Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis

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Abbreviations

ART	antiretroviral therapy
ARV	antiretroviral
CAB-LA	long-acting injectable cabotegravir
DALY	disability-adjusted life-year
DVR	dapivirine vaginal ring
GAHT	gender-affirming hormone therapy
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HBV	hepatitis B virus
HCV	hepatitis C virus
HIVST	HIV self-testing
ISR	injection site reaction
LA-PrEP	long-acting pre-exposure prophylaxis
LEN	lenacapavir
NAT	nucleic acid test
PEP	post-exposure prophylaxis
PICO	population, intervention, comparator, outcome
PPPY	per-person per-year
PrEP	pre-exposure prophylaxis
RDT	rapid diagnostic test
STI	sexually transmitted infection
TAF	tenofovir alafenamide
TAF/FTC	tenofovir alafenamide/emtricitabine
TDF	tenofovir disoproxil fumarate
TDF/FTC	tenofovir disoproxil fumarate/emtricitabine
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

Definitions of key terms

Age groups	In these guidelines the following definitions for adults, adolescents, children and infants are used in recommendations for specific age groups. Some countries may have other definitions under national laws. • An adult is a person older than 19 years of age. • An adolescent is a person 10–19 years of age inclusive. • A child is a person from one year of age to younger than 10 years of age. • An infant is a child younger than one year of age.
Long-acting lenacapavir (LEN)	LEN is an HIV-1 capsid inhibitor. It is given to people who do not have HIV, at a dose of 927 mg (2 x 1.5mL injections), subcutaneously, every 26 weeks for the prevention of HIV acquisition. People starting LEN also take an oral loading dose of 600 mg (2 x 300 mg tablets) over two consecutive days, beginning on the day of the first injection.
Key populations	Key populations are defined groups who are at increased risk of HIV, viral hepatitis or sexually transmitted infections (STIs), irrespective of the epidemic type or local context. Also, they often experience legal and social issues due to stigma and discrimination that increase their vulnerability to HIV. WHO defines the five key populations to be: 1) men who have sex with men, 2) people who use injectable drugs, 3) people in prisons and other closed settings, 4) sex workers and 5) trans and gender-diverse people.
Risk of HIV acquisition	HIV acquisition risk varies considerably within populations and between geographical locations. Population-level HIV incidence is an important determinant of individual-level risk of HIV acquisition, and it is important to also consider the characteristics and behaviours of individuals and their partners that could lead to HIV exposure. Even in locations with a low overall HIV incidence, there may be individuals at risk who could benefit from pre-exposure prophylaxis (PrEP) services. Individuals requesting PrEP should be offered PrEP, since requesting PrEP indicates that there is likely to be a risk of acquiring HIV.
Rapid diagnostic tests (RDTs)	RDTs are a type of assay that produces test results quickly, generally in under 30 minutes. The broad class of HIV RDTs are serology-based, use fingerprick/capillary whole blood or oral fluid samples and either lateral-flow (immunochromatographic) or vertical-flow (immunofiltration) assays.
HIV self-testing (HIVST)	A process in which a person collects their own specimen (oral fluid or blood) using a simple rapid HIV test and then performs the test and interprets their result when and where they want.
Long-acting injectable cabotegravir (CAB-LA)	CAB-LA is an integrase strand-transfer inhibitor. It is given to people who do not have HIV infection, at a dose of 600 mg intramuscularly, four weeks apart for the first two injections and every eight weeks thereafter, for the prevention of HIV acquisition.
Long-acting injectable PrEP	The use of injectable antiretrovirals that provide extended protection for the prevention of HIV acquisition among people who are HIV-negative.

Executive summary

Purpose

Ending the HIV epidemic as a public health threat requires high-impact HIV prevention and testing services. Pre-exposure prophylaxis (PrEP) is a key component of combination HIV prevention. For people at substantial risk of HIV, the World Health Organization (WHO) in 2015 recommended oral PrEP containing tenofovir disoproxil fumarate (TDF), in 2021 the dapivirine vaginal ring (DVR) for cisgender women at substantial risk of HIV and in 2022 the long-acting injectable cabotegravir (CAB-LA). Expansion of access to and use of oral PrEP have accelerated in recent years, and more countries have included CAB-LA and the DVR in their national guidelines and have begun programmatic implementation.

Potential barriers to the uptake and effective use of oral PrEP, as well as CAB-LA and the DVR, include not wanting to take an oral pill regularly and desire for less frequent clinic visits. These barriers may be overcome with new PrEP products that offer protection for longer periods of time. With these guidelines, WHO recommends offering the six-monthly injectable lenacapavir (LEN) as an additional HIV prevention option. Offering additional PrEP choices has the potential to increase uptake and effective use of PrEP and of HIV prevention overall, as it allows people to choose a method that they prefer.

> **With these guidelines, WHO recommends offering the six-monthly injectable lenacapavir (LEN) as an additional HIV prevention option.**

Testing services are a critical component of PrEP delivery. Effective and efficient testing services can help streamline service provision and support a broader public health approach. To ensure effective and equitable access to PrEP, HIV testing services should be feasible, accessible and scalable. These guidelines highlight the latest evidence on the benefits of using simple rapid diagnostic tests (RDTs) when providing long-acting injectable PrEP, rather than more complex and costly nucleic acid testing (NAT) techniques or laboratory-based testing. Simplified testing approaches reduce barriers, minimize delays, improve sustainability and reduce per-test cost.

WHO continues to recommend HIV RDTs and HIV self-testing (HIVST) as part of standard HIV testing services. With these guidelines, WHO recommends using HIV RDTs for individuals initiating or continuing long-acting injectable PrEP, such as CAB-LA and LEN. HIVST remains a recommended option for oral PrEP, the DVR and post-exposure prophylaxis (PEP), as it may offer additional flexibility across PrEP programmes. Further implementation research is needed to fully determine the role of HIVST in delivering long-acting injectable PrEP.

