral PrEP after an episode of possible exposure as a fallback option has not previously been widely discussed. Although use in this context is clearly no longer *pre-exposure* prophylaxis, for clarity we have reserved the terms 'PEP' and 'post-exposure prophylaxis following sexual exposure (PEPSE)' for the prescribing of three antiretroviral agents (usually TD-FTC and raltegravir at present in the UK) after an episode of risk. We have used the term 'PEP' throughout, to include post-exposure prophylaxis for sexual and all other types of exposure, except in those cases where we refer to sexual exposures only.

2.4.4 Exposure and risk

- 'Exposure' and 'risk' with respect to HIV transmission include condomless sex, and the sharing of needles and/or injecting equipment, with a person with unknown HIV status who is not taking PrEP, or who is living with HIV and has a viral load >200 copies/mL.

2.4.5 Condomless sex

- Condomless sex as referred to in these guidelines includes penile, vaginal, neovaginal or anal sex without using either a male or female condom. 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.

2.5 References

1. Medicines and Healthcare products Regulatory Agency. Press Release: New cabotegravir formulations approved to help prevent HIV-1 infection in adults and adolescent. 3 May 2024. Available at: https://www.gov.uk/government/news/new-cabotegravir-formulations-approved-to-help-prevent-hiv-1-infection-in-adults-and-adolescents (accessed 25th April 2025).
2. emc. Apretude 600 mg prolonged-release suspension for injection. Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/15696/smpc (accessed 25th April 2025).
3. Scottish Medicines Consortium. Cabotegravir (Apretude). February 2025. https://scottishmedicines.org.uk/medicines-advice/cabotegravir-apretude-full-smc2718/ (accessed 25th April 2025).

3 PrEP equity and access

Recommendations for PrEP equity and access
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 (Grade 1D).
GPPs
• PrEP provision should be commissioned outside of specialist sexual health services including within, but not limited to, community pharmacies, drug and alcohol services, primary care and community settings likely to be accessed by people who would benefit from PrEP, as well as online services. There should be clear governance connections and locally defined referral criteria to specialist level 3 genitourinary medicine services.
• Sexual and reproductive health promotion information should include information and advice about PrEP that is co-designed with communities that would benefit from PrEP and should be targeted at those groups with poorer access to PrEP.
• Organisations working with communities that would benefit from PrEP and/or that deliver outreach work should ensure that information on PrEP is integrated into their work.
• 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 is required of PrEP users (e.g. resources, knowledge and behaviour) 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 and access

3.1 Inequity in PrEP awareness and access

- PrEP uptake has been highest among GBMSM across the UK since the beginning of its provision through NHS services (and in PrEP trials) [1,2]. PrEP has a significant impact on reducing new HIV infections in this group [3]. This inequity has continued despite some evidence of increases in uptake in other demographic and risk exposure groups [4,5]. Poor and uneven awareness and uptake of PrEP in the UK, and internationally, has been reported among racially minoritised individuals [6,7], transgender and non-binary communities, heterosexual women [8] and men, and younger gay and bisexual men [1,9,10]. Access and uptake are significantly constrained by health and socioeconomic disparities and geographical differences.

- 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 for those wanting to start PrEP for the first time [11]. This lack of capacity/availability is a major factor influencing individual decisions to self-source and self-fund PrEP, which is not an option available to those impacted by socioeconomic difficulties. There are limited data on awareness of and access to PrEP by those who take part in practices that are highly stigmatised and often criminalised, such as sex work and injecting drug use [12,13]. These groups are known to be disproportionately affected by higher rates of HIV infection, later HIV diagnoses and poorer health outcomes [8]. 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.

Box 1. Key groups currently under-represented among NHS PrEP users

- Black African and Black Caribbean communities
- Queer communities of colour (including Black, Brown, Latinx and other groups)
- Migrant communities
- Transgender 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 in any other key groups)
- Men who have sex with men who do not 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 [14]. Issues of equity should be considered at each stage of the PrEP care continuum: *settings; access; awareness; knowledge; uptake; and retention.* Providers should review and address barriers to PrEP equity according to these issues.

1. Settings: identify and address barriers within PrEP-related settings, including the physical space, experience of new users and marginalised communities, collection of data on exclusion and lack of connection 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 marginalised communities that 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 among all practitioners and potential PrEP users.

6. Retention (adherence and support): develop targeted strategies to support PrEP initiation and sustained use that work for marginalised groups with higher rates of discontinuation such as those of lower socioeconomic status, people who use drugs and younger people.

3.2.1 Settings

- Settings in which 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 marginalised 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 them, thereby risking being deported or imprisoned. Cultural factors and stigma surrounding 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, affordability and adequacy are all important considerations.

    - *Accessibility* means 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 people's homes, means of access (such as online/phone/drop-in) and availability (enough capacity to address need).

    - *Affordability* means balancing the effort spent in accessing and using services with the existing time and resource constraints affecting potential PrEP users.

    - *Adequacy* means access to health workers who are equipped to consider and address the needs of all individuals who might benefit from PrEP.

- Evidence from PrEP implementation programmes [14,15], pilots [16-18] and research with communities [19-21] suggests that offering multiple ways of accessing a PrEP service can increase equity. Online booking systems may provide more flexibility and privacy for young adults living at home with their families. Telemedicine clinics and online PREP services with clinical assessment (including renal monitoring) and drug delivery are being piloted and offer benefits in terms of convenience and efficiency, but

alternatives are required to address digital exclusion. 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, from accessing 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 groups. An opportunistic approach to starting PrEP, ensuring that PrEP assessment and initiation can be undertaken as part of a range of sexual health consultations, is possible and could be extended to other settings.

- Physical distance and/or limited financial resources can restrict 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 where PrEP is usually provided. Local general practitioner (GP)- and pharmacy-based PrEP provision, which can range from medication collection to PrEP assessment and initiation, remains relatively limited and may also help to address geographical isolation [11,13,22].

3.2.3 Awareness

- Awareness of PrEP is influenced by age, sex, gender, sexual orientation, proximity to HIV, race and geography [23]. It is also affected by social norms within communities where PrEP is, or is not, discussed and used, and wider community networks [7,24]. In marginalised communities that 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 [25] 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 marginalised communities [26]; and
  - Integrating PrEP information and provision into existing generic services [27].

Case study 1: creating PrEP awareness pathways

Josef is a 27-year-old man 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 the GP that 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 in 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 the intention of 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 the healthcare system in unfamiliar settings.

3.2.4 Knowledge

- PrEP knowledge goes beyond awareness and the provision of information. PrEP literacy [28,29] 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 the capacity to apply learned PrEP information within their sexual and social lives;
  - Have the capacity to engage with others about PrEP information and related sexual behaviours.

Case study 2: supporting PrEP knowledge and 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 but is uncontactable for partner notification. He is HIV negative. He presents 8 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 by 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.

3.2.5 Uptake (candidacy)

- Candidacy is the process through which individuals identify themselves as candidates for particular interventions [30]. Awareness and knowledge may not be enough to convince people or health practitioners of their candidacy for PrEP. For example, a study in transgender women reported 82% PrEP awareness, but only 27% of participants had ever taken PrEP [20,31].

Risk assessment by the individual

- People not seeing themselves as candidates for PrEP may be attributed to poor understanding of their personal risk of HIV or inaccurate risk assessment. This could

include not recognising 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 such as gender-affirming hormone therapy (GAHT).

Risk assessment by the practitioner

- Not all health practitioners will consider people as potential PrEP users. This may be because:
  - They do not appear to be members 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 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: recognising 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 emerges 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 decides 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 marginalised communities mitigated the barriers to access for this person.

3.2.6 Retention (adherence and support)

- Adherence and support in sustaining PrEP use may be seen as 'more challenging' for PrEP users from marginalised communities and may affect PrEP prescribing practices [32]. In a study of PrEP users, discontinuation of PrEP remained high among those of lower socioeconomic status, people who use drugs and younger people [10].

- Programmes successfully working with people using recreational drugs who are unlikely to attend sexual health services have shown that support outside of a formal clinical setting can help to initiate and maintain PrEP use [16,17]. Key elements that 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 had no difficulty maintaining 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 three doses per week or taking extended breaks from PrEP. He is becoming anxious as he is having condomless anal sex more than once a week and knows he is putting himself at increased risk. The clinical team offers additional support such as telephone check-ins and referral to a psychologist and advises him about using PrEP after exposure as a fallback option. He is also linked into online support spaces such as Prepster (https://prepster.info/). All these interventions provide Stephen with increased confidence and a plan to manage PrEP adherence in relation to his new circumstances.

Case study 5: alternative dosing options for women

Patience is a 28-year-old Zambian woman who successfully started 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 they last have 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.

3.3 New PrEP technologies

- Long-acting injectable cabotegravir (CAB-LA) is progressing through licensing and approval processes in the UK, injectable lenacapavir has been submitted for approval to

international and national bodies including the European Medicines Agency (EMA) and NICE and other injectable and long-acting oral options are in development. Other PrEP formulations may be being used by individuals visiting the UK, or arriving to live, work or study in the UK, having been prescribed before arrival.

- There is evidence that injectable options have high levels of user acceptability [33] and PrEP persistence [34,35], especially among those populations that are least likely to use oral PrEP, and may serve to increase access and adherence to 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 CAB-LA injections.

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4 Efficacy and safety

Recommendations for PrEP efficacy and safety
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 GBMSM who are at elevated risk of HIV-acquisition through condomless sex (Grade 1A); • HIV-negative individuals having condomless sex with HIV-positive partners whose plasma viral load is not <200 copies/mL on antiretroviral therapy (ART) (Grade 1A); • Heterosexual men and women at greater risk of HIV acquisition* (see section 5) (Grade 1B). • Transgender women (Grade 1B) and transgender men and non-binary people (Grade 1D) at greater risk of HIV acquisition*; • People who inject drugs and who might share injecting equipment (Grade 1B); • People who, regardless of gender or sexual orientation, are likely to have condomless sex with people at risk of HIV (Grade 2B).
4. We recommend that young people (aged 15–22 years) should be offered PrEP in accordance with their risk (Grade 1A) and that those aged under 18 years should be offered TAF-FTC as PrEP (Grade 1B).
5. We recommend that young people on PrEP should be offered additional support and monitoring to optimise adherence (Grade 1B).
6. We recommend that PrEP using TD alone can be offered to heterosexual men and women if FTC is contraindicated (Grade 1A).
7. We suggest 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 (Grade 2C).
GPPs
• 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.
• Specific reassurance should be given to transgender people that there are no expected drug–drug interactions between PrEP and GAHT.

*Defined as where HIV risk is likely to be in excess of that of the background UK population and where benefit outweighs clinical risk of PrEP [1-3].

Key evidence summary for PrEP efficacy and safety

4.1 PrEP efficacy

4.1.1 GBMSM

- PrEP efficacy in GBMSM has been well studied in PrEP clinical trials and there is high-quality RCT evidence demonstrating the efficacy of PrEP (TDF-FTC) in this population with both daily (iPrEx and PROUD studies) [4,5] and on-demand (the IPERGAY study) [6] dosing.

- In the iPrEx daily TDF-FTC open-label extension (OLE) study, in which 1533 participants were GBMSM, there were no HIV seroconversions in those taking four or more pills per week [7].

- One RCT compared daily TAF-FTC and TDF-FTC (the DISCOVER trial; 98.6% GBMSM) [8] and demonstrated that TAF-FTC was non-inferior to TDF-FTC for HIV prevention.

- OLE trials, Phase 2 pilot studies and post-marketing data have further demonstrated effectiveness of both daily and on-demand TDF-FTC as PrEP in GBMSM [7,9-12].

- There has been one trial of TDF monotherapy as PrEP in GBMSM, which was conducted by the US Centers for Disease Control and Prevention [13]. This study demonstrated safety, but was not powered for efficacy assessment, and TDF monotherapy is not recommended as PrEP for GBMSM.

- One RCT has shown that CAB-LA is superior to daily oral TDF-FTC in preventing HIV acquisition in GBMSM [14].

4.1.2 Heterosexual populations

- Efficacy of PrEP (TDF-FTC and TDF alone) in heterosexual populations has been demonstrated in RCTs conducted in sub-Saharan Africa.

- Partners PrEP [15] and TDF-2 [16] were Phase 3 RCTs carried out in East Africa and Botswana among serodifferent heterosexual couples and sexually active heterosexual individuals at high risk of HIV; the reported efficacy of daily TDF-FTC PrEP was 75% and 62% respectively.

- Partners PrEP [15] included a daily TDF only PrEP arm which had comparable overall efficacy (67%). This allows for the possibility of TDF-only PrEP in circumstances in which there are contraindications to the use of FTC. This situation is rare and TDF as PrEP is not routinely available in the UK.

- In Partners PrEP, the HIV protective effects of TDF and TDF–FTC were not statistically different according to sex [15].

- 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).

- One RCT has shown CAB-LA to be superior to daily oral TDF-FTC at preventing HIV infection in women [17].

4.1.3 Transgender people

- Both transgender men and transgender women are at increased risk of HIV infection and are identified as key groups 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 transgender people.

- Transgender women have formed a minority of oral PrEP RCT participants [8,18], and there are no data for transgender men.

- In a subgroup analysis of iPrEx, the effectiveness of daily oral TDF-FTC was lower in transgender women compared to GBMSM, primarily due to lower adherence [18]. However, there were no seroconversions in transgender women with drug concentrations compatible with four or more TDF-FTC tablets per week [18].

- In the DISCOVER trial (daily TAF-FTC *vs* TDF-FTC), none of the 74 transgender women acquired HIV during the study. The majority of the transgender women participating in the trial were taking feminising GAHT: 71% in the TAF-FTC arm; 72% in the TDF-FTC arm [18].

