PrEP & EACS Guidelines: Practical aspects

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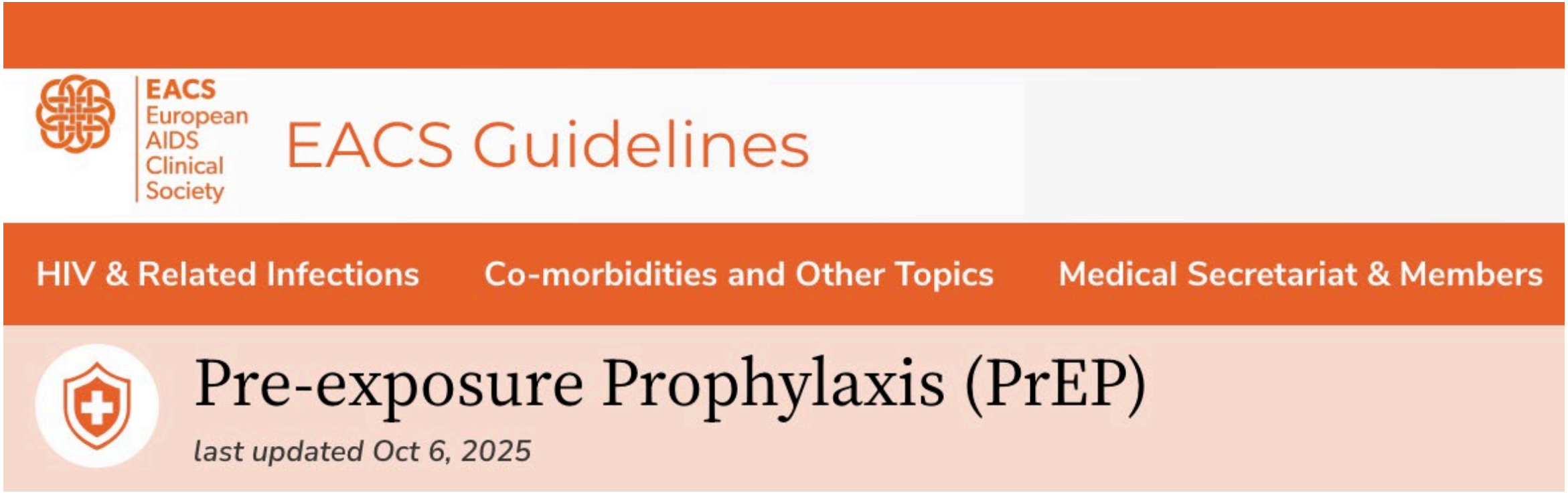

-GL are updated yearly, last update presented at EACS Conference, Paris 2025

-Consider timing for approval, availability & implementation in different countries (E.g large differences in availability of long-acting ARVs in Europe –CAB LA approved by EMA but implemented in few countries-)

Some general considerations

- The level of evidence differs for each recommendation:

Examples:

-Efficacy of CAB and LEN LA for PrEP (**very high**, based on large phase 3 RCT)

-Time to reach protective concentrations in different compartments such as rectal tissue, or female genital tract (**low**, based on animal models, PK modelling & small pilot studies)

-PrEP-to-PEP or PEP-to-PrEP (**very low**, mostly based on expert opinion)

Some general considerations

- PrEP is a preventive elective tool: in face of poor level of evidence, a more conservative approach is appropriate.

- PrEP is not a unique or isolated preventive measure, it only provides protection against HIV (HBV) and should be considered as one tool within a larger sexual health & prevention approach

1. Principles

PrEP should be offered to sexually active individuals likely to be exposed to HIV when condoms are not used consistently.

- Recommended in HIV-negative men who have sex with men (MSM) and transgender individuals when condoms are not used consistently with casual partners or with partners with HIV who are not virally suppressed on treatment. A recent STI, use of post-exposure prophylaxis or chemsex (see Chemsex) may be markers of increased risk for HIV
- Recommended in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and may have partners with untreated or inadequately suppressed HIV infection

Practical aspects → proportion of cis-women on PrEP extremely low across Europe

2. Procedures

PrEP is a medical intervention that provides a high level of protection against HIV acquisition but does not protect against other STIs or pregnancy and should be used in combination with other preventive interventions. PrEP should be supervised by a doctor, experienced with sexual health and use of HIV medicines, possibly as part of a shared care arrangement

Practical aspects → medical involvement not required during the entire process of PrEP administration, but essential for supervision & processes such as diagnosis & treatment of STI, or interpretation of diagnostic tests for HIV

Recommended procedures (I)