Flexible HIV testing approaches are essential for ensuring that testing does not become a barrier to accessing or continuing PrEP, including long-acting injectable options. Aligning testing frequency with PrEP refill and injection visit schedules is often practical. To enhance access and choice, alternative testing schedules may also be needed and can be considered, particularly as part of efforts to adopt simplified and differentiated PrEP delivery (for example, greater task sharing, multi-month dispensing, pharmacy PrEP, TelePrEP and other online distribution models).

The primary audience for this guideline is national and subnational programme managers and policy-makers responsible for the national health sector response to HIV, particularly in low- and middle-income countries.

Guideline development methodology

In response to emerging new evidence on the efficacy of LEN for the prevention of HIV acquisition across diverse populations, and on testing for long-acting prevention products, the WHO Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes led the development of new guidance, with support from the Guideline Development Group (GDG) and External Review Group, from January to May 2025.

The WHO steering group formulated two population, intervention, comparator, outcome (PICO) questions, one on LEN as PrEP and another on the use of RDTs in the context of long-acting prevention. External researchers, supported by WHO, conducted the systematic reviews of the evidence to answer these questions. They synthesized the evidence and incorporated it into an evidence-to-decision framework to help inform the discussions at a virtual GDG meeting that occurred over three days from 28 to 30 January 2025, chaired by two members of the GDG and facilitated by an independent methodologist. The GDG members made judgements on the potential benefits and harms of the intervention, stakeholder values and preferences, acceptability, feasibility, resource use and considerations of human rights and equity. Taken together and using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, these judgements contributed to determining the strength and direction of the recommendations. The recommendations were formulated through consensus.

New recommendations

Recommendation [NEW]

Long-acting injectable lenacapavir should be offered as an additional prevention choice for people at risk of HIV, as part of combination prevention approaches. *(strong recommendation, moderate to high certainty of evidence)*

Recommendation [NEW]

Rapid diagnostic tests may be used for HIV testing for initiation, continuation and discontinuation of long-acting PrEP. *(strong recommendation, very low certainty of evidence)*

The GDG concluded that, at the time of convening, there was insufficient evidence to recommend HIV self-testing for long-acting injectable PrEP (LA-PrEP). Evidence reviewed did suggest, however, that HIVST could increase flexibility and testing frequency as well as further decentralize testing access. Further implementation research is needed to understand the potential role of HIVST within LA-PrEP. HIVST continues to be recommended for oral PrEP, the DVR and PEP.

Implications for implementation

LEN should be delivered as an additional choice alongside other HIV PrEP and prevention options. As countries plan for the introduction of LEN, considerations should include differentiated service delivery models and integration to maximize acceptability and accessibility; population-specific needs; awareness raising and demand generation activities; provider training. At the same time, monitoring and surveillance systems should be designed, to support safety and service quality improvement such as adverse event monitoring during pregnancy and breastfeeding, seroconversions and drug resistance; and the relative costs and potential of LEN to achieve impact. Successful introduction of LEN will be enhanced by the full participation of communities in designing, implementing and monitoring programmes.

Availability of LEN to date has been restricted to trial settings, and the follow-up time has been limited. There are evidence gaps regarding the optimal testing strategies, the best approaches to support access, adherence to the dosing schedule, persistence, alternative dosing and administration, product switching, ideal provision in some populations and geographies, and the costs and impacts of LEN. However, the GDG stressed that, despite the evidence gaps identified, further research should not delay the programmatic implementation of LEN in countries.

Simple HIV testing strategies that rely on RDTs and are aligned to WHO guidance are needed to support injectable LA-PrEP implementation within broader PrEP programmes. Adopting this approach will provide consistency, quality and efficiency to programmes and enable countries to use their standard national testing algorithm. Using HIV RDTs also makes it possible to provide same-day injectable LA-PrEP initiation and, thus, to facilitate effective and continuous use.

1. Introduction

1.1 Background

HIV remains a major public health issue, with estimated 39.9 million people living with HIV and 1.3 million people newly diagnosed with HIV in 2023 *(1)*. While the African region has made substantial progress in preventing new HIV infections, comparable progress is less evident elsewhere, where most people acquiring HIV are members of key populations. With the Political Declaration on HIV and AIDS adopted by the United National General Assembly in 2021, member states committed to reducing annual HIV infections to under 370 000 by 2025, reducing AIDS-related deaths to fewer than 250 000 globally and to ensuring that 95% of people at risk of HIV have access to HIV prevention options.

To end HIV as an epidemic, focus is needed on a comprehensive approach that includes combination HIV prevention. This includes biomedical options such as HIV testing, pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), voluntary medical male circumcision and condom promotion. Rapid, wider access to PrEP and its effective use could significantly reduce the number of new HIV infections, especially among key populations and people in areas where HIV incidence is high. The total number of people using PrEP rose from a little over 200 000 in 2017 to about 3.5 million in 2023 but still falls far short of the global 2025 target of 10.6 million person-years of PrEP protection *(1)*. Only the African region is making meaningful progress towards the 2025 PrEP targets; this progress has been achieved primarily through funding from the US President's Emergency Plan for AIDS Relief.

Currently, WHO recommends multiple PrEP products, including oral tenofovir disoproxil-fumarate (TDF)-based PrEP, long-acting injectable cabotegravir (CAB-LA) and the dapivirine vaginal ring (DVR) *(2)*. As the range of PrEP products expands, a focus on choice to meet users' different needs and preferences is at the centre of differentiated and simplified delivery models for HIV prevention. This includes offering different dosing and multi-month dispensing options, as well as PrEP delivery online, in pharmacies, in communities and in other primary care facilities.

> **Choice is at the centre of differentiated and simplified delivery models for HIV prevention.**

Service delivery models that take a public health approach must include testing and follow-up that can be adapted to meet client needs. Simplified and affordable testing approaches, including HIV rapid diagnostic tests (RDTs) and self-tests, are important to ensuring access to and uptake of PrEP services by those who may benefit.