- In one RCT that included transgender women, CAB-LA was shown to be superior to daily oral TDF-FTC [14]. Of 570 (12.5%) transgender women in the trial, two acquired HIV in the CAB-LA arm (of 13 CAB-LA recipients overall) and there was no evidence of a difference in efficacy compared to GBMSM in the trial [14].

- Several small studies have demonstrated no effect of PrEP (TDF-FTC) on feminising GAHT levels (oestradiol) [19,20].

- Interactions between antiretroviral agents and oestrogen and anti-androgen preparations used in male-to-female GAHT have been examined by the University of Liverpool (see www.hiv-druginteractions.org), indicating that no clinically significant interactions are expected.
- However, the possibility of drug–drug interactions between PrEP and GAHT remains a concern for some transgender people and reassurance should be given that there are no expected interactions.

- Evidence from two small studies suggested that the use of GAHT may reduce the concentrations of TDF and FTC among transgender women on PrEP by 12–27% [21,22].

- According to the 2022 World Health Organization (WHO) implementation guidance for PrEP, while a lower PrEP concentration is unlikely to affect the efficacy of daily oral PrEP, the efficacy of event-based dosing PrEP in people assigned male at birth who are taking oestradiol-based hormones 'is unclear' [23].

- Other studies found that transgender men and transgender women had comparable TFV-DP concentrations with daily TDF-FTC PrEP compared to cisgender men [24]. In addition, TDF levels remained in the protective range in transgender participants and similar PrEP efficacy should be expected in transgender people compared to cisgender people particularly for daily dosing [19-21].

4.1.4 People who inject drugs

- There is limited evidence for the efficacy of PrEP in people who inject drugs.

- 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 people who inject drugs [25].

- The BTS demonstrated a 49% reduction in HIV incidence, with efficacy strongly linked to adherence. However, it is difficult to distinguish the impact of PrEP on parenteral HIV transmission from its impact on sexual transmission in people who inject drugs [25].

4.1.5 Young people

- There have been limited studies designed to explore the efficacy of TDF-FTC in young people with most data from small demonstration studies with no control group [26-30].

- Studies have demonstrated the feasibility and acceptability of PrEP in young GBMSM [28,29], 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 studies demonstrating decreased use of TDF-FTC over time [26-30].

- One study of 451 sexually active adolescent girls and young women aged 16–22 years in South Africa and Zimbabwe demonstrated high levels of oral PrEP (95%) uptake with 55% persisting on PrEP at 12 months [26]. Adherence dropped during the trial with dried blood spot testing demonstrating detectable TFV-DP levels in 84% at 1 month, 57% at 6 months and 31% at 12 months. One large Australian study found that within 2 years of their first supply, 49% of individuals aged <30 years had discontinued PrEP compared to 32% of those >40 years [31].

4.2 PrEP safety

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

4.2.1 Impact of PrEP on renal function

- RCTs have shown very good renal safety for daily and on-demand oral TDF-FTC as PrEP in GBMSM and transgender women [5,6,32,33]. Further, RCTs in sub-Saharan Africa have shown good renal safety for daily oral TDF-FTC as PrEP in men and women [15,34,35].

- While 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.

- 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 included lower baseline estimated glomerular filtration rate (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 [36].

- Two RCTs (in GBMSM and transgender and cisgender women) demonstrated good renal safety for CAB-LA PrEP. In both HPTN 083 and HPTN 084 there were no significant differences in renal adverse events between the CAB-LA group and the TDF-FTC group [14,17].

Impact of creatine supplements on serum creatinine levels

- Creatine supplements can increase levels of serum creatinine and affect the 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 [37,38].

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

- The available evidence suggests that PrEP does not affect the effectiveness of hormone-based contraceptive 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, depot medroxyprogesterone acetate [DMPA] or hormonal implants) [39].

- 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 [40,41] and this is consistent with findings from studies of pregnant women living with HIV or hepatitis B (HBV) and treated with TDF [42]. 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 breastfeeding [43,44]. There is extensive experience of TDF-FTC use in women with HIV who are breastfeeding. These data confirm that very low median concentrations of both FTC and TDF are secreted in breast milk [43,44].

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

4.2.3 Impact of PrEP on bone mineral density (BMD)

- There are small, but statistically significant reductions in the mean BMD of less than 2% as determined by mean percentage reduction in Z-score over time measured by dual-energy X-ray absorptiometry (DXA) scanning at the hip and lumbar spine observed in study populations with varied demographic characteristics exposed to oral PrEP including TDF and TDF-FTC in comparison to placebo [45-48].

- 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 decrease over time [45].

- There is no published evidence on BMD 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) [48,49].

- Although long-term data are lacking, there is no evidence of an increased rate of fractures while on TDF-containing PrEP or during currently available follow-up observation [32,40,41].

Impact of PrEP on BMD 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 adolescents and young adults.

- Small studies of BMD in adolescent and young GBMSM (aged between 15 and 22 years) taking TDF PrEP have demonstrated declines in spine, hip and whole-body BMD Z-scores, with greatest declines seen in individuals aged 15–19 years compared to those aged 20–22 [28,29]. Spine, hip and whole-body Z-scores remained below baseline after PrEP discontinuation in the younger age group, but not in 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 aged 18–25 years (n = 25) in the DISCOVER bone substudy, reductions in BMD on TDF were numerically greater in individuals ≤25 than in those >25 years (–2.2% *vs* –0.9% and –2.3 *vs* –1.0 % at the hip and spine, respectively, at 48 weeks) and greater at 48 than at 96 weeks [8].

- Factors recognised to be associated with reduced bone mass include vitamin D insufficiency, low dietary calcium, low body weight and possibly amphetamine and inhaled nitrite use [46], and these factors 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 progestogen-only injectable contraception norethisterone enanthate (NET-EN), or with progestogens used in GAHT [45].

Impact of non-TDF-containing PrEP regimens on BMD

- 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 versus TDF-FTC, increases in average BMD 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 hip and spine BMD increased by 0.2–1.0% at 48 and 96 weeks in an approximately linear fashion in the TAF-FTC arm and decreased by –1.0% to –1.4% in the TDF-FTC arm ($p < 0.0001$, analysis of variance [ANOVA] model at both sites and both time points) [8,50].

- 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 arm than in the TDF arm, and results were similar for those with >5% increase in BMD. At the hip, an increase of >3% was seen in a significantly greater proportion in the TAF than the TDF arm [50].

- In men under the age of 25 (n = 25) in the DISCOVER bone substudy [8], numerically greater increases in BMD on TAF-FTC were observed in those aged <25 than in those aged 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 an ANOVA analysis. HPTN

069, a comparison of maraviroc (MVC) or MVC-FTC with MVC-TDF or TDF-FTC in GBMSM, transgender women and cisgender women showed a significantly greater bone loss at 48 weeks in the TDF-containing arm at the hip, but not the lumbar spine [8,50,51].

- CAB-LA PrEP does not have a bone safety signal. In data presented at CROI in 2023 from the HPTN 083 trial in GBMSM and transgender women, BMD gain was seen in those on CAB-LA PrEP over 2 years of study follow-up, whereas BMD loss was observed in those on TDF-FTC PrEP [52].

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 years), 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, parathyroid hormone or 25-OH vitamin D3 [53].

- In a study of 100 Thai males aged 15-24 years (39% 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 BMD by DXA compared to baseline (67.6% *vs* 42.9%; p = 0.03), despite incomplete adherence both to PrEP (52%) and vitamin D/calcium (66%) [54].

- In a Canadian survey of 161 current or prospective PrEP users, 31% reported adequate dietary calcium intake but over 90% were willing to take supplements [55].

- NICE guidance on assessing the risk of fragility fracture, last updated in 2017 and due for a full review in 2025, should be used to guide assessment [56].

4.2.4 Gastrointestinal side effects, PrEP absorption and gastrointestinal conditions

- Gastrointestinal side effects (most commonly nausea, vomiting and diarrhoea) are reported by a minority (5–11%) of users within a month of starting oral PrEP and usually regress within 3 months. In a meta-analysis of RCTs including TDF-based PrEP, the odds of vomiting as an adverse event in five studies in which it was recorded was significantly greater with TDF than placebo (odds ratio 1.81, 95% confidence interval [CI] 1.20–2.73, p < 0.005) but in eight studies reporting nausea as an adverse event, there was no significant difference between TDF and placebo and there was no difference in rates of reported diarrhoea in 10 studies comparing TDF to placebo or CAB-LA [57].

- Daily PrEP may be a better option for individuals experiencing more troublesome gastrointestinal side effects, particularly where this is related to a double-dose start (the double dose can also be separated; see GPPs in section 8). Symptomatic treatment with anti-emetics, muscarinic antagonists and anti-diarrhoeal medication may be prescribed in more severe cases and changing preparation to a product supplied by a different manufacturer, with different excipients, may reduce or resolve symptoms. In the DISCOVER trial, there was no difference in reported gastrointestinal adverse events between TDF-FTC and TAF-FTC [58].

- The tenofovir area under the curve (AUC) is increased (by approximately 40% with TDF-FTC and 60% with TAF-FTC) when the dose is taken with a high-fat meal (~700–1000 kcal containing 40–60% fat) compared to fasting but not with a light meal. The maximum concentration (C_{max}) is also increased in the case of TDF-FTC but not TAF-FTC and emtricitabine levels are unaffected by food. Dosing with food may reduce gastrointestinal side effects and taking with a high-fat meal may be helpful where there are concerns about absorption or drug levels, or when PrEP is taken after exposure (see section 8).

- Following gastrointestinal surgery and in the presence of inflammatory gastrointestinal disorders, absorption of TDF is thought to be in the duodenum and effects may therefore depend on the specific type of surgery or the site of inflammation: see www.hiv-druginteractions.org/prescribing_resources/hiv-guidance-gastric-surgery. A case report and small case series showed lower levels of both tenofovir and FTC after total gastrectomy and bariatric surgery and with gastrointestinal disorders [59]. Colonic surgery and colectomy are thought unlikely to affect absorption, but if exposure is through receptive anal sex when a rectal stump remains following colostomy/ileostomy, daily PrEP is recommended because of the likely contribution of local absorption to effectiveness at this site: see www.hiv-druginteractions.org/prescribing_resources/hiv-guidance-prep.

- As therapeutic drug monitoring for oral PrEP agents is not routinely available, decisions regarding suitable PrEP agents and dosing in such cases will be made on a case-by-case basis, informed by the PK and PD properties of oral PrEP agents (see section 8).

- A reduction in absorption is likely to depend on the specific effect of the condition/surgery on the duodenum.

- Daily dosing will be preferred to event-based or TTSS dosing.

- Dosing with a high-fat meal may increase levels (although this may not be practical or desirable for daily dosing).

- TAF-FTC is likely to be more 'forgiving' than TD-XTC because of higher levels of TDF in tissues.

- CAB-LA is unaffected by absorption issues and may be the preferred option.

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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 (Grade 2B); • People at risk of HIV*(Grade 1A–2C depending on group, see Table 1); • People who, regardless of gender or sexual orientation, are likely to have condomless anal or vaginal sex with people at risk of HIV* (Grade 2B); • People who inject drugs who might share injecting equipment (Grade 1A). PrEP is suitable for the populations, and in the presence of the indicators, shown in Table 1. *Defined as where HIV risk is likely to be in excess of that of the background UK population and where benefit outweighs clinical risk of PrEP (see section 4) [1-3].
When should PrEP be prescribed?
9. We recommend that PrEP should be prescribed for people for whom it is suitable as soon as HIV risk is identified as benefit is immediate and toxicity is uncommon and delayed (Grade 1A).
GPPs
PrEP offer
• PrEP suitability should be considered in people identifying or identified as being at risk of HIV infection. For example, all attendees to sexual and reproductive health services, wherever HIV testing is performed, or where an individual presents for regular or emergency contraception or STI testing.
Reviewing risk–benefit of PrEP
• Regular review of the risks and benefits of PrEP should be undertaken as these can change over time.
Assessment of PrEP suitability
• 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 PEP 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.

Table 1. Populations or indicators associated with suitability for PrEP

PrEP is suitable for the following:
Populations • GBMSM (Grade 1A) [7,8] • Black African men and women (Grade 1A) [7,8] • Transgender women (Grade 1A) [7,8] • Recent migrants (Grade 1D) [10] • People who inject drugs (Grade 1A) [7,8] • People who report sex work or transactional sex (Grade 1A for GBMSM and transgender women, Grade 2C for female sex workers [7,8,11]
Behavioural and personal indicators • Condomless anal or vaginal sex with one of the groups listed above (Grade 2D) • Condomless anal or vaginal sex where a sexual partner may have undiagnosed or untreated HIV infection (Grade 1A) [12,13] • Chemsex or group sex (Grade 1B for GBMSM) • Injecting drug use using shared equipment (Grade 1A) [7,8] • Travel to countries with high HIV prevalence where sex with people from those countries is likely (Grade 2D)
Other clinical markers • Other STI (Grade 1C) [9] • Hepatitis C virus (HCV) infection (Grade 1C) [9] • PEP use (Grade 1C) [14]
Injecting drug use • Injecting in an unsafe setting, sharing injecting equipment or limited access to needle and syringe programmes or opiate substitution treatment (Grade 1A) • Sexual risk in people who use drugs (Grade 1A)
Reduced sexual health autonomy • Drug and alcohol use (Grade 2D) • Safeguarding, consent and vulnerability issues (Grade 2D) • Inability to negotiate and/or use condoms (or employ other HIV prevention methods) with sexual partners (Grade 2D) • Coercive and/or violent power dynamics in relationships (e.g. intimate partner/domestic violence) (Grade 2D) • Precarious housing or homelessness and/or other factors that may affect material circumstances (Grade 2D) • Risk of sexual exploitation and trafficking (Grade 2D)

****** 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 PEP use after sexual exposure in GBMSM [14]), reported/likely sexual behaviour and drug use and vulnerability factors affecting sexual autonomy.