- Documented negative fourth generation HIV test a week prior or on the day PrEP is initiated
- An HIV RNA test on plasma should be performed before or on the day of PrEP initiation, or upon PrEP re-initiation if PrEP has been discontinued, in particular when high-risk exposure has happened in the preceding 6 weeks (see Primary HIV Infection (PHI))or when PrEP with injectable cabotegravir or lenacapavir is used. The delay in receiving HIV RNA results should not delay PrEP initiation in high-risk patients
- During PrEP, a fourth generation HIV test should be repeated at one month and then every 2-4 months. In stable long-term users who are on 6 monthly prescriptions, an interim fourth generation test can be performed without a visit to clinic. When PrEP with cabotegravir is used, an HIV RNA test can be performed before injections but is not mandatory
- PrEP should be immediately changed to a standard triple-drug ART without interruption in case of early clinical signs of HIV seroconversion or a positive HIV diagnostic test which may necessitate referral for evaluation to a specialised HIV unit, see ART initiation
- PrEP may continue during pregnancy and breastfeeding if the risk of acquiring HIV persists

Practical aspects → categoric exclusion of very recent primary HIV infection is not always possible. If a risk contact has occurred <7 days, no test can reliable exclude eclipse phase of Primary HIV infection.

-If risk contact is <72 hs, consider PEP and then PrEP. Follow-up testing for late HIV seroconversion after PEP-to-PrEP switch is not clearly established.

-In very selected cases, beyond PEP window, consider delaying PrEP initiation and repeat NAT-based test (not available in many settings)

Recommended procedures (II)

- Before or on the day PrEP is initiated, HBV serology status should be documented. If HBsAg positive, see PrEP in persons with chronic HBV co-infection below, Clinical Management and Treatment of HBV and HCV Co-infection
- Counsel that PrEP does not prevent other types of STIs; screen for STI (syphilis, chlamydia, gonorrhoeae, HAV, HCV) when starting PrEP and regularly during use of PrEP, see Assessment of Initial & Subsequent Visits and STI screening and treatment)
- All persons taking PrEP should be offered vaccinations against HAV, HBV, HPV and mpox virus and doxycycline post-exposure prophylaxis when indicated (see STI screening and treatment)and Prophylaxis for Bacterial STIs)
- Counsel that TDF-based PrEP may rarely impact renal and bone health, see Bone Disease: Screening and Diagnosis, Approach to Fracture Reduction, Kidney Disease: Definition, Diagnosis and Management, ARV-associated Nephrotoxicity. Check renal function within the first 3 months of starting PrEP and check renal function and bone health during PrEP according to guidelines on TDF use and switch to TAF accordingly
- Counsel that PrEP, like other prevention methods, only works when it is taken. An adherence check early after starting PrEP is recommended, and counselling may be required during follow-up
- Counsel that PrEP can be prescribed long-term but that each consecutive PrEP prescription should cover the period to the next visit and could be a maximum of 6 months in stable long-term users (over one year of daily PrEP)

Practical aspects → Adherence to PrEP is ESSENTIAL.

-Most studies addressing breakthrough HIV diagnoses in PrEP users highlight low adherence in the majority of people who seroconverted

-Prevention of other STI EQUALLY ESSENTIAL. Frequency and indication for testing very different across Europe

PrEP Adherence and HIV seroconversion

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Incidence and Clinical, Virological, and Resistance Characteristics of HIV Infections Among pre-Exposure Spain (SCOPE Study): A Multicentre rospective Cohort Study

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Summary

Background Implemented in Spain in 2019, pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention strategy that reached an estimated 28,800 users by 2024. We aimed to address HIV incidence and characteristics in PrEP users.

Methods Ambispective observational cohort study conducted across 12 centers in Spain. Data from adults diagnosed with HIV who had used oral PrEP within six months prior to seroconversion were collected from August 2024 to March 2025. Main outcomes were HIV incidence among PrEP users, and clinical, virological, and drug resistance characteristics at diagnosis for all cases, as well as 12-month follow-up data for retrospective cases.

Findings Until March 2025, 53 seroconversions occurred among 19,884 PrEP users, yielding an incidence of 0.06 cases per 100 person-years (95% CI: 0.01–0.15). Most individuals were cisgender men who have sex with men (91%), median age of 32 years [IQR:27–37], and from Latin America (31/52; 60%) or Spain (17/52; 33%). Chemsex was reported by 24 (45%), and 49% had a concomitant sexually-transmitted infection. Daily emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) was the most frequent regimen (36/50; 72%). PrEP interruptions occurred in 71% (32/45) and 42% (15/36) had suboptimal adherence. Time on PrEP at diagnosis was 8 months [IQR:3–19] and time from last negative to first positive HIV test 3.6 months [was 14,917 copies/mL [IQR:825–221,000]. Resistance testing was s nucleos(t)ide reverse transcriptase inhibitor-related substitutions Thirty-five retrospective cases completed 1-year follow-up, with VL s

Interpretation PrEP interruptions and/or poor adherence were very prevalent. Most cases were migrants and chemsex use was frequent. Resistance substitutions were frequently found. Despite overall low HIV incidence, some subgroups of PrEP users require additional interventions to prevent HIV.