1.2 Objectives and intended audience

These guidelines are intended to provide evidence-informed recommendations for lenacapavir (LEN) as PrEP for HIV prevention and on testing for long-acting PrEP (LA-PrEP). These guidelines seek to support countries' achievement of national targets for reducing the numbers of new HIV infections. To operationalize these guidelines, it is important to address critical aspects of implementation, including improved and simplified HIV testing algorithms, for long-acting PrEP, as HIV testing services are a gateway to prevention and treatment services.

The primary audience for this guideline is national and subnational programme managers and policy-makers responsible for the national health sector response to HIV, particularly in low- and middle-income countries. Programme managers in nongovernmental and community-based organizations will also find these guidelines useful. The audience also includes all types of PrEP providers, particularly in primary health and community health services, as well as personnel in laboratories that support testing services. Finally, these guidelines are also important for people who could benefit from PrEP, including those from communities affected by HIV. This guideline can also help donors, development agencies and international organizations effectively plan and support various HIV prevention and testing programmes.

1.3 Guiding principles

The following principles have informed the development of this guideline and should guide the implementation of the recommendations across settings:

- Deliver HIV prevention and testing services within an evidence-based public health and universal health coverage framework that is centred on people, communities and human rights.
- Promote and protect equity and the human rights of people at risk of HIV, making PrEP and HIV testing services available, accessible and acceptable without stigma and discrimination to anyone who can benefit from PrEP.
- Ensure that PrEP and HIV testing remain voluntary, never resorting to coercive or mandatory approaches, by adhering to the principles of autonomy, informed consent and choice.
- Implement prevention programmes that are responsive to local contexts, including HIV epidemiology, availability of resources, the organization and capacity of the health system and anticipated cost–effectiveness.
- Implement new recommendations with the full participation of affected communities in developing and implementing PrEP and testing services.

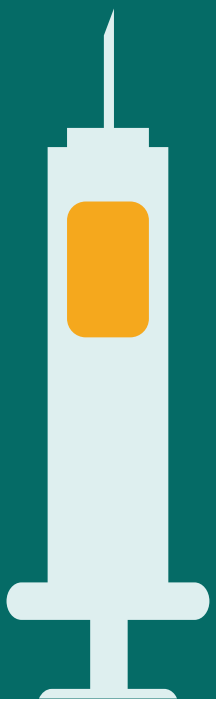
2. Methods for guideline development

This guideline was developed in accordance with procedures established by the WHO Guidelines Review Committee *(3)*. Its recommendations were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to reviewing evidence and formulating recommendations *(4)*. Consistent with previous WHO guidelines, this guideline is based on a public health approach that considers effectiveness, acceptability, feasibility and resource needs across a variety of settings.

All external contributors to the guidelines, including members of the Guideline Development Group (GDG) and the External Review Group, completed a WHO declaration of interests form in accordance with WHO policy for experts (Web Annex A).

The systematic reviews, one on LEN for PrEP (Web Annex B) and one on HIV testing services for injectable LA-PrEP (Web Annex D), followed a research question in population, intervention, comparator, outcome (PICO) format. The systematic review findings were prepared in accordance with the GRADE process, and they were shared in advance and presented at the GDG meetings, where an independent methodologist facilitated the discussions.

Details on methods used to develop these guidelines are presented in Annex 1 of this document. In addition, all Web Annexes are available on the WHO website at https://www.who.int/publications/i/item/9789240111608.



3. Rationale and supporting evidence: lenacapavir for HIV prevention

3.1 Summary of review findings

Evidence on the safety and efficacy of LEN for HIV prevention was collected in a systematic review of peer-reviewed scientific reports, including published results papers, conference presentations, study protocols, clinical trial registries and other supporting documentation. The review also included unpublished research or research undergoing peer-review. Twelve eligible reports were included, containing data from two studies. The two included studies, PURPOSE 1 *(5)* and PURPOSE 2 *(6)*, were multi-centred, double-blind, randomized, active-controlled trials. Both studies assessed the efficacy of LEN compared with a background HIV incidence cohort as well as with daily oral PrEP (tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)). Notably, PURPOSE 1 also assessed the efficacy of daily tenofovir alafenamide/emtricitabine (TAF/FTC). However, since the focus of the review was on LEN, the TAF/FTC arm was not included.

The study population of PURPOSE 1 included cisgender adolescent girls and young women ages 16–25 years in South Africa and Uganda. The study population of PURPOSE 2 included cisgender gay, bisexual and other men who have sex with men; transgender women; transgender men and gender non-binary persons, who were at least 16 years of age, in Argentina, Brazil, Mexico, Peru, South Africa, Thailand and the United States of America. Overall, 8660 individuals underwent randomization across the two trials, with 4333 individuals randomized to receive active LEN. No studies were identified on LEN for prevention in people who inject drugs; however, a randomized clinical trial on LEN for prevention of HIV in this population is underway (PURPOSE 4). No studies sought to include sex workers or people in prisons or other closed settings.

3.1.1 Reduction in HIV infection

Across both PURPOSE 1 and PURPOSE 2, LEN resulted in a large reduction in HIV acquisition (high certainty of evidence). In PURPOSE 1 no participants randomized to LEN acquired HIV, while in PURPOSE 2, two HIV infections were identified in the LEN group. When

compared with background HIV incidence, LEN showed 100% efficacy in PURPOSE 1 (RR: 0.00; CI 95%: 0.00-0.04) and 96% efficacy in PURPOSE 2 (RR: 0.04; CI 95%: 0.01-0.18). When compared with daily oral PrEP with TDF/FTC, LEN showed 100% efficacy in PURPOSE 1 (RR: 0.00; CI 95%: 0.00-0.10) and 89% efficacy in PURPOSE 2 (RR: 0.11; 95% CI: 0.02-0.51) *(5, 6)*.