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 (see section 4, section 6 and section 7) [7,8].

5.2 The move away from trial eligibility criteria

- Focusing 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 is important to ensure that people are not excluded. A wider range of population-level and individual-level indicators is 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 GBMSM and transgender 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 engage in sexualised drug use (chemsex), people who have condomless anal or vaginal sex with a partner of unknown HIV status where they or their partner are GBMSM and/or from a country with a high HIV prevalence, people who inject drugs and who share injecting equipment, and people 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 is appropriate for those who request it. Exceptions include where individual risk is not higher than that of the background UK population or where the clinical risk of PrEP outweighs the benefit [7,8] (see section 4). Whenever clinicians or other health workers are reviewing the risk of STI, including HIV, or discussing contraception with an individual, 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 PEP 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 discussion within a multidisciplinary team (MDT) may be appropriate to determine the appropriate advice for 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 regarding 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 Undetectable = Untransmittable (U=U) messages and contribute to HIV stigma.

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6 Baseline testing and clinical management

Recommendations for baseline testing and clinical management
HIV testing
10. We recommend that baseline HIV testing with a combined antigen/antibody serology test is undertaken prior to commencing PrEP (Grade 1A).
11. We recommend that PrEP can be initiated while awaiting the result of a laboratory HIV antigen/antibody test unless there are symptoms suggestive of HIV seroconversion (Grade 1A); in individuals at ongoing high risk who have not had a laboratory HIV test in the last 45 days, a blood-based point-of-care test (POCT) may be indicated (Grade 1A).
12. We recommend that people 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 (Grade 1C). Atypical testing results should be discussed with a regional expert (Grade 1C).
STI and blood-borne virus testing
13. We recommend that testing for STIs should be undertaken at baseline (Grade 1B).
14. We recommend that testing for HBV should be undertaken at baseline according to local screening protocols (Grade 1A).
15. If there is no evidence of current or previous infection or immunity, we recommend that HBV vaccination should be offered (Grade 1A).
16. Oral PrEP may be started pending results of hepatitis B surface antigen (HBsAg) testing, but results should be reviewed at the earliest possible time as TD-FTC and TAF-FTC are active against HBV (Grade 1A).
17. We recommend that individuals with HBV infection should be referred for assessment including need for HBV treatment according to national guidelines (Grade 1A).
18. We suggest that for individuals with HBV but not requiring treatment for HBV, daily oral PrEP would be the preferred option, but event-based oral PrEP can also be offered (Grade 2C).
19. We recommend that individuals with chronic HBV should be counselled that there is a potential risk of HBV reactivation if PrEP is stopped, and that following PrEP discontinuation they will require monitoring with HBV DNA and liver function tests for 12 months if not on other HBV treatment (Grade 1C).
20. We recommend that testing for HCV should be undertaken at baseline in GBMSM and other at-risk groups; if positive, the individual should be referred to specialist services for further investigation and consideration of early direct-acting antiviral (DAA) treatment (Grade 1B).
Renal function (see Flowchart 1)
21. We recommend that serum creatinine level and eGFR should be determined at baseline (Grade 1A). 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, and PrEP can be commenced while waiting for the results (Grade 1A).
22. We suggest that eGFR for individuals starting TD-FTC should be ≥60 mL/min/1.73 m^2 (Grade 2A).
23. We recommend that if eGFR ≥90mL/min/1.73 m^2 at baseline and the person is aged <40 years, with no risks for renal disease, then annual eGFR testing should be conducted (Grade 1A).
24. We suggest that if eGFR is ≥90 mL/min/1.73 m^2 at baseline and the person is ≥40 years or has risks for renal disease, then eGFR should be repeated at 6 months (Grade 2B).
25. We suggest that if eGFR is between 70 and 89 mL/min/1.73 m^2 at baseline, risks for renal

disease should be assessed, reduced exposure to oral PrEP should be considered (e.g. with event-based or intermittent dosing of oral PrEP) and eGFR repeated at 3 months; where renal function is stable, monitoring can continue every 6–12 months (Grade 2B).
26. We suggest that if eGFR is 60–69 mL/min/1.73 m^2 at baseline, eGFR should be repeated in 2–4 weeks, having stopped any creatine/protein supplements, risks for renal disease should be assessed and reducing exposure to oral PrEP should be considered with event-based or intermittent dosing (Grade 2B). Where renal function is stable, monitoring can continue every 6 months.
27. We recommend that individuals with an eGFR between 30 and 60 mL/min/1.73 m^2 at baseline should have the full assessment recommended in Flowchart 1 and are recommended TAF-FTC PrEP (Grade 1A).
Bone function
28. We recommend that oral PrEP recipients should be informed of the risk of reduction in BMD of approximately 1.5–2% at the hip and spine following 48 weeks of TDF-FTC PrEP (Grade 1B) but that there is no evidence of an increased risk of fractures while taking PrEP (Grade 1A).
29. We recommend that all oral PrEP recipients should be assessed for markers of increased absolute fracture risk, including previous fracture(s) at the wrist, spine or hip, smoking, high alcohol intake, menopause and high-dose oral or systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for ≥3 months), or other causes of secondary osteoporosis (Grade 1D).
30. We recommend that those aged under 18 years should be offered TAF-FTC as PrEP (Grade 1B).
31. We recommend that in those aged ≥50 years and/or with risk factors for osteoporosis, fracture risk should be calculated using the QFracture® or FRAX® online assessment calculators (Grade 1B). Those at high risk (risk score >10%) should be offered a DXA scan [1] (Grade 1C).
32. We suggest that in people with markers of increased fracture risk and/or with confirmed osteoporosis on DXA scanning (see GPPs below) who require continuous daily oral PrEP, alternatives to TD-FTC PrEP (currently TAF-FTC only) should be advised (Grade 2B).
33. We suggest 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 (Grade 2C).
Pregnancy
34. We suggest that if an individual is pregnant when starting PrEP and there is an ongoing risk of HIV acquisition, PrEP should be continued during pregnancy and breastfeeding, after discussing the potential risks of TD-FTC (Grade 2B).
GPPs
• PrEP should be offered as part of a package of care including condom provision, regular HIV and STI testing and monitoring of renal function.
• People who could benefit from PrEP should be informed of the evidence for the effectiveness and safety of PrEP.
• 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.
• The possibility of reduced renal function with TD-FTC should be discussed with individuals who have pre-existing chronic renal disease or risk factors for renal disease (diabetes, hypertension, >40 years of age or eGFR <90 mL/min/1.73 m^2).
• 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 20 years of age.

• Routine monitoring of BMD is not recommended in individuals taking PrEP with no other risk factors for reduced BMD.
• 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.
• People at low risk (risk score <10%) should not be offered a DXA scan, but given lifestyle advice and fracture risk checked annually while on PrEP.
• Vitamin D and calcium supplementation should be recommended to PrEP recipients of all ages with risk factors for reduced BMD, particularly those under the age of 25 years.
• PrEP initiation in the presence of a negative blood POCT and absence of symptoms of acute HIV infection should not be delayed while awaiting laboratory or confirmatory results.
• Access to PrEP among people at high risk of HIV infection is not delayed; wherever possible aim to initiate on the day of testing. At the time of PrEP initiation, all tests should be undertaken, results reviewed as soon as possible and PrEP prescription modified accordingly once results become available.
• We suggest that clinicians remain alert to acute HIV infection among 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 for pregnancy should be conducted in women and other people who can get pregnant who are not using reliable contraception, if indicated.
• Adverse events should be reported through the yellow card scheme (https://yellowcard.mhra.gov.uk/).

6.1 Summary of baseline testing and management

- Testing for STIs and blood-borne viruses (HIV, HBV and HCV) 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, HBV, human papillomavirus (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, PEP should be considered prior to transitioning to PrEP.
- If transitioning from PEP to PrEP, HIV testing should be performed 6 weeks after starting PEP 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 for 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, initiation of PrEP should be delayed until HIV infection can be reliably excluded.
- If HIV seroconversion on PrEP is suspected, we recommend that ART is intensified.

6.2 Assessment for consideration of PEP

- 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 PEP prior to transitioning to PrEP (see section 8).

- Testing for HIV should be performed in line with current PEP guidelines [2].

- However, if immediately transitioning to PrEP after a course of PEP, HIV testing should be performed 6 weeks after starting the course of PEP and again 6 weeks after starting PrEP.

6.3 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, blood-based POCTs may be performed by service providers, although the possibility of both false-positive and, in early infection, false-negative results should be considered.

- In the absence of symptoms of acute HIV infection [3], PrEP can be started immediately to mitigate any ongoing risk of infection while the result of a combined antigen/antibody HIV test is awaited and in the presence of a negative blood-based POCT test if available.

- 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, an HIV viral load test to exclude acute HIV infection could be considered in addition to a combined HIV antigen/antibody test prior to starting PrEP.

- A combined antigen/antibody HIV test should be repeated 45 days after PrEP initiation in individuals where a risk occurred in the 6 weeks prior to initiating PrEP, and then at 90 days post-PrEP initiation. A face-to-face appointment is not required for testing.

- A person with a positive HIV test at baseline should be managed in accordance with current guidelines with referral to start ART from an HIV specialist unit [4].

6.4 Acute HIV infection

- PrEP is indicated for individuals at risk of HIV acquisition and clinicians should therefore consider the possible risk of acute HIV infection and take an appropriate symptom history, noting that only a proportion (40–90%) with acute HIV infection will be symptomatic.

- The symptoms most strongly associated with acute HIV infection are fever and rash [3]. Other symptoms include headache, malaise, arthralgia and sore throat. However, symptoms of acute HIV infection may be non-specific and people may fail to report them, so diligence is required to exclude acute HIV infection 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 for starting PrEP, although starting PrEP should be deferred in those with signs or symptoms consistent with acute HIV infection currently, or in the previous 3 weeks, until HIV infection can be reliably excluded with additional HIV viral load nucleic acid amplification testing 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 monitoring guidelines [4].

6.5 Atypical and indeterminate HIV test results

- Atypical HIV test results include: (i) unchanging antibody reactivity in two or more consecutive samples that do not fit with a pattern usually associated with confirmed positivity; and (ii) 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 antibody response, with non-reactive or atypical and non-progressive HIV serology and Fiebig profiles seen, in a setting in which viral load is likely to be undetectable.

- Atypical testing cases should be discussed with a regional expert and investigated further for possible seroconversion. For specialist advice, referral to a national NHS clinical service can be made (Indeterminate Retrovirus Infection Service [IDRIS] run at Imperial College NHS Trust, London: 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, 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 antigen/antibody testing, western blotting and HIV DNA testing) should contain information on whether the individual has been taking either PEP or PrEP, and if so, when and for how long, to allow for better interpretation of atypical results. Complex cases should be referred to the UK Health Security Agency (UKHSA)/IDRIS clinic for review (imperial.idris@nhs.net).

6.6 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 test 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 [7] and clinicians should intensify ART while awaiting review with a specialist in HIV medicine.

6.7 STI testing prior to starting PrEP

- STI testing is recommended at baseline in accordance with national recommendations and guidelines. This includes nucleic acid amplification tests for gonococcal and chlamydial infection at sites of exposure (genital, rectal and pharyngeal sites) 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 who change partner less frequently (i.e. every 3–6 months).

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

6.8 Assessment of viral hepatitis status when prescribing PrEP

6.8.1 HBV

- Testing for HBV should be undertaken at baseline according to local screening protocols. If there is no evidence of current or previous infection or immunity, HBV vaccination should be offered as per current guidelines [8].

- Oral PrEP may be started pending results of HBsAg testing, but results should be reviewed at the earliest possible time as TD-FTC and TAF-FTC are active against HBV and may be used simultaneously as treatment for chronic active HBV infection and as PrEP.

- Individuals found to have undiagnosed HBV infection at baseline should be referred to specialist hepatology services for full assessment, including the need for HBV treatment.

- Stopping anti-viral therapy in people with chronic HBV has been associated with a small risk of HBV DNA reactivation and hepatic flares, particularly in those with underlying liver disease [9].

- There is limited published evidence evaluating the risk of HBV reactivation in people with chronic HBV on TDF-containing oral PrEP, largely as most PrEP clinical trials have excluded potential participants with chronic HBV. Of the available evidence, a Phase 2 clinical trial of TDF as PrEP among women in sub-Saharan Africa reported no cases of hepatic flares in 23 participants with HBsAg-positive serology who were followed up for nearly 1 year [10]. In iPrEx, six participants with chronic HBV were randomly assigned to TDF-FTC. After drug discontinuation, liver function tests were performed for five of the six participants in the active arm at follow-up. Liver function tests remained within normal limits at post-discontinuation visits except for a grade 1 elevation in alanine aminotransferase (ALT) in one participant at week 12 after discontinuation [9]. There was no evidence of hepatic flares [11].

- HBV flares after withdrawing TDF PrEP appear to be rare, particularly in people with normal baseline liver tests and no fibrotic liver disease. In addition, any risk may exist for both daily and event-based PrEP as starting, stopping and restarting of PrEP is not uncommon [9]. In view of this, the WHO recommends that both daily and event-based oral PrEP dosing can be offered to people with HBV [12].

- In view of the lack of current evidence for the use of event-based PrEP in people with HBV not requiring treatment for HBV, daily oral PrEP would be the preferred option, but event-based PrEP can also be offered.

- Individuals with chronic HBV should be counselled that there is a potential risk of HBV reactivation if oral PrEP is stopped and that they will require regular monitoring with HBV DNA and liver function tests for up to 12 months after PrEP discontinuation if not on other HBV treatment.