Funding ISCIII (PI23/00355).

STI testing

- Value of regular testing in asymptomatic persons currently revisited:

-The Belgium experience

Randomized Controlled Trial > Lancet HIV. 2024 Apr;11(4):e233-e244.
doi: 10.1016/S2352-3018(23)00299-0. Epub 2024 Feb 26.

Effect of screening for Neisseria gonorrhoeae and Chlamydia trachomatis on incidence of these infections in men who have sex with men and transgender women taking HIV pre-exposure prophylaxis (the Gonoscreen study): results from a randomised, multicentre, controlled trial

Thibaut Vanbaelen [1], Achilleas Tsoumanis [2], Eric Florence [3], Christophe Van Dijck [2], Diana Huis In 't Veld [4], Anne-Sophie Sauvage [5], Natacha Herssens [2], Irith De Baetselier [2], Anke Rotsaert [6], Veronique Verhoeven [7], Sophie Henrard [8], Yven Van Herrewege [2], Dorien Van den Bossche [2], Jean-Christophe Goffard [8], Elizaveta Padalko [9], Thijs Reyniers [6], Bea Vuylsteke [6], Marie-Pierre Hayette [10], Agnes Libois [11], Chris Kenyon [2]

3. PrEP regimen

- The most common drug available is a generic version with 300mg of tenofovir (formulated as disoproxil fumarate/maleate/phosphate) combined with 200mg of emtricitabine (TDF/FTC). In certain countries, TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate)
- The effectiveness of daily TDF/FTC has been evaluated in clinical efficacy studies in men, women, transgender women and people who inject drugs
- The effectiveness of on-demand regimens of TDF/FTC has only been evaluated in clinical studies in MSM and transgender women, but is supported for use by women and people who inject drugs by pharmacokinetic/pharmacodynamic (PK/ PD) studies
- Oral TAF/FTC could be considered, if available, when creatinine clearance or bone mineral density preclude TDF/FTC. TAF/FTC has been evaluated as a daily regimen in comparison to TDF/FTC in men and transgender women with limited data in women
- Long-acting injectable cabotegravir and long acting lenacapavir can be considered, if available, as an alternative to TXF/FTC when creatinine clearance or bone mineral density preclude TXF/FTC, or when adherence to oral PrEP is low. The effectiveness of CAB-LA and LEN-LA has been shown superior to daily TDF/FTC in men, transgender women and women because of better adherence

Practical aspects → TDF/FTC (generic formulations) is the regimen offered in all settings

-Despite superiority of CAB and LEN over oral PrEP in phase 3 studies very few European countries have approved CAB and none has approved LEN
-In countries where CAB is approved, indication is highly restricted due to cost concerns

Oral regimens

- Regimen: TDF/FTC 300*/200mg or TAF/FTC 25/200mg DAILY (2 tablets loading dose followed by 1 tablet qd) and ON-DEMAND double dose of TDF/FTC 2 to 24 hours before exposure, followed by two single doses of TDF/FTC, 24 and 48 hours after the first dosing
- Starting: starting TDF/FTC PrEP with two tablets taken together achieves clinically effective levels in all compartments 2 hours later based on pharmacokinetic/pharmacodynamic studies (all populations) and confirmed in clinical effectiveness studies (ci-smen and transgender women)
- Stopping (male): clinical studies support men stopping TDF/FTC PrEP by taking two single doses 24 and 48 hours after the last sexual intercourse
- Stopping (non-male populations): pharmacokinetic/pharmacodynamic studies support other populations stopping TDF/FTC PrEP by taking TDF/FTC daily for 7 days after the last exposure
- PK/PD studies comparing TAF/FTC to TDF/FTC suggest that the recommendations for starting and stopping TAF/FTC can be extrapolated from TDF/FTC

Practical aspects → Stopping recommendations in non-male populations and for TAF based regimes are are supported by PK/PD data

- Rates of adverse eGFR declines are generally low for those using TDF for PrEP, but PrEP users with the highest risk of adverse renal outcomes on TDF and most in need for systematic monitoring of renal function are older individuals (> 50 years) and those with pre-existing renal impairment. On demand PrEP may improve renal outcomes vs daily PrEP. Data on renal outcomes with use of TDF vs. TAF in those on PrEP with renal impairment is limited, recommendations to follow guidelines on TDF use in persons with HIV, see Kidney Disease: Definition, Diagnosis and Management, ARV-associated Nephrotoxicity, Indications and Tests for Proximal Renal Tubulopathy (PRT)
- Any person presenting with low PrEP adherence and a condomless at risk sexual intercourse should benefit from post exposure prophylaxis. Low adherence is defined:
  - For men and women on daily regimen: less than 4 pills a week, regardless of the distribution
  - For men on on demand regimen: non compliance to the 2-1-1 scheme
- If PEP is indicated in an individual using oral PrEP, it is advisable to take two tablets of the oral PrEP regimen as soon as possible after the exposure, followed by one tablet daily until medical evaluation, in order to avoid delaying the initiation of an active PEP regimen

Practical aspects → PrEP tolerability is very high.