> **In the two randomized, controlled trials, LEN greatly reduced HIV acquisition.**

In PURPOSE 1, 16 incident HIV infections occurred in the TDF/FTC group (1.69 per 100 person-years; 95% CI: 0.96–2.74), whereas no infections were observed in the LEN group (0 per 100 person-years; 95% CI: 0.00–0.19). In PURPOSE 2, nine incident HIV infections were identified in the TDF/FTC group (0.93 per 100 person-years; 95% CI: 0.43–1.77) compared with two in the LEN group (0.10 per 100 person-years; 95% CI: 0.01–0.37).

Both participants who acquired HIV in the LEN group of PURPOSE 2 had LEN levels consistent with the expected pharmacokinetic range. These infections occurred after the first injection but before the second, at weeks 13 and 26. Investigators noted that there was no evidence of delayed HIV detection in either of these cases.

Key messages

- **The PURPOSE 1 and 2 trials demonstrated the high efficacy of lenacapavir**, showing a statistically significant reduction in HIV acquisition compared with both background incidence and daily oral PrEP arms. (HIGH certainty evidence)
- **Data remain limited for some key populations**, such as people who inject drugs, underscoring the need for expanded studies across diverse demographics and regions.
- **Mathematical models suggest that LEN could substantially reduce new HIV infections**, especially where uptake and adherence are optimized (Box 1).

Adherence patterns differed between the LEN and TDF/FTC groups in both trials. LEN adherence was measured as on-time injections, defined as within 28 days of the scheduled dose, while TDF/FTC adherence was assessed through tenofovir diphosphate levels in dried blood spots from a randomly selected subset of participants. At week 52, 92.8% of participants receiving LEN in both trials had received injections on time. In PURPOSE 1 adherence to TDF/FTC was low for most participants and declined over time, with many taking fewer than two pills per week. In PURPOSE 2, 82% of participants had high adherence to oral TDF/FTC (four or more pills per week) at week 8, but this declined to 62% at week 52.

Box 1

Reducing HIV infection at the population level:
evidence from mathematical modelling on LEN

Mathematical models have assessed the potential impact of LEN for HIV prevention. Six HIV transmission modelling studies, reporting final or preliminary findings, estimated the impact of LEN introduction in different settings. An additional nine studies were identified as ongoing or planned (Web Annex E: Mathematical modelling on LEN: impact and cost–effectiveness). In South Africa one model estimated that LEN could reduce new infections by 27–41% over 20 years, with a greater impact than scaling up oral PrEP or CAB-LA *(7)*. Another study, in South Africa, western Kenya and Zimbabwe, found that focusing on key populations, including adolescent girls and young women, female sex workers and individuals with multiple sex partners, could reduce infections by 12–33% over 10 years with population coverage of 2–8% *(8)*. A third study, also in South Africa, western Kenya and Zimbabwe, found that prioritizing LEN for the highest-risk populations could reduce new infections over 35 years by up to 41%, compared with a maximum of 24% with untargeted scale-up, highlighting the greater impact of prioritizing higher-risk groups *(9)*.

Among men who have sex with men in Thailand, one model predicted that transitioning 95% of oral PrEP users to LEN, with a two-year duration of use, could reduce new infections by 37% over 10 years *(10)*. However, if LEN use was limited to six months – the average duration of oral PrEP use in this population – the impact was projected to be minimal, averting only 1% of new infections compared with oral PrEP over the same period.

When used with high uptake, LEN has the potential to reduce new HIV infections substantially, in some models surpassing oral PrEP or CAB-LA due to higher effectiveness, increased coverage and better persistence of use. The potential for LEN to outperform other PrEP options is largely driven by its capacity to increase overall PrEP coverage and uptake, although even under optimistic scenarios, many new HIV transmissions are projected still to occur at the population level.

3.1.2 Safety

The PURPOSE 1 and 2 trials found little to no differences in rates of adverse events (excluding injection site reactions (ISRs)) between those receiving LEN and those receiving TDF/FTC (high certainty of evidence). In PURPOSE 1, 76.3% of participants in the LEN arm and 77.6% of participants in the TDF/FTC arm reported at least one adverse event (RR: 0.98, CI 95%: 0.94–1.02) *(5)*. In PURPOSE 2, 73.6% of participants in the LEN arm and 73.8% in the TDF/FTC arm experienced any adverse events (RR: 1.00, CI 95%: 0.96–1.04) *(6)*.

Both trials reported on the proportion of participants experiencing a grade 3 or 4 adverse events, finding that LEN probably results in little to no difference in grade 3 or 4 adverse events as compared with TDF/FTC (moderate certainty of evidence). In PURPOSE 1, 4.1% of participants receiving LEN and 4.7% of participants receiving TDF/FTC experienced grade 3 or 4 adverse events (RR: 0.88, CI 95%: 0.63–1.24) *(5)*. In PURPOSE 2, 4.2% in the LEN arm and 6.0% in the TDF/FTC arm experienced grade 3 or 4 adverse events (RR: 0.70, CI 95%: 0.51–1.95) *(6)*.

ISRs, including nodules, pain and erythema, were frequently reported in both studies and were generally mild. ISRs were reported both in participants receiving LEN injections and in participants receiving placebo injections in the oral TDF/FTC arms. In PURPOSE 1, 68.8% of participants randomized to LEN experienced ISRs compared with 33.9% in the TDF/FTC arm (RR: 2.03, CI 95%: 1.86–2.21) *(5)*. In PURPOSE 2, 83.2% of participants in the LEN arm reported ISRs compared with 69.5% in the TDF/FTC arm (RR: 1.20, CI 95%: 1.15–1.25) *(6)*. The frequency of ISRs and their severity decreased over time. The systematic review concluded that LEN results in an increase in ISRs compared with the placebo injections in the TDF/FTC arm (high certainty of evidence).