6.8.2 HCV

- A high background prevalence of HCV has been reported in HIV-negative GBMSM before starting PrEP in both clinical trials and PrEP demonstration projects [13,14].

- Screening for HCV should be undertaken at baseline in GBMSM and other at-risk groups as recommended in national guidelines [8].

- People with previously undiagnosed HCV should be referred to specialist services for assessment and consideration of DAA treatment.

- No data on HCV prevalence are 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.

6.8.3 Hepatitis A

- Screening and vaccination for hepatitis A should be undertaken in line with national guidelines and targeted at those at greater risk (GBMSM, people who inject drugs and those with HBV or HCV infection) [8].

6.9 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, were rarely of clinical significance and the incidence of serious renal events was very low and these events were mostly reversible [15-19]. People taking TAF-containing PrEP regimens are less likely to suffer renal adverse events [20]. For further details of the evidence regarding impact of PrEP on renal function, see section 4.2.1.

- It is necessary to assess the risk of chronic kidney disease at baseline. Factors that may indicate an individual is at higher risk of chronic kidney disease 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 [21,22].

- 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 the use of any concomitant nephrotoxic drugs or drugs that have interactions with TD-FTC.

- Serum creatinine level and eGFR should be determined at baseline. PrEP may be started immediately, but results should be reviewed as soon as possible.

- A number of studies have demonstrated that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation is more accurate than the Cockcroft–Gault formula or the Modification of Diet in Renal Disease (MDRD) estimate, especially at eGFR ≥60 mL/min/1.73 m^2 [21]. The most effective way to calculate eGFR is therefore using the CKD-EPI 2021 equation.

- 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 for creatinine elevation (0.7%) [15]. 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 [23].

- For details on how to manage eGFR results at baseline, see Flowchart 1.

6.10 Assessment of BMD

- Small but statistically significant reductions in mean BMD 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 details on how to assess and manage BMD at baseline, see Flowchart 2.

6.11 Assessment of pregnancy

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

6.12 Prescribing PrEP

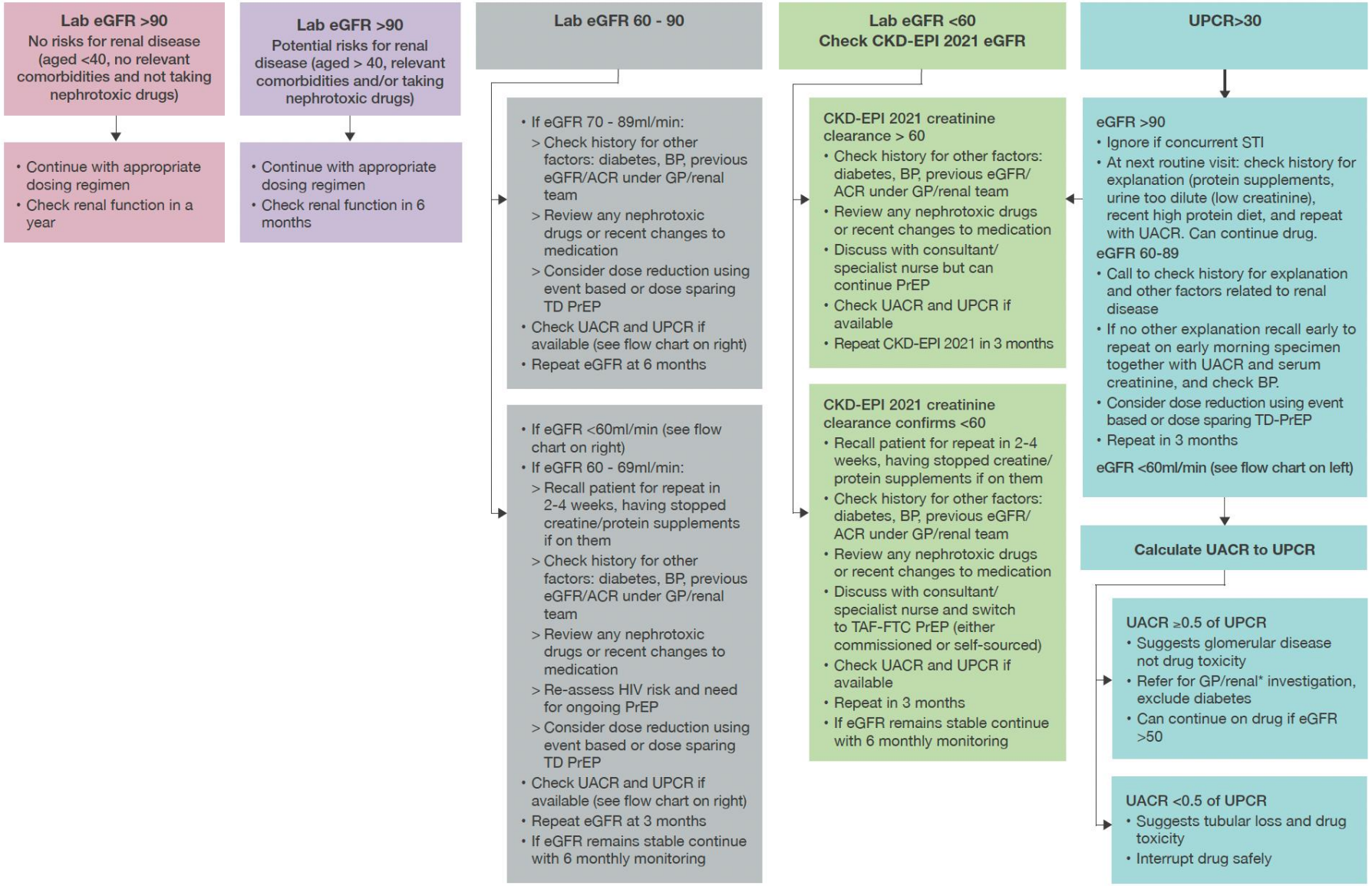
- We recommend that TD-FTC is used for PrEP for GBMSM, transgender women, transgender men and heterosexual men and women. For heterosexual men and women only, TD alone could be considered, although it is not routinely prescribed as PrEP in the UK and carries no significant advantages in terms of cost or toxicity. Of note, event-based dosing is not recommended for any group with TD alone.

- We recommend TAF-FTC for individuals with poor renal function (eGFR <60 mL/min/1.73 m^2), those with proven osteoporosis and those aged <18 years.

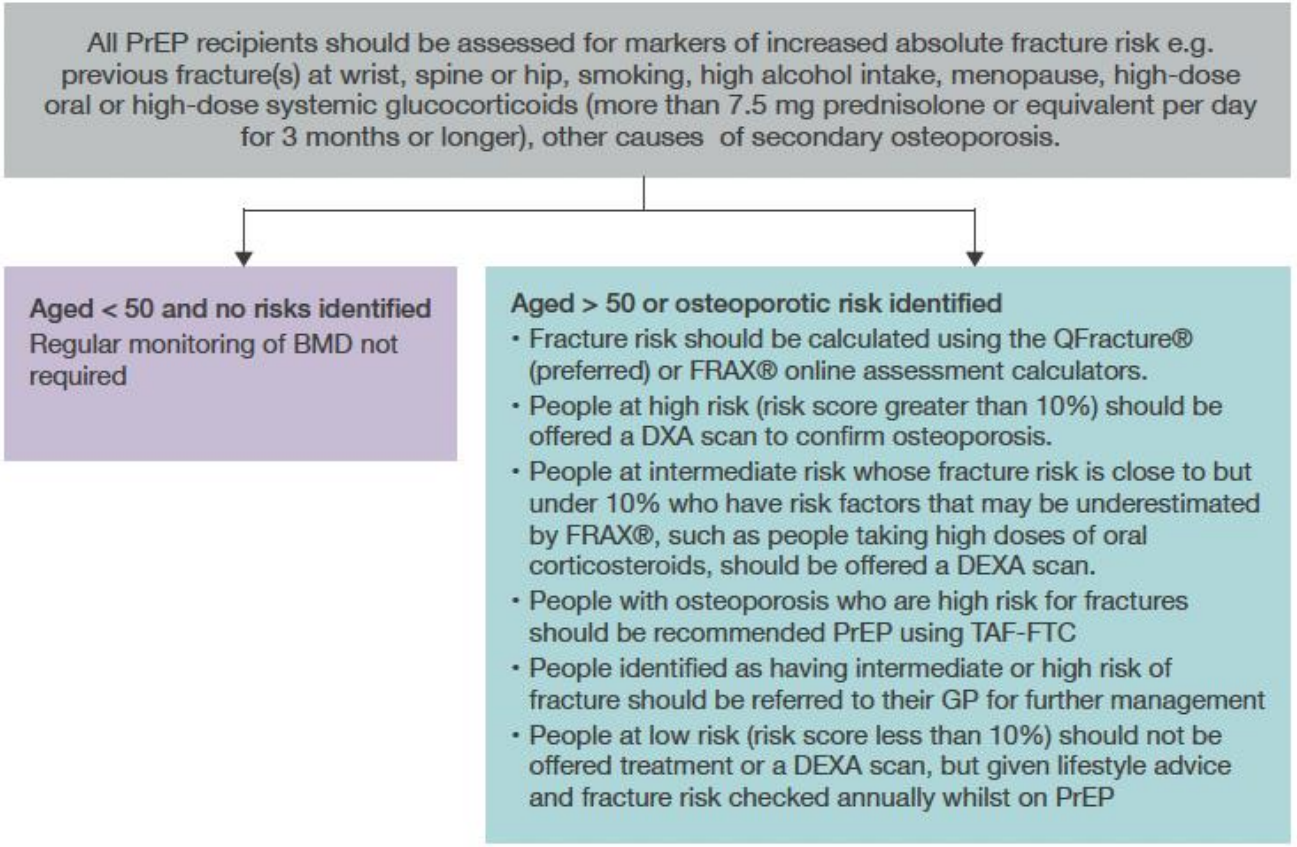
- When first starting PrEP (and when restarting), dispensing a 90-day supply of medication is usually recommended.

- For individuals with a 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.

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/

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7 On-going clinical management and monitoring

Recommendations for on-going clinical management and monitoring
HIV testing
35. We recommend that HIV testing should be undertaken every 3–6 months for people taking PrEP with a laboratory combined HIV antigen/antibody test (Grade 1A) or a blood-based POCT (Grade 1B).
36. Following the discontinuation of PrEP, we recommend retesting for HIV 45 days after the last risk (Grade 1B).
37. In the presence of indeterminate HIV test results, for people having reported use of intermittent PrEP or PEP, we recommend serology with samples being sent to the reference laboratory at the UKHSA for detailed analysis, including western blotting and HIV DNA testing. We recommend continuation of PrEP until results of additional HIV testing is known. In complex cases we recommend referral to the UKHSA/IDRIS clinic for expert review (imperial.idris@nhs.net) (Grade 1B).
38. We recommend baseline resistance testing for people with confirmed primary HIV infection, to look for evidence of resistance-associated mutations to tenofovir or FTC along with other transmitted mutations (Grade 1B).
STI and blood-borne virus testing and management
39. We recommend 3-monthly STI screening (chlamydia, gonorrhoea and syphilis) for people taking PrEP who have new or multiple sexual partners (Grade 1A).
40. We recommend that GBMSM and others at ongoing risk should be screened using HBV serology annually if they have not been vaccinated (Grade 1B).
41. We recommend that referral to specialist care should be made for follow-up care and management of active HBV infection and assessment of the need for HBV treatment (Grade 1A).
42. Where oral PrEP is stopped in individuals with chronic HBV who are not on treatment for HBV, we recommend regular testing with HBV DNA and aminotransferases for 12 months following discontinuation of PrEP (Grade 1C).
43. We recommend that GBMSM and others at ongoing risk should be screened for HCV in line with hepatitis testing guidelines [1,2]; if positive, the individual should be referred to specialist services for further investigation and consideration of early DAA treatment (Grade 1B).
Testing and management of renal function (see Flowchart 1)
44. We recommend ongoing monitoring of renal function with serum creatinine and eGFR (Grade 1A).
45. We recommend that if eGFR remains ≥90 mL/min/1.73 m^2 and the person is aged <40 years with no risks for renal disease, eGFR should be assessed annually (Grade 1A).
46. We suggest that if an individual experiences 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 (Grade 2B).
47. We suggest that where a significant drop in eGFR is experienced, it is confirmed with the CKD-EPI 2021 equation to calculate creatinine clearance (Grade 2B).
48. We suggest that if a significant drop in eGFR is not confirmed with the CKD-EPI 2021 equation, eGFR is repeated at 3 months and renal monitoring continued every 6–12 months (Grade 2B).
49. We suggest that if eGFR is between 70 and 89 mL/min/1.73 m^2 while taking PrEP, risks for renal disease should be assessed, reduced exposure to TD with event-based or TTSS dosing considered, and eGFR repeated at 3 months. Where renal function is stable, monitoring can continue every 6–12 months (Grade 2B).