PrEP to PEP if low adherence and high risk exposure <72 hs. Until seeking medical advice, two PrEP pills may be appropriate (PrEP as PEP)

Injectables long-acting regimens

- Oral lead-in with 1 month of oral cabotegravir 30mg DAILY before initiating cabotegravir injections is optional
- Cabotegravir LA 600 mg intramuscularly is administered every month for the first two months then every two months
- Time to protection with cabotegravir LA is unknown and one week overlap with oral PrEP (cabotegravir or TDF/FTC) or condoms is recommended in order to reach high enough cabotegravir concentrations in plasma following the first injection
- A missed injection is defined as one given more than 7 days after the scheduled target date. If injections resume within one month of the target date, the original dosing schedule may be maintained without adjustment
- In people missing their injections, suitability of LA CAB should be reassessed

Practical aspects → Time to protection with CAB is unknown

Few European countries have implemented LA-PrEP, with very specific recommendations

- Because LA-cabotegravir can suppress viral replication and delay/diminish the Ab expression, breakthrough HIV infection can be difficult to diagnose with LA-cabotegravir (LEVI syndrome) and is often delayed. Repeated testing (HIV RNA and 4th generation laboratory based Ag/Ab test) is recommended. Expert advice is needed if there is an atypical Ab result in a laboratory ELISA on more than one occasion, even if the HIV RNA assay is negative. Expert advice is not needed if HIV is above the limit of detection in the HIV RNA assay on more than one occasion, even if the Ab reaction remains atypical
- Lenacapavir LA is administered subcutaneously at the dose of 927 mg (two injections of 1.5 ml each) every 6 months. It is critical to use a two-day oral loading dose with 2 pills of 300 mg of lenacapavir (600 mg per day), starting the day of the first injection to reach high enough plasma concentrations. Oral bridging with 300 mg orally once weekly should also be used if injections are delayed by more than 14 days from the target date
- Cabotegravir and lenacapavir have no activity against HBV and vaccination against HBV is highly recommended before LA-PrEP. In people with chronic HBV infection see clinical management and treatment of HBV

Practical aspects → diagnosis of incident infections can be much more difficult on injectable PrEP, especially on CAB

LEN oral lead-in advised, time to protection not clearly established

After LEN injection delays >14 days, no protection should be assumed

PrEP in persons with chronic HBV co-infection

- Before oral PrEP is initiated, HBV serology and vaccinal status should be assessed, however if not available it should not be a reason to defer PrEP. In that case, HBV serology should be done at the next visit
- If HBsAg, anti-HBc and anti-HBs are negative, vaccination against HBV is recommended (see Vaccination)
- Individuals with chronic HBV infection (HBsAg positive) should be assessed for the need for treatment according to national/international guidelines
- Individuals with chronic HBV infection (HBsAg positive) who are at substantial risk of HIV acquisition should be evaluated for HIV PrEP
- For those requiring HBV treatment and also requiring PrEP, daily tenofovir/emtricitabine is the treatment of choice, as tenofovir/emtricitabine-based PrEP is active against HBV infection
- For those not requiring HBV treatment, but needing PrEP, daily tenofovir/emtricitabine PrEP should be recommended as limited evidence is available on the rates of HBV reactivation and/or resistance development in PrEP users with HBV, discontinuing PrEP or using on-demand PrEP
- If PrEP is stopped, or in case of on-demand PrEP, there is a potential risk of HBV reactivation and resultant hepatic flares (hepatitis, acute liver failure)
- All people with HBV infection who initiate PrEP should be counselled on the risks related to PrEP cessation, the need for close laboratory monitoring in case of PrEP discontinuation, and the possibility of needing treatment for HBV if reactivation with significant flares occurs
- In cases where PrEP is known to be stopped, we recommend testing for HBV DNA and aminotransferases at least once every 3 months for at least 12 months in all individuals with chronic HBV infection following PrEP discontinuation

Practical aspects → Daily oral PrEP must be used. PrEP discontinuation very risky, seek advice of specialists

Conclusions and take-home messages

- PrEP is expanding in Europe, increasing number of users, medications and regimens
- In some situations, an accurate quantification of risk is not possible → go safe
- Injectable PrEP has shown superioriority in clinical trials, mostly related to higher adherence → Oral PrEP highly effective in adherent people
- Chronic HBV require oral daily PrEP and expert advice in case of PrEP discontinuations

Thanks for your attention!

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