Key messages

- **Overall rates of adverse events were similar between LEN and oral TDF/FTC,** and most events were mild or moderate in severity.
- **Injection site reactions were common but typically mild**, decreasing in frequency over time without leading to high discontinuation rates.

3.1.3 Antiretroviral resistance among those diagnosed with HIV

Resistance to LEN was analysed among participants who acquired HIV during PURPOSE 1 and PURPOSE 2. In PURPOSE 1 there were no HIV acquisitions in the LEN arm, and thus no cases of resistance were reported *(5)*. In PURPOSE 2 two, participants in the LEN arm were diagnosed with HIV, and both had a mutation associated with resistance to HIV-1 capsid inhibitors (N74D) *(6)*. The evidence suggests that LEN use may increase antiretroviral resistance to capsid inhibitors (low certainty of evidence).

Given the overall high efficacy of LEN and the rarity of breakthrough infections, resistance to LEN is unlikely to have a significant public health impact at present. This is because LEN is a first-in-class drug; no other antiretrovirals of this class are routinely used for prevention or treatment. Moreover, currently available evidence suggests that regimens that include capsid inhibitors may retain some activity despite resistance selected by LEN. The N74D mutation reduces susceptibility to LEN by approximately 20-fold *(11-13)*. Although it is associated with an estimated 50% reduction in replication capacity in vitro *(11-13)*, the clinical significance of this decrease remains uncertain. However, mutations with diminished replication capacity often revert to undetectable levels within months of their emergence. Evidence from the CAPELLA trial, which evaluated LEN in combination with an optimized background regimen for antiretroviral therapy (ART) in heavily treatment-experienced individuals, suggested that LEN may retain activity despite resistance-associated mutations *(14)*. As LEN is introduced for PrEP and possibly in the future for treatment, more data will be needed to confirm that LEN-associated drug resistance would not impact treatment combinations that included capsid inhibitors.

Continued surveillance of LEN resistance will be important as LEN-based prevention and treatment strategies expand. Wider use of LEN, especially in settings where acute HIV infection may go undetected, could lead to increased opportunities for LEN-resistant variants to emerge and circulate. Monitoring the frequency and clinical significance of any additional LEN resistance mutations that arise will be essential for maintaining the effectiveness of LEN-based regimens and informing future programme and policy decisions (Web Annex F: Drug resistance).

Key messages

- **Two breakthrough infections in PURPOSE 2 showed a capsid inhibitor resistance mutation (N74D)**, highlighting the importance of ongoing surveillance to understand potential population level impact as LEN scale-up continues.
- **LEN is first in its drug class for prevention**, and so the current public health impact of possible resistance is considered limited, but long-term monitoring remains essential.

3.1.4 Pregnancy and birth-related outcomes

The systematic review found that LEN probably has little to no effect in terms of adverse pregnancy and birth outcomes compared with oral TDF/FTC (moderate certainty of evidence). PURPOSE 1 did not require contraception for participation in the trial, but it provided contraception if pregnancy was not desired *(5)*. If women became pregnant, they could continue the study drug, after receiving additional counselling on risks and benefits and giving informed consent. In PURPOSE 2, which enrolled, among others, transgender individuals, transgender men assigned female at birth who had the ability to become pregnant were required to use contraception due to a high prevalence of the use of testosterone (a teratogen) among transgender men *(6)*. In PURPOSE 1, 193 pregnancies were confirmed among 184 women assigned to LEN, with 105 pregnancies having outcomes to date *(5)*. Rates of any grade 3 or higher pregnancy-related complications (such as hypertension, nausea or fetal distress) were similar between the LEN arm (1.1%) and the TDF/FTC arm (1.5%) (RR: 0.75, CI 95%: 0.40–1.41). Rates of birth outcomes (live birth, still birth, miscarriages) did not differ significantly between the LEN and oral PrEP arms and were not significantly different from background rates in the studied population. One minor congenital anomaly (polydactyly) was observed in an infant born to a woman in the LEN group who had a family history of the condition. No pregnancies were reported in PURPOSE 2 *(6)*.

Available data from 184 women with LEN exposure who became pregnant and have outcomes to date suggest that it is possible to rule out a two-fold increase in risk for adverse pregnancy outcomes with a background prevalence of >10% (miscarriage, prematurity, low birth weight), due to the sample size to date *(15)*. Analysis of pharmacokinetic data suggests that no dose adjustment for LEN is needed during pregnancy *(16)*.

More data on pregnancy outcomes in PURPOSE 1 are anticipated, as additional pregnancies occurred in the randomized trial since the interim analysis, and it is anticipated that pregnancies will also occur during the PURPOSE 1 open-label extension. Additionally, detailed pharmacokinetic studies of LEN in pregnancy and during lactation will be available soon. However, more research and safety surveillance in pregnancy are needed to monitor for less common adverse pregnancy and infant outcomes, particularly rare adverse events, through the surveillance of PrEP in larger surveillance programmes or antiretroviral (ARV) pregnancy registries.

Key messages

- **LEN showed no increase in adverse pregnancy or birth outcomes** among the 193 pregnancies reported in PURPOSE 1 so far.
- **No dose adjustment is likely to be required during pregnancy**, with pharmacokinetic data indicating standard dosing remains effective.

Box 2 presents updated data on pregnancy-related outcomes for other PrEP products.

Box 2

Beyond LEN: safety of oral PrEP, DVR and CAB-LA in pregnancy

Based on the available safety data, WHO concludes that PrEP with any of the available products need not be discontinued during pregnancy and breastfeeding for HIV-negative women with a high likelihood of exposure to HIV. The choice to start, continue or discontinue PrEP when someone becomes pregnant should be made by the individual, following discussion of the risks and benefits with a health care provider.