50. We suggest that if eGFR is 60–69 mL/min/1.73 m^2 while taking PrEP, eGFR should be repeated in 2–4 weeks, having stopped any creatine/protein supplements, to assess the risk of renal disease and reducing exposure to TDF should be considered with event-based or TTSS dosing. Where renal function is stable, monitoring can continue every 6 months (Grade 2B).
51. We recommend that if eGFR is <60 mL/min/1.73 m^2, the risks and benefits of continuing PrEP should be assessed on a case-by-case basis. Local MDT advice should be sought to determine the need for further investigations and frequency of monitoring (Grade 1C).
52. Individuals with an eGFR <60 mL/min/1.73 m^2 should be recommended TAF-containing PrEP (Grade 1A).
53. We recommend that that if eGFR <60 mL/min/1.73 m^2, the risks and benefits of continuing PrEP should be assessed on a case-by-case basis. Specialist renal input should be obtained to determine further investigations and frequency of monitoring (Grade 1C).
Changing PrEP and weight gain
54. We recommend that individuals switching from TD-FTC (or CAB-LA) to TAF-FTC PrEP should be advised of the possible risk of modest weight gain compared to TD-FTC, due to the suppressive effect of TD on weight (Grade 1B).
Testing and management of bone function
55. We suggest that for individuals with markers of increased fracture risk and/or with confirmed osteoporosis on DXA scanning (see GPPs below) who are taking continuous daily PrEP, alternatives to TD-containing PrEP (currently TAF-FTC only) should be advised (Grade 2B).
56. We suggest 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 (Grade 2B).
57. We recommend that in those aged ≥50 years and/or with risk factors for osteoporosis, fracture risk should be calculated annually using the QFracture® or FRAX® online assessment calculators (Grade 1B).
58. We recommend that people at high risk (risk score >10%) should be offered a DXA scan to confirm osteoporosis according to local guidance and referral pathways (Grade 1C).
59. 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 according to local guidance and referral pathways (Grade 1A).
60. We recommend that people with osteoporosis who are at high risk of fractures should be switched to TAF-FTC (Grade 1B).
61. We recommend that people at low risk (risk score <10%) should not be offered a DXA scan but given lifestyle advice and fracture risk checked every 3 years while on PrEP (Grade 1B).
Pregnancy
62. We suggest that individuals who becomes pregnant while on PrEP should continue PrEP during pregnancy or breastfeeding if there is an ongoing risk of HIV acquisition, after discussing the potential risks of TD-FTC (Grade 2B).
GPPs
• PrEP should be offered as part of a package of care that includes comprehensive sexual and reproductive healthcare services.
• PrEP should be supplied according to the testing and monitoring guidance outlined in these guidelines, but the need for STI testing or toxicity monitoring should not be a barrier to PrEP resupply. Supply should never be contingent on testing or monitoring [3].
• Healthcare professionals should remain alert to acute HIV infection among people at risk of HIV, particularly in the presence of any symptoms which are often non-specific in nature,

and counsel and manage accordingly.
• Pregnancy status should be assessed in those not using reliable contraception if indicated.
• 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 there are 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 used to assess the need for a DXA scan and potential treatment for reduced BMD.

Note: follow-up testing and monitoring of individuals receiving PrEP should focus on excluding HIV, screening for and treating STIs 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.

- Individuals who have new or multiple partners should have an HIV test every 3 months.

- Less frequent HIV testing may be appropriate for individuals who are assessed to be at lower risk of HIV acquisition, for example those who change partner less frequently i.e. every 3 to 6 months. 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, including how to access specialist advice, see section 6.5.

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 of STIs. High rates of STIs were seen in an Australian study of nearly 3000 PrEP users (98.5% of whom were GBMSM), but mostly in a subset of participants; 76% of all STIs occurred in 25% of participants [4].

- 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 who change partner less frequently than 6 monthly.

- Sexually transmissible enteric infections are associated with high risk and dense sexual networks in GBMSM [5-7]. This includes GBMSM using PrEP and clinicians should consider sexually transmissible enteric infections as the cause of any gastrointestinal symptoms among GBMSM PrEP users and arrange suitable testing and treatment.

- The findings of a cross-sectional community-based survey suggested that up to 10% of GBMSM using HIV PrEP may also be taking antibiotics as PrEP and PEP for STIs [8]. Following this, trials such as the US-based doxycycline PEP (DoxyPEP) study in GBMSM and transgender women observed a 62–66% lower frequency of bacterial STIs in the active arm (200 mg doxycycline taken within 72 hours after condomless sex) compared to the 'standard of care' arm [9]. 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, based on current BASHH guidance [10]. BASHH guidelines on DoxyPEP are expected in 2025.

7.3 HBV testing

- GBMSM and others at ongoing risk should undergo annual HBV serology screening if they have not been vaccinated.

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

- Where PrEP is stopped in individuals who are not on treatment for HBV, HBV DNA and aminotransferase testing should be undertaken every 3 months for 12 months due to the small risk of HBV reactivation and hepatic flair (or local guidelines should be used for testing after stopping nucleoside therapy in chronic HBV).

7.4 HCV testing

- GBMSM and others at ongoing risk should be screened for HCV annually.

- If the anti-HCV test result is positive, HCV RNA should be tested and, if positive, the person referred to specialist services for further investigation and consideration of early DAA treatment.

- For individuals who are anti-HCV positive who have previously cleared HCV, HCV RNA or HCV core antigen testing would be needed.

7.5 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 [11] which, although statistically significant, were rarely of clinical significance and the incidence of serious renal events was very low and these events were mostly reversible [11-15].

- For information on how to monitor renal function and manage reductions in eGFR, see Flowchart 3**.** 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 15 mL/min/1.73 m^2 or of 25% in the past 12 months.

- For an evidence review of PrEP and renal function, see section 4.2.1.

7.6 BMD

- Small but statistically significant reductions in the mean BMD 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 an increased risk of fractures in people taking TDF- containing PrEP.

- For information on how to monitor BMD, see Flowchart 4.

- For an evidence review of PrEP and BMD, see section 4.2.3.

7.7 Oral PrEP, weight change and lipids

- In a meta-analysis dof TDF PrEP, in six RCTs of TDF PrEP versus placebo, the odds ratio for reporting >5% weight loss was 1.48 (95% CI 1.06–2.07, p = 0.005) [16].

- In studies of TDF-FTC versus placebo (iPrEx) [17], CAB-LA (HPTN) [18] or TAF-FTC (DISCOVER) [19], weight loss tended to occur in the first 24 weeks before individuals returned to normal weight with a weight gain trajectory matching the comparator arm.

- In the DISCOVER trial [20], which compared daily TDF-FTC and TAF-FTC for PrEP in GBMSM and transgender women, weight gain among participants who took TAF-FTC was comparable to the expected weight gain observed in the population and was greater than in those taking TDF-FTC (median weight gain at week 96: 1.7 *vs* 0.5 kg, p < 0.0001). Study participants who received TDF-FTC experienced decreases in lipid levels after both 48 and 96 weeks, whereas lipid levels were stable to 96 weeks in individuals who received TAF-FTC.

- TDF-based ART has been associated with reductions in serum lipid levels in people living with HIV [21,22]. The evidence suggests that users should be advised that TD-FTC may have a small suppressive effect on weight and a favourable effect on lipids. Switching from TD-FTC (or CAB-LA) to TAF-FTC may result in weight gain due to a normalised weight trajectory and a change in lipid profile. It seems likely that discontinuing regular TD-FTC PrEP use may have the same effect.

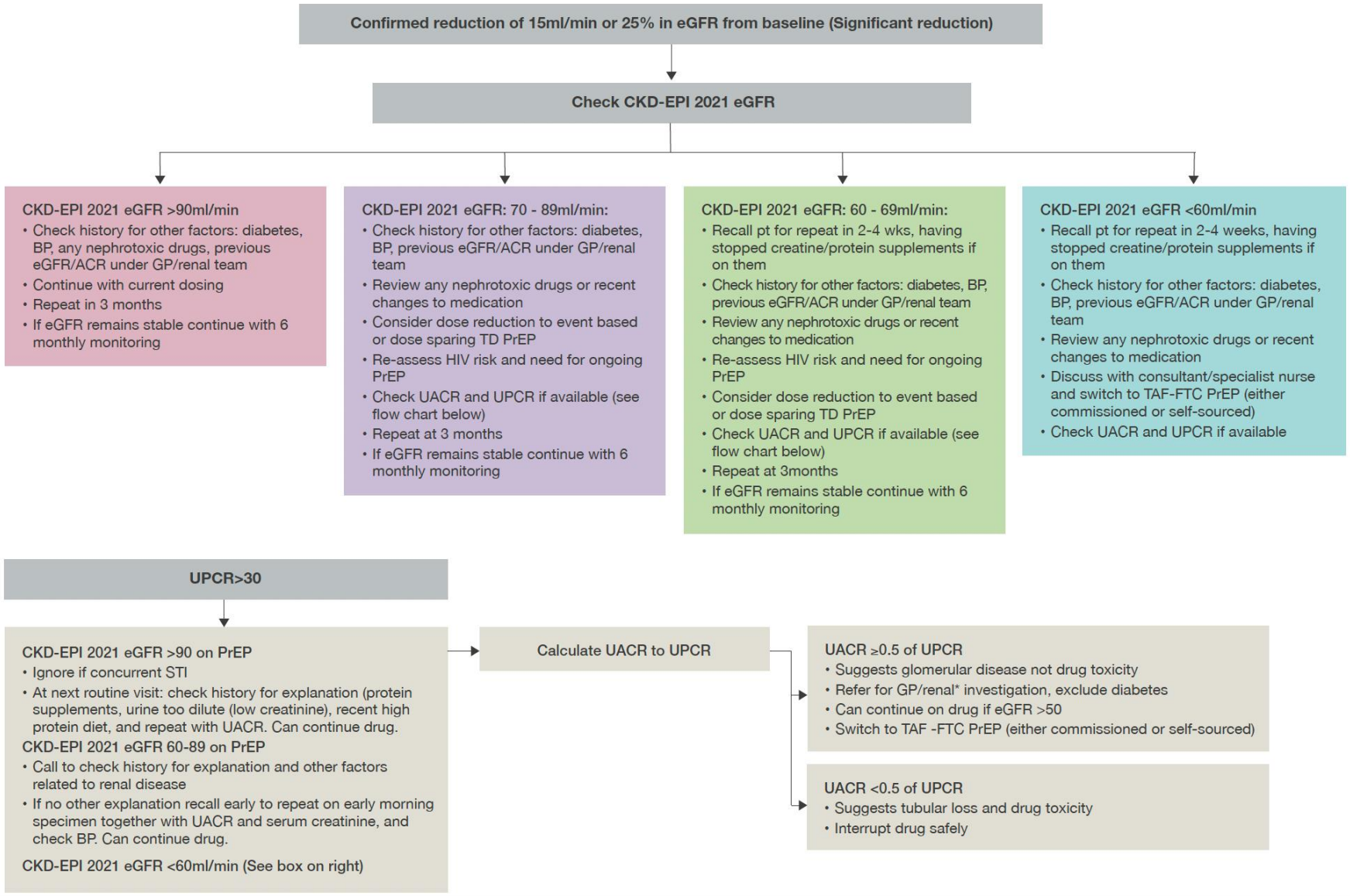
7.8 Pregnancy and conception

- 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.

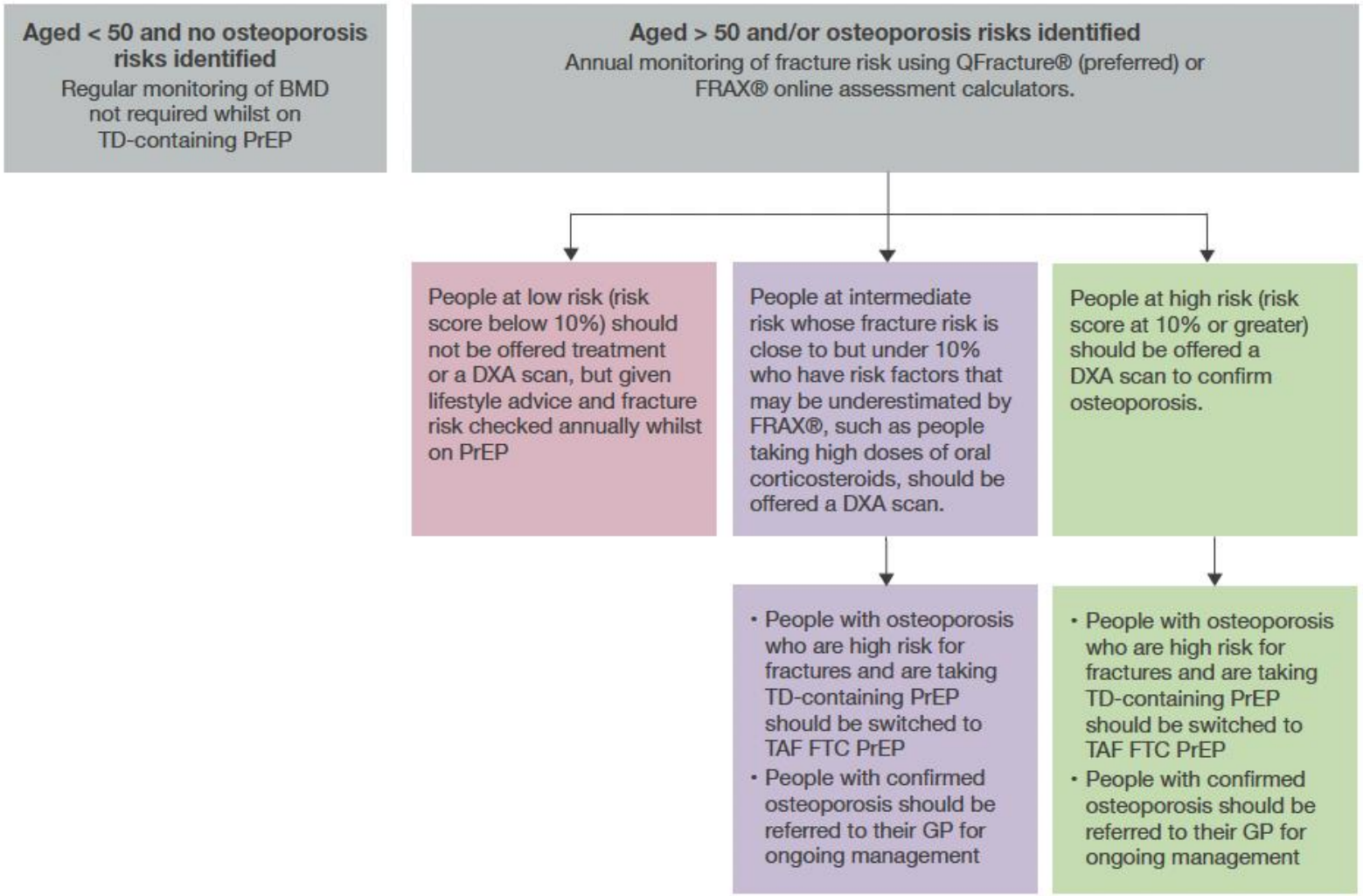
- Regular assessment of pregnancy status should be undertaken in women and other people who could become pregnant who are not on reliable contraception.

- If an individual becomes pregnant while on PrEP, a discussion of the known risks and benefits of taking TD-FTC or TAF-FTC during pregnancy is recommended. After discussing the potential risks, continuation of PrEP during pregnancy or breastfeeding should be recommended for those at ongoing risk of HIV acquisition. Information regarding use of PrEP during pregnancy should be reported to the Antiretroviral Pregnancy Registry (https://www.apregistry.com/).

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



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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8 Starting and stopping PrEP and indications for PEP in PrEP users

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

Recommendations for starting and stopping TD-FTC and TAF-FTC PrEP
63. We recommend that continuous daily dosing of oral PrEP can be used by all individuals for all types of exposure (TD-FTC and TAF-FTC, Grade 1A).
64. 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 2 days after the last risk (includes 2:1:1 event-based dosing) (TD-FTC, Grade 1A; TAF-FTC, Grade 1B).
65. We recommend that, if the risk of HIV acquisition is through insertive vaginal/neovaginal/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 2 days after the last risk (includes 2:1:1 event-based dosing) (TD-FTC: insertive anal sex, Grade 1A; insertive vaginal/neovaginal sex, Grade 1B; TAF-FTC: insertive anal/vaginal/neovaginal sex, Grade 1B).
66. 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 7 days after the last risk (includes 2:7 event-based dosing) (TD-FTC and TAF-FTC: receptive vaginal sex, Grade 1C; receptive neovaginal sex, Grade 1D).
67. 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 risk and safely stopped with single dose daily for 7 days after the last risk (includes 2:7 event-based dosing) (TD-FTC and TAF-FTC, Grade 1C).
GPPs
• Taking the initial dose of PrEP with food may reduce gastrointestinal side effects and increase total drug absorption (AUC) of TDF by approximately 40% and of TAF by 60%.
• It is important to stress that for event-based dosing for receptive vaginal/neovaginal sex and injecting drug use, users need to continue TD-FTC PrEP for 7 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 (i.e. when four or more doses have been taken in the week prior to an exposure), four doses per week in subsequent weeks are likely to provide good protection for all types of risk exposure. TTSS dosing may be an option for all users for all types of exposure, where reduced dosing is indicated for toxicity reasons and event-based dosing is not suitable.
• 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 within the 2- to 24-hour window period. The second tablet should be taken at least 2 hours before risk.

Note on recommendations

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

The lack of direct evidence for the use of TAF-FTC in populations other than GBMSM and transgender women has generated uncertainty in the use of this combination for daily or event-based dosing in women. We recommend TAF-FTC for all women and other people at risk of HIV acquisition and the use of TAF-FTC for event-based dosing, applying identical

dosing advice in every situation as for TD-FTC, albeit supported by a lower grade of research evidence.

Key evidence summary for starting and stopping TD-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 transgender 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 the 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 among those who had discontinued PrEP, suggesting the biological efficacy is close to 100%.

- This level of protection is further supported by the open-label cohort study Prevenir [2], PK studies [3] including one with ex vivo tissue challenge [4], animal challenge data [5] and observational data from routine use in Europe since 2016. It is also of note that only 42% and 50% of participants in the blinded and open-label phases, respectively, in the IPERGAY study reported correct adherence, defined as at least one pill before and one after sex and in participants included in an analysis of drug levels by dried blood spot testing, the median level was consistent with two to three doses per week [6], also suggesting that the recommended dosing provides a very high level of protection.

- Two large RCTs showed that daily TDF-FTC is effective for insertive vaginal sex in heterosexual men [7,8]. Although lead-in times for insertive vaginal sex have not been assessed in placebo-controlled clinical trials, a PK/PD study evaluated a double-dose start of TDF-FTC and TAF-FTC and found that both were sufficient to reduce HIV transmission across foreskin tissue and peripheral blood mononuclear cells (PBMCs) in ex vivo challenge [9]. This, and the fact that the IPERGAY study [1] 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 cisgender 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 following a double-dose (two pills) start, protective levels of TDF-FTC in the female genital tract (FGT) were achieved in 99% of women 2 hours after dosing (*vs* 81% in rectal tissues) [4]. The data support a double-dose (two pills) lead-in (or one pill a day for 3 days) before receptive vaginal sex as the recommended dosing regimen for PrEP and for simplicity we have recommended a double-dose start for all types of exposure and for everybody (see Table 2 below). 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 RCTs of PrEP have included a significant population of transgender 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 2 hours prior to sex for the FGT and colorectal tissues; the 90% effective concentration (EC_{90}) was achieved in 98% and 81% of the population in FGT and colorectal tissues respectively [4]. After a double-dose start, administered 2 or 24 hours before sex, followed by single doses 24 and 48 hours later (2:1:1, event-based dosing or the '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. This suggests that if tissue levels are important in protection, 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 findings from 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 [HR] *vs* placebo 0.29, 95% CI 0.13–0.63 for TDF alone; HR 0.34, 95% CI 0.16–0.72 for TDF-FTC) [11]. As TDF alone does not (ever) reach EC_{90} in the FGT in the large majority of the population, this observation suggests that the level of drug in PBMCs is likely to be more important in preventing an established infection than levels in the FGT.

- The evidence in totality suggests that drug levels in PBMCs play the major role in protection. However, there is still some uncertainty regarding the implications of the more rapid decline in effective drug levels in the FGT, so we recommend continuing daily dosing for a full 7 days after receptive vaginal or neovaginal exposure, following a double-dose start, and lower tolerance of missed doses (three or more in the last week) when considering single-dose restart or the need for PEP (see Table 2, section 8.2 and Table 3).

- 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 conducted by Zhang et al in 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 lack of) efficacy of PrEP reported in heterosexual cisgender women is a function of low adherence rather than tissue drug concentrations [16].

- If PBMC drug levels are the relevant marker of protection, as the accumulating evidence suggests, then three to four 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 PK properties as opposed to adherence is

incompletely understood, but recent evidence suggests that adherence is the main and possibly sole driver of the observed difference in efficacy in heterosexual women. A pooled analysis and PK evidence published since 2023 support the suggestion that four doses per week provides high levels of protection for all types of exposure including receptive vaginal/neovaginal sex [12,17]. On this basis we suggest that regular TTSS dosing is a reasonable option for any user who needs or wishes to reduce oral PrEP dosing, although it is not possible to define the level of protection offered in comparison to daily dosing.

- When protection is known to depend on PBMCs alone, as is the case for blood-borne risk, FTC-TP is the active metabolite that first reaches protective levels, but it is useful to consider the number of doses required to achieve 16 fmol/M TFV-DP, the accepted benchmark for 90% protection [10,18]. Of interest, 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 of TDF-DP are maintained for at least another 7 days in PBMCs, with active metabolites still detected 14 days after the last dose [18].

- Modelling drug levels in PBMCs based on the Cottrell model and studies in women and applied to blood-borne risk in people who inject drugs suggested that for both TD-FTC and TAF-FTC, a single dose would provide protection within 0.5 hours and last for at least 84 hours for at least 99% of the population [19]. Two regular doses per week maintained protection in 100% of the population. For people who inject drugs, 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 PBMCs than following TDF [9], and 2-fold higher in foreskin tissue. Several studies have confirmed that levels of TFV-DP are lower in rectal tissues after TAF compared to TDF [20,21]; in spite of this, clinical equivalence was demonstrated in the Phase 3 RCT DISCOVER comparing daily TAF-FTC to TDF-FTC [22]. There were fewer 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 4 hours in genital tissues and PBMCs and is the main driver of potency in the FGT [20]. TFV-DP levels in PBMCs are also higher with TAF-FTC and maintained for longer than for TD-FTC [19]. Of the limited available clinical efficacy trial data comparing TDF-FTC and TAF-FTC in women, in the control arm of the Purpose 1 study of injectable lenacapavir [23], there was no statistical difference in HIV incidence between TAF-FTC and TDF-FTC, and adherence was very low in both arms. Based on the reviews and modelling studies suggesting that the low and variable efficacy of TDF-FTC in cisgender women is a function of adherence rather than biology [17,24], we believe that this is likely to apply equally to TAF-FTC, and based on the PK evidence, that TAF-FTC is at least as effective as TDF-FTC.

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

	TD-FTC 200/245 mg or TAF-FTC 200/25 mg fixed-dose combinations		
	Time to start of protection	**Safely stopping**	**Restarting**
Receptive anal sex	Double dose (2 pills) 2–24 hours before risk	Continue single dose daily for 2 days after last risk	Restart with a single dose if less than 7 days since last dose*
Insertive vaginal/ neovaginal/anal sex	Double dose (2 pills) 2–24 hours before risk	Continue single dose daily for 2 days after last risk	Restart with a single dose if less than 7 days since last dose*
Receptive vaginal/ neovaginal sex	Double dose (2 pills) 2–24 hours before risk	Continue single dose daily for 7 days after last risk	Restart with a single dose if less than 3 days since last dose*
Injection drug use	Double dose (2 pills) 2–24 hours before risk	Continue single dose daily for 7 days after last risk	Restart with a single dose if less than 4 days since last dose*

*Last dose of a complete course (i.e. time to start of protection + time to safely stop) according to exposure, or daily dosing. If doses have been missed, see section 8.2 and Table 3 below.

8.2 Indications for PEP in PrEP users

Recommendations for PEP in PrEP users who have medication available (see Table 3)
Sexual risk* through condomless anal sex/insertive vaginal sex
68. We recommend that if the risk of HIV acquisition is through condomless insertive or receptive anal sex or insertive vaginal or neovaginal sex, and if ≤7 days have elapsed since the last oral PrEP dose, PrEP should be resumed with a double dose as prescribed** (Grade 1B).
69. We recommend that if more than 7 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 24 hours (Grade 1B) after exposure and no later than 72 hours (Grade 2C), and continued daily while seeking advice from clinical services on possible intensification to PEP.
Sexual risk* through condomless receptive vaginal/neovaginal sex
70. We recommend that if the risk of HIV acquisition is through condomless receptive vaginal or neovaginal sex, and if ≤3 days have elapsed since the last oral PrEP dose, PrEP should be resumed with a double dose as prescribed (vaginal, Grade 1B; neovaginal, Grade 2C).
71. We recommend that if more than 3 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 24 hours

after exposure (vaginal, Grade 1B; neovaginal, Grade 2C) and no later than 72 hours (Grade 2C), and continued daily while seeking advice from clinical services on possible intensification to PEP.
Blood-borne risk for people who inject drugs
72. We recommend that, if the risk of HIV acquisition is through injecting drug use and if ≤4 days have elapsed since the last oral PrEP dose, PrEP should be resumed with a double dose as prescribed (Grade 1D).
73. We recommend that, if more than 4 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 24 hours after exposure and no later than 72 hours, and continued daily while seeking advice from clinical services on possible intensification to PEP (Grade 1D).
Missed post-coital dose for event-based PrEP
74. We recommend that, for event-based (2:1:1) 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 (Grade 1B); the second post-coital dose should be taken 24 hours after the first to complete the course.
75. We recommend that if more than 48 hours have elapsed after the last risk or for 2:7 dosing, the first dose should be taken and daily dosing continued until advice is sought from clinical services (Grade 1B).
GPPs
• PrEP users should routinely be given advice about what to do in the event of an HIV risk, with or without PrEP medication available.
• It is important that PrEP users understand that PrEP and PEP only reduce the risk of HIV acquisition when medication 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.
• PEP should be considered if there has been significant risk exposure within the preceding 72 hours at the point of first initiating PrEP. If there are two or more risk episodes more than 72 hours before initiation, so PEP is not indicated, PrEP should be initiated with HIV testing as recommended in section 6.3.
• PrEP users should be informed about how to access PEP advice in a timely manner.

*Sexual risk: no condom, partner not on suppressive ART or PrEP.

**We recommend that when PrEP tablets are started or restarted after an exposure, the initial dosing regimen is used. This means that a double-dose start should be used in every case. We acknowledge that for people having insertive or receptive anal sex, or insertive vaginal or neovaginal sex, the prescribed starting dose if a PrEP tablet has been taken within the last 7 days would be a single tablet dose (as per the 'IPERGAY regimen'; see Table 2). The need for a double dose will depend on the type of exposure, the time elapsed since exposure (up to 72 hours) and the absolute number of doses taken in the preceding 7 days. Where a total of four or more tablets have been taken in the last 7 days, it is likely that levels will be protective with an additional single tablet but for consistency and given the lack of direct evidence in this area, we suggest that a double dose is used routinely.

Note on recommendations

PrEP users need to understand how to use their PrEP after exposure (or in cases where PrEP was initiated with a double-dose less than 2 hours before exposure) if required. If there is insufficient drug in the tissues at the time of exposure to HIV, PrEP users have two of the three drugs usually used as PEP available. The aim is that PrEP should be self-initiated as soon

after exposure as possible and in most cases this should be within a few hours. For clarity, we do not use the term 'PEP' (to include PEPSE) for the taking of PrEP tablets after exposure.