Existing data on safety and efficacy for the use of PrEP in pregnant and breastfeeding women, as well as individuals who conceive while taking PrEP, is highlighted below for the three other PrEP options – oral TDF-based PrEP, the DVR and CAB-LA.

Oral TDF-based PrEP

Available data are reassuring regarding the use of oral TDF-based PrEP during pregnancy and breastfeeding. A systematic review including 13 studies assessing 8712 pregnant women in Africa found that oral PrEP, compared with no PrEP, was not associated with adverse perinatal outcomes including fetal loss, prematurity, low birth weight or neonatal death *(17)*. In follow-up of 455 mother–infant pairs, comparing 228 exposed to oral PrEP in utero with 227 without exposure, there was no evidence of an association between in utero oral PrEP exposure and infant growth (weight, length, head circumference) in the first 18 months of life *(18)*. A pharmacokinetic and safety study of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for PrEP in HIV-negative women during breastfeeding found that drug levels in breast milk were low (3.2 ng/mL for tenofovir diphosphate (TFV-DP) and 212.5 ng/mL for FTC). Tenofovir was not detected in 94% of infant plasma specimens, suggesting that PrEP can be used safely during breastfeeding, with minimal infant drug exposure *(19)*. Additionally, use of oral PrEP had no effect on bone mineral density or bone mineral content in 300 breastfeeding women receiving oral PrEP *(20)*. Also, *in utero* exposure to oral PrEP in infants born to HIV-negative women receiving oral PrEP during pregnancy was not associated with differences in bone mineral content during the first 18 months of life between those exposed and unexposed to oral PrEP during pregnancy *(21)*.

The DVR

Safety studies of DVR use during pregnancy have shown a favourable safety profile among pregnant women and their infants; there is no evidence of negative impact on pregnancy or infant outcomes. Among those who used the DVR during pregnancy, no differences in preterm labour, stillbirths or pregnancy complications were seen during randomized control trials, as described below. Similarly, studies of the DVR and oral PrEP use during breastfeeding found favourable safety profiles among breastfeeding mother–infant pairs and low drug levels in breast milk and infant blood samples *(19, 22)*.

Box 2

Beyond LEN: safety of oral PrEP, DVR and CAB-LA in pregnancy *(continued)*

- **DVR safety during pre-conception and early pregnancy.** While the original randomized clinical trial of the DRV, MTN-020/ASPIRE, did not enrol pregnant individuals, 86 incident pregnancies occurred among participants using the DVR, providing pre-conception and early pregnancy exposure safety data *(23)*. Additionally, 58 pregnancies occurred during the open-label extension of the ASPIRE trial (HOPE) *(24)*. Among participants in both studies, there was no impact on fertility rates and no association with preterm birth, pregnancy loss, congenital anomalies or poor infant growth.

- **DVR safety during pregnancy.** The MTN-043/DELIVER study enrolled pregnant individuals in three gestational age cohorts (≥36 weeks, 30–35 weeks and 12–29 weeks' gestation) randomized to use the DVR or oral PrEP through delivery *(25)*. The DVR had no association with preterm birth, stillbirth or maternal or infant serious adverse events. There were no HIV seroconversions, and pregnancy complications were uncommon, similar to the background rates observed in study communities.

- **DVR safety during breastfeeding.** The MTN-043/B-PROTECTED study enrolled approximately 200 exclusively breastfeeding mother–infant pairs. Participants were randomized to the DVR (n=148) or oral PrEP (n=49), and products were used for 12 weeks. The study was designed to assess maternal and infant safety, adherence and acceptability. Key findings showed an excellent safety profile in both mothers and infants, with no serious adverse events related to the DVR and very little dapivirine present in milk, with even less passed to infants; median dapivirine levels were below the limit of quantification at all visits *(22)*. Similarly, in those receiving oral PrEP (TDF/FTC), median TFV-DP levels were low and not observed in infant blood specimens (all levels below quantification at all visits).

CAB-LA

More data are available on the use of CAB-LA during pregnancy and breastfeeding, with research ongoing and no concerns identified to date. In the original efficacy study in cisgender women, HPTN 084, excluded pregnant and breastfeeding women from enrolment and any participants who tested positive for pregnancy were switched from CAB-LA to oral PrEP. The ongoing open-label extension of the HPTN 084 study allows participants to continue using CAB-LA if they became pregnant. Findings will be analysed separately for those exposed to CAB-LA before or during pregnancy. A number of implementation studies underway in several countries are allowing the use of CAB-LA PrEP during pregnancy and breastfeeding. Pregnancy, birth and newborn outcomes will be monitored and reported.

- **CAB-LA safety during pre-conception and early pregnancy.** Available data from a small number of women who became pregnant in the HPTN 084 trial suggest CAB-LA is safe during pregnancy; CAB-LA was well tolerated, there have been no complications in pregnancy or delivery due to CAB-LA, and there were no congenital anomalies reported *(26)*. Recent evidence from the HPTN 084 open-label extension included over 300 individuals who became pregnant while using CAB-LA and stayed on the regimen *(27)*. In this group CAB-LA was well tolerated, with consistent maternal and pregnancy outcomes (infant growth, birth weight, median gestational age) across study participants and background rates in the general population.
- **CAB-LA concentrations during the tail period during pregnancy.** Available data on the pharmacokinetics of CAB-LA during pregnancy suggest that drug concentrations decrease over time during pregnancy, with lowest levels in the third trimester, but levels remained above the minimum level needed for protection, and so dose modifications are not needed *(27)*. Additional analysis is ongoing.

- **CAB-LA safety during breastfeeding.** A pharmacokinetic and safety study of CAB-LA during breastfeeding is planned as part of the HPTN 084 open-label study. Data are anticipated by mid-2025.