Key evidence summary for PEP in PrEP users

- There is consistent evidence from animal challenge studies supporting the effectiveness of short-course antiretroviral prophylaxis (one or two timepoints only) that is started prior to challenge or within 24 hours [5,25-28]. Starting PEP beyond 24 hours has been evaluated in two animal challenge experiments using simian–human immunodeficiency virus (SHIV) challenge models [25,28].

- In the study by Otten et al [25], protection was seen in 4/4 animals 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 PEP, even when only TDF-FTC is used, are highly effective if administered in the first 24 hours after exposure [15,27,28]. Bekerman et al evaluated TAF-FTC-bictegravir 100 mg taken 48 and 72 hours after challenge and 3/6 animals were protected [28].

- The earliest estimate for completion of the viral cycle is 28 hours [29] and this explains why PEP is most effective when started within 24 hours. Within a few days HIV viral replication in $CD4^+$ T cells becomes exponential with expansion to gut-associated lymphoid tissue, lymph nodes and spleen and beyond. Fiebig profiles estimated the window period to detection of HIV RNA to be 5 days. 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 [30] 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 PBMCs, effective drug levels associated with 90% reduction in risk, as defined by Anderson et al in 2012 [31], are maintained for at least 7 days in both compartments once achieved [31,32]. Although PBMCs are not impacted by gender, effective levels are only maintained for 2–3 days in the FGT, where the principle driver of protection is FTC-TP. If tissue levels in the FGT are important, 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 EC_{90} level of 16 fmol/M for TFV-DP in PBMCs was established based on a pharmacological study (STRAND) and a case–control analysis of iPrEx by Anderson et al [31]. In HPTN 066 and STRAND dosing was observed for regimens of one (HPTN 066 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 PBMCs considered to be 90% effective and two doses a week somewhat below this in both studies (9 and 11 fmol/M respectively). Other studies confirmed the compartment differences with effective drug levels persisting for longer in colorectal tissues and for a shorter time in the FGT.

- TFV-DP concentration is dose proportional so higher doses, and more frequent doses (e.g. daily), result in higher drug concentration in tissues. Provided at least two tablets a week have been taken, drug levels are likely to be boosted to adequate protection with the next single dose in PBMCs and colorectal tissues. Although drug levels in PBMCs are likely to be far more important for protection than those in genital tissues, we take the cautious approach of advising a double dose (two tablets) to boost levels in the FGT. For consistency, we also suggest a double-dose start in all cases where PrEP is restarted following exposure.

- 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 concentration–dose proportionality and compartmental variation are consistent. A double dose (two tablets) will result in higher concentrations of TFV-DP in tissues and PBMCs within 24 hours, 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 PEP (noting that PEP [including PEPSE] as prescribed in the UK routinely involves the use of three drugs, usually TDX-FTC and raltegravir).

Table 3. Summary for PrEP users who have medication available

Note: if no PrEP medication is available, seek urgent PEP assessment.

Sexual risk (no condom, partner not on ART or PrEP)	**Time between last PrEP dose before exposure and resumption of PrEP**	**Recommendation after exposure**	**Level of evidence**
Insertive/receptive anal sex or insertive vaginal sex	≤7 days	Resume PrEP with a double dose as prescribed	1B: PK/PD; RCT
	>7 days	Take a double dose of PrEP as soon as possible in the 24 hours after exposure, continue daily and seek urgent advice from clinical services for intensification to PEP	1B: animal challenge; PK/PD
Receptive vaginal sex	≤3 days	Resume PrEP with a double dose as prescribed	1B: PK/PD
	>3 days	Take a double dose of PrEP as soon as possible in the 24 hours after exposure, continue daily and seek urgent advice from clinical services for intensification to PEP	1B: animal challenge; PK/PD
Receptive neovaginal sex	≤3 days	Resume PrEP with a double dose as prescribed	2C
	>3 days	Take a double dose of PrEP as soon as possible in the 24 hours after exposure, continue daily and seek urgent advice from clinical services for intensification to PEP	2C
Injecting drug use	≤4 days	Resume PrEP with a double dose as prescribed	2C
	>4 days	Take a double dose of PrEP as soon as possible in the 24 hours after exposure, continue daily and seek urgent advice from clinical services for intensification to PEP	2C

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9 Buying generic PrEP online

Recommendations for buying generic PrEP online
76. We recommend that clinicians should ensure full PrEP support, including renal monitoring, for individuals who are taking oral PrEP that they have sourced online (Grade 1D).
77. We recommend that therapeutic drug monitoring is **not** required for those taking self-sourced oral PrEP (Grade 1B).
For those self-managing their PrEP use
78. We recommend that HIV testing with a laboratory antigen/antibody test is undertaken prior to commencing oral PrEP, which can be provided through self-sampling (Grade 1A).
79. We recommend that 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 (Grade 1A) or a blood-based POCT (Grade 1B).
80. Self-testing for HIV (using saliva or blood samples) is not recommended for people at initiation of PrEP and ongoing regular monitoring should be undertaken with blood-based combined HIV antigen/antibody self-sampling or clinic-based testing (Grade 1B).
GPPs
• Clinicians can signpost individuals to IWantPrEPnow or PrEPster if they are unable or unwilling to access PrEP on the NHS. These sites offer support and advice and the ability to source generic drugs as safely as possible.
• The discussion of self-sourcing PrEP online needs to be fully informed including the risks and benefits described in section 4 and section 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 Food and Drug Administration (FDA) and that it is advisable to order in advance in case of delays in delivery.
• Clinicians should recommend that people buying TD-FTC or TAF-FTC ensure that they 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 these guidelines.

Key evidence summary for buying generic PrEP online

- While data from annual PrEP user surveys [1] conducted by PrEPster, iwantPrEPnow and UKHSA suggest 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].

- Despite oral PrEP being routinely available through publicly funded clinics in all four nations of the UK, and through a range of private clinics, some people still prefer to self-source PrEP online [2]. Online PrEP provision is available through mainstream UK pharmacy services, often incorporating online clinical assessment and advice, or online pharmacies based outside the UK. Some people prefer the flexibility of self-managing

check-ups as needed. Others who are geographically isolated or feel highly burdened by 3-monthly check-ups, or are affected by other barriers to access as outlined in section 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 these guidelines 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.

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

- For some people, self-sourcing may be the only option if different types or formulations of PrEP are required. 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.

9.1 Authenticity of TD-FTC and TAF-FTC 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 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 to the UK is substandard (i.e. contains less or variable amounts of active ingredients), nor has there ever been evidence of counterfeit PrEP in circulation.

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

9.2 Importing medicines bought online

- In the UK, the 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 of authorisation, but the 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.

9.3 References

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10 New therapies

Note: guidance on CAB-LA in this section was written in advance of NICE regulatory approval being granted.

Recommendations for new therapies not yet commissioned
81. We recommend that CAB-LA should be offered under compassionate release to those at risk of HIV, but who have contraindications to oral PrEP options (Grade 1A).
82. We recommend that CAB-LA is strongly supported as an alternative to a daily PrEP pill (Grade 1A).
83. We suggest that an oral lead-in for CAB-LA as PrEP is optional for people worried about side effects (Grade 2B).
84. We recommend that 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 (Grade 1B).
85. We recommend that people are advised that protective levels of CAB-LA are achieved 7 days following the first injection (Grade 1A).
86. We recommend that the second CAB-LA injection is given a month after the first (Grade 1A).
87. We recommend that people are advised that protective levels of CAB-LA are maintained for 2 months after the second and subsequent injections (Grade 1A).
88. We recommend that people on CAB-LA have both HIV antigen/antibody and HIV viral load testing every 8 weeks (Grade 1A).
89. We recommend that when CAB-LA is discontinued and risk of HIV continues, an alternative PrEP agent is initiated, starting at 2 months and continuing to at least 12 months after the last CAB-LA injection or as long as risk continues (Grade 1B).
90. We recommend that routine renal, liver and lipid monitoring are not required for those on CAB-LA for PrEP (Grade 1A).
91. 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 (Grade 1A).
92. We recommend that CAB-LA should be avoided in people taking certain anticonvulsants (e.g. carbamazepine and phenytoin) and anti-mycobacterial agents such as rifampicin and rifabutin as drug–drug interactions with these medications significantly reduce cabotegravir plasma concentrations to subtherapeutic levels (Grade 1C).
93. We recommend that a monthly 25 mg dapivirine ring provides a modest, but significant, reduction in HIV incidence in women for whom alternative forms of PrEP are unacceptable or unsuitable [1,2] (Grade 1A).
GPPs
• People considering switching from TD-FTC to CAB-LA should be advised of the risk of modest weight gain due to removal of the weight gain suppressive effect of TD-FTC. Individuals initiating CAB-LA who are PrEP naïve, or switching from non-TD-FTC-based PrEP (such as TAF-FTC), should expect similar weight trajectories to the general population.
• Where individuals are already established on new PrEP therapies on arrival in the UK, clinicians should endeavour 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 therapies not yet commissioned

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

10.1 CAB-LA

- Injectable cabotegravir (Apretude) for PrEP was licensed by the EMA in September 2023 [3]. CAB-LA for PrEP received UK approval from the MHRA in May 2024 [4]. The application for SMC authorisation was approved in February 2025. At the time of writing, NICE approval is under consideration.

10.1.1 Efficacy of CAB-LA

GBMSM and transgender women

- CAB-LA was superior to oral TDF-FTC PrEP in a published RCT reporting data from the blinded study period in GBMSM and transgender women (HPTN 083) [5,6].

- After a final ascertainment of HIV status, there were 13 versus 39 incident HIV infections in the CAB-LA and the TDF-FTC groups respectively (HR 0.31, 95% CI 0.16–0.58, p < 0.001) [5]. In those who acquired HIV infection in the active TDF-FTC group, none had protective plasma levels of drug.

Cisgender women

- CAB-LA was also superior to oral TDF-FTC PrEP in an RCT reporting data from the blinded study period in heterosexual cisgender women at high risk of HIV in sub-Saharan Africa (HPTN 084) [6].

- After a final ascertainment of HIV status, there were 4 versus 36 incident HIV infections in the CAB-LA and the active TDF-FTC groups respectively (HR 0.10, 95% CI 0.04–0.27, p < 0.0001) [6].

Young people

- A subpopulation of 55 female adolescents recruited from three African countries in HPTN 084 (age range 12–17 years, mean 16 years) found CAB-LA to be safe, tolerable and acceptable, and preferable to oral PrEP in 92% [7].

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 CAB-LA/rilpivirine [8,9]. The impact of subtype A6 on efficacy of CAB-LA for PrEP is currently unknown and should not inform choice of PrEP agent [10].

10.1.2 Time to protection for CAB-LA

- Plasma cabotegravir concentrations above the in vitro protein-adjusted 90% maximal inhibitory concentration (PA-IC_{90}) provided protection in 97% of male macaques challenged intrarectally and 4x PA-IC_{90} provided protection for 90% of female macaques challenged intravaginally with SHIV [11,12].

- In Phase 1 trials of healthy human adults, median plasma target levels (>4x PA-IC_{90}) of CAB-LA (600 mg intramuscular injection) were achieved within 3 days (first measurement taken at 3 days) after ultrasound-guided gluteal injection and reached maximum plasma concentrations with median time to reach maximum concentrations (T_{max}) at 7 days. The target level of >4x PA-IC_{90} was maintained for 2 months in 100% of participants [13].

- The CAB-LA tail is approximately 1 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-IC_{90}) consistently last up to 8 weeks after the last injection.

- In a Phase 1/2 study of cabotegravir (with rilpivirine) for treatment of HIV in 23 adolescents aged 12–17 years, plasma levels were comparable to those observed in an RCT of adults [16].

10.1.3 Oral lead in

- Oral lead-in for cabotegravir as PrEP should be optional for people worried about side effects. Available PK data indicate that CAB-LA trough concentrations were similar with and without oral lead-in ($p > 0.3$) [17]. Without oral lead-in, it was predicted that 80% of participants achieve 4× PA-IC_{90} in 1.2, 1.8 and 2.8 days after the first injection after the first injection in three different study populations (male, 50% female/50% male and female) respectively, and 50% achieve 8× PA-IC_{90} in 1.4, 2.1 and 3.8 days, respectively, supporting optional oral lead-in use.

10.1.4 Safety for CAB-LA

Monitoring

- Based on the clinical trial evidence [18], renal, liver and lipid monitoring are not required for those on injectable CAB-LA.

Adverse events

- In HPTN 083 (GBMSM and transgender women), 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 in the active arm who permanently discontinued injections due to an injection-site reaction [5].

- In the HPTN 084 trial, injection-site reactions were less commonly reported, with only 38% of participants in the CAB-LA arm reporting injection-site reactions, compared with 10.8% in the placebo injection arm, and none discontinued for this reason. Most injection-site reactions were reported at the first injection and diminished over time [6]. A warm compress and simple analgesia such as paracetamol can be used to counteract the pain of injection-site reactions.

- There were no differences in grade 2 or 3 adverse events relating to creatinine clearance in HPTN 083 or HPTN 084 for CAB-LA versus TDF-FTC (HPTN 083 grade 2 adverse events 69.6% *vs* 73.1% and grade 3 adverse events 7.0% *vs* 8.3% for CAB-LA *vs* TDF-FTC, respectively; HPTN 084 grade 2 adverse events 72.2% *vs* 74.3% and grade 3 adverse events 6.8% *vs* 7.8%, respectively) [5,6]. The WHO recommends that renal monitoring is not required for CAB-LA [19].

- There were no differences in grade 3 adverse events of raised ALT or aspartate aminotransferase (AST) in HPTN 083 or HPTN 084 (HPTN 083 ALT 1.0% *vs* 1.4% and AST 2.3% *vs* 3.0% 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) [5,6]. CAB-LA is not active against HBV or HCV.

Weight gain

- There was a small, but statistically significant difference in annualised weight gain between CAB-LA and TDF-FTC in HPTN 083 and HPTN 084 [5,6]. In HPTN 083 (GBMSM and transgender women), differences in weight change were 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 (cisgender women in sub-Saharan Africa), 25% of participants were obese (body mass index ≥30 kg/m^2) at baseline with a mean weight gain of 2 kg/year and no difference by trial arm. Therefore, people considering switching from TD-FTC to CAB-LA should be advised of the risk of modest weight gain due to removal of a weight gain suppressive effect of TD-FTC.

- Individuals initiating CAB-LA who are PrEP naïve, or switching from non-TD-FTC-based PrEP (such as TAF-FTC), should expect similar weight trajectories to the general population.

Hepatitis status

- Testing for HBV and HCV is indicated with referral for those with positive test results to specialist services. CAB-LA is not active against HBV and TDF-based oral PrEP should be offered as the preferred PrEP option for people who are HBsAg positive.

Pregnancy

- Pregnancy was a contraindication to recruitment in HPTN 084 with a requirement to use long-acting contraception, however 138 pregnancies were recorded during the study including 63 in the CAB-LA group. No known adverse pregnancy outcomes were recorded related to CAB-LA [6].

- Maternal, pregnancy and infant outcomes with CAB-LA for PrEP were reported for the HPTN 084 OLE [20]: 2472/3224 (76.7%) participants entered the HPTN 084 OLE phase and were offered a choice of CAB-LA or TDF-FTC for HIV PrEP. Maternal, pregnancy and infant safety outcomes during the HPTN 084 OLE were evaluated (pregnancy incidence, maternal adverse events and poor pregnancy outcomes). A total of 351 pregnancies in 334 participants were reported. No maternal deaths were reported. One major congenital anomaly was observed in the CAB-LA PrEP during pregnancy group. Incidence of pregnancy-related adverse events (per 100 person-years) was reported as: (i) CAB-LA PrEP during pregnancy, 43.7 (95% CI 30.9–60.0); (ii) CAB-LA PrEP before pregnancy, 52.9 (95% CI 24.2–10.5); and (iii) CAB-LA PrEP not used, 40.0 (95% CI 14.7–87.1). CAB-LA for PrEP was generally well tolerated during pregnancy, with consistent outcomes across exposure groups.

Young people

- Safety data are limited in people under 18 years. In HPTN 084, 52 young participants completed up to week 33 injections and three stopped CAB-LA for unrelated drug adverse events [16].

Transgender people

- CAB-LA for PrEP has demonstrated efficacy and tolerability among transgender women, with PK concentrations not affected by GAHT [21].

Metabolism

- CAB-LA is metabolised by uridine diphosphate glucuronosyl transferase (UGT) 1A1. Possible drug interactions due to induction of UGT1A1 and UGT1A9 should be considered when prescribing CAB-LA. These include interactions with anticonvulsants and antimycobacterial agents such as rifampicin; see table 6 in the summary of product characteristics (SmPC) [22]. The co-administration of oral antacid products with oral CAB-LA 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 [23].

Breakthrough HIV infection

- CAB-LA is highly effective at preventing HIV infection. However a total of five incident and 15 prevalent infections were observed in the CAB-LA arms of HPTN 083 and 084 combined, of which six (all in HPTN 083) were regarded as possible pharmacological failures having evidence of on-time CAB-LA injections with adequate CAB-LA levels [24]. Long-acting early viral inhibition has been described on CAB-LA PrEP where HIV viral suppression and delayed/diminished antibody expression persisted for months, even after CAB-LA injections were discontinued. Testing with a sensitive RNA assay (30-copy lower limit of detection) detected most infections before integrase inhibitor (INSTI) resistance emerged [25-27].

Resistance

- In HPTN 083 [27], INSTI resistance was detected in one of the four baseline infections and four of the nine incident infections (compared with nucleoside reverse transcriptase inhibitor 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 showed that one case was susceptible to dolutegravir, one case susceptible to bictegravir and one partially susceptible to bictegravir. Two cases were resistant to cabotegravir, elvitegravir and raltegravir.

10.1.5 Monitoring on CAB-LA

- MHRA and EMA guidance is that individuals must be tested for HIV prior to initiating CAB-LA and at each subsequent injection of CAB-LA. A combined antigen/antibody test as well as an HIV RNA-based test should both be negative. Prescribers are advised to perform both tests, even if the result of the HIV RNA-based test will become available after CAB-LA injection. This is based on the SmPC [28,29] and the 62-day delay in diagnosis observed in HPTN 083 [4,27] when HIV RNA testing was not conducted in real-time. Incident infections in adherent users of CAB-LA were very infrequent in the clinical trials, but RNA testing (plus HIV antigen/antibody testing) on the day of the switch is recommended. Other tests recommended when starting oral PrEP in the UK (see section 6) should also be conducted, although there is no evidence from clinical trials to suggest that ongoing routine renal or hepatic monitoring is indicated.

- MHRA guidance is that individuals who miss a scheduled injection visit should be reassessed to ensure resumption of PrEP remains appropriate. If a delay of more than 7 days from a scheduled injection date cannot be avoided, it will be a missed dose; therefore, cabotegravir 30 mg tablets may be used once daily, for a duration of up to 2 months, to replace one scheduled injection visit. The first dose of oral therapy should be taken approximately 2 months (+/- 7 days) after the last injection of CAB-LA. For oral PrEP durations greater than 2 months, an alternative PrEP regimen is recommended. Injection dosing should be resumed on the day oral dosing is completed or within 3 days thereafter [28,30].

- According to the SmPC recommendations, people using CAB-LA for PrEP should have HIV RNA testing every 2 months. RNA screening is highly sensitive, but may lead to false positives [31]. People with detectable HIV RNA while on CAB-LA should be urgently recalled to assess history of adherence, discuss the risks and consider antiretroviral intensification. Repeat fourth-generation HIV antigen/antibody testing, HIV RNA and resistance testing (including INSTI resistance) should be undertaken and any concerns of HIV confirmation testing referred to the UKHSA/IDRIS clinic for discussion (imperial.idris@nhs.net). Consider intensification according to BHIVA HIV treatment guidelines [32].

10.2 Dapivirine ring

- The dapivirine ring is inserted vaginally, has a 24-hour lead-in and releases dapivirine locally over a month with no systemic release. The dapivirine ring resulted in modest

protection when compared to a placebo ring in two RCTs (27% and 35% reduction in HIV incidence) [1,2]. Although there was evidence of some use in over 80% of participants 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 3/4 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 STIs between the two groups in this trial.

- Continuing use of the 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 CAB-LA for HIV prevention is available outside of the USA. The manufacturer (ViiV) will facilitate access to CAB-LA through a compassionate release scheme in UK jurisdictions in which CAB-LA is not yet reimbursed. CAB-LA is no longer available through compassionate release in Scotland (following the SMC decision in February 2025) but is available in the other nations pending relevant approvals. Requests by the treating physician can be made via the manufacturer's website: https://viiv-cu-portal.idea-point.com/. Registration and online request forms need to be completed.

- The Population Council has taken on responsibility for the International Partnership for Microbicides, a non-profit organisation that develops HIV prevention technologies (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 permission to import the ring.

10.4 Switching from dapivirine ring or CAB-LA 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 enzyme-linked immunoassay should be performed on the day of the switch, together with any other tests recommended when starting oral PrEP in the UK (see section 6).

- Men, women and transgender populations using CAB-LA who are established on the 8-weekly regimen can switch to oral PrEP 8 weeks after the last injection. Because of the long PK 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. The results of Phase 3 clinical trials of the use of lenacapavir as PrEP (PURPOSE 1 and 2) using lenacapavir as a subcutaneous injection given every 26 weeks (6 months) were reported in 2024.

- The interim results of the PURPOSE 1 trial of lenacapavir for PrEP, comparing subcutaneous lenacapavir versus TAF-FTC or TDF-FTC in adolescent girls and young women in South Africa and Uganda, demonstrated superiority to daily oral TDF-FTC and TAF-FTC, with no HIV acquisitions reported in the 2134 women receiving lenacapavir [33].

- In the parallel PURPOSE 2 trial comparing subcutaneous lenacapavir versus TDF-FTC in cisgender men, transgender women, transgender men and gender non-binary individuals who have sex with partners assigned male at birth, there were only two incident infections in 2180 participants receiving lenacapavir [34].

- Both the PURPOSE 1 and 2 trials are scheduled to run until 2027.

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	Cisgender women	Median age: 26 years (IQR: 22–31). African women 100%	Vaginal	Monthly dapivirine ring *vs* placebo	Overall rate of retention 85%, no significant difference between the two arms. PK: 82% plasma samples >95 pg/mL; 84% returned rings in substudy <23.5 mg and correlation with plasma samples although the range included discordant values including high residual when plasma levels >95 mg/mL	71/1313 *vs* 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% of 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	Cisgender women	Mean age: 26years (range 18–45). Black African 99%, other 1%	Vaginal	Monthly dapivirine ring *vs* placebo	PK: 84% of plasma samples ≥95 pg/mL 83% rings ≤23.5 mg with at least 73% of participants at all visits fulfilling both criteria	77/1300 *vs* 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% *vs* 2%)
HPTN 083 [5]	RCT 1:1	USA, Latin America, Asia, Africa	4566	Cisgender GBMSM and transgender women	Median age: 26 years GBMSM 87.4%, transgender women 12.5%,	Rectal	CAB (OLI+LA) and TDF-FTC placebo *vs* CAB-LA placebo and 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/mL; 86.0% tenofovir concentrations >0.3 ng/mL	13 *vs* 39 infections HR 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)	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

					unspecified 0.1%. Of 1698 US participants, 49.8% identified as Black				HR 0.37 (95% CI 0.19–0.65)	
HPTN 084 [6]	RCT 1:1	Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zimbabwe	3224	Cisgender women	Median age: 25 years (IQR 22–30)	Vaginal	CAB-LA and TDF-FTC placebo *vs* CAB-LA placebo and TDF-FTC	TDF-FTC subgroup (362), 48% tenofovir concentrations >40 ng/mL. 64.0% tenofovir concentrations >0.3 ng/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) HR 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) [35]	OLE	Malawi, South Africa, Uganda, Zimbabwe	1456	Cisgender women (ASPIRE extension)	Median age: 31 years (IQR 27–37). African women 100%	Vaginal	Monthly dapivirine ring offered	PK: 89% had more than 0.9 mg 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 100 PY (95% CI 1.9–3.8) *vs* 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. 4.4/100 PY predicted by simulations based on the placebo group of preceding ASPIRE trial
DREAM IPM032 [36]	OLE	South Africa Uganda	931	Cisgender 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 100 PY (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

IQR, interquartile range; ITT, intention to treat; mITT, modified intention to treat; NNRTI, non-nucleoside reverse transcriptase inhibitor; OLI, oral lead-in; PY, patient-years; ROB, risk of bias.

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11 List of abbreviations

3TC	Lamivudine
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the curve
BASHH	British Association for Sexual Health and HIV
BHIVA	British HIV Association
BMD	Bone mineral density
BTS	Bangkok Tenofovir Study
CAB-LA	Long-acting injectable cabotegravir
CEG	BASHH Clinical Effectiveness Group
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum concentration
CROI	Conference on Retroviruses and Opportunistic Infections
DAA	Direct-acting antiviral
DoxyPEP	Doxycycline post-exposure prophylaxis
DXA	Dual-energy X-ray absorptiometry
EACS	European AIDS Clinical Society
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EC_{90}	90% effective concentration
FDA	Food and Drug Administration
FGT	Female genital tract
FTC	Emtricitabine
FTC-TP	Emtricitabine triphosphate
GAHT	Gender-affirming hormone therapy
GBMSM	Gay, bisexual and other men who have sex with men
GP	General practitioner
GPP	Good practice point
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIV4P	HIV Research for Prevention
HR	Hazard ratio
IAS	International AIDS Society
IDRIS	Indeterminate Retrovirus Infection Service
INSTI	Integrase inhibitor
IPERGAY	Intervention Préventive de l'Exposition aux Risques avec et pour les Gays
IQR	Interquartile range
ITT	Intention to treat
MDRD	Modification of Diet in Renal Disease
MDT	Multidisciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention to treat
MVC	Maraviroc
NET-EN	Norethisterone enanthate
NICE	National Institute for Health and Care Excellence

NNRTI	Non-nucleoside reverse transcriptase inhibitor
OLE	Open-label extension
OLI	Oral lead-in
P1NP	Procollagen-I N-terminal propeptide
PA-IC_{90}	Protein-adjusted 90% maximal inhibitory concentration
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic
PEP	Post-exposure prophylaxis
PEPSE	Post-exposure prophylaxis following sexual exposure
PICO	Population, Intervention, Comparison, Outcome
PK	Pharmacokinetic
POCT	Point-of-care test
PrEP	Pre-exposure prophylaxis
PY	Patient-years
RCT	Randomised controlled trial
ROB	Risk of bias
SHIV	Simian–human immunodeficiency virus
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STI	Sexually transmitted infection
TAF	Tenofovir alafenamide fumarate
TDF	Tenofovir disoproxil fumarate
TDF-FTC	Tenofovir disoproxil fumarate-emtricitabine (Truvada)
TD-FTC	Generic forms of tenofovir disoproxil with emtricitabine
TD-XTC	Tenofovir disoproxil salts with emtricitabine or lamivudine
TDX	Tenofovir disoproxil
TDX-FTC	Tenofovir disoproxil-emtricitabine (Descovy)
TFV-DP	Tenofovir diphosphate
T_{max}	Maximum concentration
UGT	Uridine diphosphate glucuronosyl transferase
U=U	Undetectable=Untransmittable
UKHSA	UK Health Security Agency
WHO	World Health Organization
XTC	Emtricitabine or lamivudine