3.1.5 Efficacy of hormonal contraception and gender-affirming hormones

The systematic review did not find evidence on the efficacy of hormonal contraception or gender-affirming hormone therapy (GAHT) when co-administered with LEN. In PURPOSE 2, which included transgender and non-binary persons, 11.6% (n=253) of study participants randomized to LEN and 12.0% (n=131) of those randomized to TDF/FTC reported taking gender-affirming hormones at baseline *(6)*. The influence of LEN on the effectiveness of GAHT was not assessed in this study. However, preliminary pharmacokinetic data analyses suggest that LEN does not result in clinically meaningful changes in hormone levels for individuals on GAHT (either testosterone-based or estradiol-based regimens) or long-acting hormonal contraceptives, and hormone regimens do not appear to affect LEN concentrations *(28)* (see Table 1, page 24).

Key messages

- **Preliminary evidence suggests that LEN has no clinically meaningful interactions with hormonal contraception or gender-affirming hormone therapy.**

3.1.6 Behavioural outcomes, including incidence of sexually transmitted infections (STIs)

The systematic review ascertained that LEN use probably results in little to no difference in STI incidence compared with oral TDF/FTC (moderate certainty of evidence). In PURPOSE 1 gonorrhoea, chlamydia and trichomonas were frequently diagnosed in both study arms, with 48.7 events per 100 person-years in the LEN arm and 48.4 events per 100 person-years in the TDF/FTC arm (RR: 1.01; CI 95%: 0.90–1.13) *(5)*. In PURPOSE 2 gonorrhoea and chlamydia were frequently diagnosed across both arms: 77.9 events per 100 person-years in the LEN arm compared with 69.4 events per 100 person-years in the TDF/FTC arm (RR: 1.12; CI 95%: 1.02 1.23) *(6)*. Syphilis rates also were similar – 14.1 events per 100 person-years in the LEN arm and 12.4 events per 100 person-years in the TDF/FTC arm. Neither study reported on behavioural outcomes, such as condom use or number of sexual partners.

Key messages

- **LEN likely results in little to no difference in STI incidence compared with oral TDF/FTC**, with high rates noted across both groups.

3.2 Values and preferences

Evidence on the values and preferences for LEN among end users was derived from a systematic review of peer-reviewed publications and conference abstracts (Web Annex C). To be included, studies must have been designed to understand values and preferences of injectable PrEP and also report on actual experiences of using or implementing injectable PrEP or report on relevant comparisons or assessments of various attributes of injectable PrEP products. The systematic review identified 26 studies meeting inclusion criteria, including six studies (across nine reports) related to experience with injectable PrEP *(29-37)*, specifically CAB-LA, and 20 studies comparing different attributes of injectable PrEP *(38-57)* (Web Annex C). Study designs included both qualitative and quantitative studies (cross-sectional surveys and discrete choice experiments. Most commonly, studies took place in the United States of America and involved gay men and other men who have sex with men.

The GDG noted that there may be uncertainty or variability in how end users value LEN as an injectable prevention option. The review found that injectable PrEP was generally a highly acceptable PrEP modality, with variation in specific preferences for PrEP between different populations and geographies. In the six studies involving those with injectable PrEP experience, there was high acceptability of injectable PrEP across diverse populations (high confidence of evidence), driven by perceptions of its low burden/perceived ease of use, fit with lifestyle (convenient, allows for discreet use) and perceived effectiveness. Concerns about injectable PrEP varied by population and context (moderate confidence of evidence) but were mostly related to burdens including side-effects (for example, pain and ISRs) and location of injection; perceptions of efficacy between injections, including inaccurate perceptions of waning efficacy between injections and structural barriers (for example, inability to get to the clinic for injection, cost and opportunity costs). The GDG identified no important uncertainty or variability in how end users valued the protection offered by LEN against HIV infection.

Findings from studies examining injectable PrEP attributes show that there was a clear preference among end users for longer duration of efficacy and less frequent dosing, with all studies that compared six- and two-month injections finding a preference for the six-month injection. No studies indicated a clear preference for the type of injection (intramuscular or subcutaneous), and the preference for the injection site on the body varied by setting and population. Self-administered injections were acceptable, especially among populations with self-injecting experience (for example, hormone injections).

The GDG observed that LEN is likely to be acceptable to stakeholders, including providers and HIV programme managers, but recognized that there may be some variability depending on the type of stakeholder. The review found that implementation of injectable PrEP was perceived as appropriate, feasible and acceptable by providers based in the United States of America, although internal and external barriers to implementation were identified (for example, challenges with injection scheduling, resource management and outreach) (low confidence of evidence). Additionally, results from a study of PrEP providers across 24 countries found high levels of support for injectable products *(58)*.

Key messages

- **Injectable PrEP was generally perceived as highly acceptable**, with users citing its convenience and potential for discreet use.
- **Concerns varied by setting**, including worries about injection-related pain, potential side-effects and scheduling challenges for follow-up doses.
- Evidence suggests **providers also find injectable PrEP acceptable**, although concerns remain about cost and logistics.

3.3 Feasibility

The GDG concluded that the introduction of LEN as an additional prevention option in HIV programmes would likely be feasible. The rationale for this judgement was that the PURPOSE 1 and 2 trials were conducted across eight countries in Africa, Latin America, North America and South-East Asia, demonstrating its feasibility across more than 120 well supported and controlled trial sites *(5, 6)*. The GDG noted that no LEN implementation has been conducted outside trial settings, limiting its ability to make thorough judgements on feasibility in real world programmes. Instead, GDG discussions considered indirect evidence from implementation studies for CAB-LA, which have shown the feasibility of integrating injectable LA-PrEP options into broader programmes *(59-61)*. These studies have focused on expanding prevention options and allowing for user choice, resulting in increased uptake and product coverage. In the systematic review on values and preferences conducted for these guidelines, US-based providers perceived implementation of injectable PrEP to be feasible (see section 3.2). However, no LEN-specific perspectives on feasibility were identified. The GDG members also noted uncertainty about the feasibility of LEN implementation due to the need for an enabling environment and political commitments.

Key messages

- **Clinical trial sites across many countries successfully delivered LEN**, suggesting that, with adequate planning, integrating this injectable PrEP into existing services may be achievable.
- **Indirect evidence from CAB-LA implementation supports the feasibility** of implementing long-acting injectable PrEP, though real-world data specific to LEN are still needed.

3.4 Cost–effectiveness

Evidence on the cost–effectiveness of LEN for HIV prevention presented to the GDG was derived from the landscaping review on mathematical modelling studies discussed in section 3.1.1 (see also Web Annex E). Two studies in South Africa found that LEN could be cost–effective if its per-person-per-year (PPPY) cost remained below certain thresholds, using a benchmark of less than US$ 500 per disability-adjusted life-year (DALY) averted *(8, 9)*. One analysis concluded that LEN could be cost–effective at up to US$ 213 PPPY (95% CI 191–232), when scaled up among key populations *(8)*. A second study estimated a maximum cost of US$ 106 PPPY (95% CI 98–114) with risk-prioritized coverage of 5% of the overall population *(9)*. A third study suggested LEN could cost up to US$ 225 PPPY to be as cost–effective as oral PrEP in South Africa *(7)*. In lower-prevalence settings, such as western Kenya and Zimbabwe, the maximum feasible PPPY cost of LEN was much lower, ranging between US$ 10–33 in western Kenya and US$ 16–42 in Zimbabwe, even when focusing on key populations *(8, 9)*. In comparison with other strategies of implementing PrEP, one study found that in Zimbabwe long-acting PrEP for female sex workers would be the most cost-efficient HIV prevention option, with an incremental cost–effectiveness ratio of US$ 1081 per infection averted *(62)*.

Across four models *(7-9, 63)* important drivers of the cost–effectiveness of LEN implementation included the annualized price of LEN in a specific setting, service delivery and implementation costs, population coverage and adherence, and the prioritization of different populations for delivery, based on risk of HIV acquisition. Most models indicate that LEN must be relatively inexpensive to meet the threshold of less than US$ 500 per DALY averted, especially at higher coverage levels or without specific risk targeting.

The GDG concluded that the introduction of LEN was probably cost–effective in the long term, due to its high efficacy. The GDG noted, however, that large scale implementation of LEN is likely to require moderate resources and that, at the time of the GDG's considerations, there was uncertainty due to the lack of available pricing information for LEN. More pricing information will be available later, as the product receives national regulatory approvals and as generic manufacturers enter the global market.

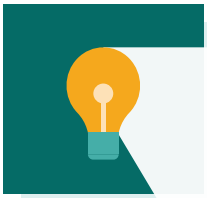
Key messages

- **Modelling studies indicate LEN can be cost–effective**, particularly if annual per-person costs remain below certain thresholds in higher prevalence settings.
- LEN can be cost-effective per DALY averted where **coverage and adherence are high and service delivery focuses on those at greatest risk for HIV acquisition**.

3.5 Equity and human rights

The GDG concluded that introducing LEN alongside existing HIV prevention options would likely increase equity. The rationale for this judgement was that expanding product choice to accommodate different users' needs and preferences would help to overcome inequities in HIV prevention. The six-monthly dosing schedule may help reduce cost and time barriers that often arise from requiring more frequent clinic visits; this reduced schedule could particularly benefit individuals with caregiving and/or employment responsibilities. This long dosing interval can also ease integration of LEN for PrEP into other preventive services, such as contraception, antenatal care and postnatal care, because LEN injections will be required only every six months.

The GDG also noted some uncertainty in how LEN introduction may affect equity. Although an injectable product may offer discretion and reduce stigma compared with daily oral regimens, the provider-administered nature of LEN could inadvertently re-medicalize prevention if it is not made available at decentralized sites or community-based venues. Centralized service delivery may limit access for those living in remote areas or facing transportation and financial constraints. To prevent reinforcing inequities when scaling up LEN, programmes should consider delivery models that prioritize users' convenience, confidentiality and community engagement. Countries can address structural stigma and discrimination by removing punitive laws, policies and practices that explicitly or indirectly exclude key populations from health services.



Key messages

- **Six-monthly injections may expand prevention options for individuals who struggle with daily pill adherence**, potentially improving equity in HIV services.
- **Centralized delivery could inadvertently limit access** if not paired with community-based or decentralized services; this highlights the need for inclusive implementation strategies.

3.6 Rationale and recommendation

The GDG noted that LEN for HIV prevention could offer substantial benefits, based on moderate-to-high certainty of evidence for its safety and efficacy, as well as on its potential acceptability to end-users and providers, feasibility of integration into existing health services, possible cost–effectiveness in certain scenarios and capacity to address equity concerns through its six-monthly dosing schedule. After considering the synthesized evidence across these domains, including uncertainties related to real-world implementation beyond the PURPOSE trials, and the lack of evidence in some key populations (for example, people who inject drugs and sex workers), the GDG made a **strong recommendation** that injectable LEN be offered as an additional prevention choice for people at risk for HIV, as part of combination prevention approaches.

The GDG recognized that data gaps remain, particularly on longer-term resource and cost implications and affordability. The GDG emphasized the need to ensure that the higher costs of LEN do not inadvertently reverse progress toward differentiated service delivery models or restrict access due to higher costs. Nevertheless, the GDG considered that the six-monthly dosing, suitability for individuals who value discretion or who have difficulties taking daily pills, and potential to expand HIV prevention options outweigh these concerns, given the high level of efficacy observed in the trials and the potential for increased coverage and uptake. The GDG emphasized that the research and evidence gaps identified should not delay programmatic implementation.

Recommendation [NEW]

Long-acting injectable lenacapavir should be offered as an additional prevention choice for people at risk of HIV, as part of combination prevention approaches. *(strong recommendation, moderate-to-high certainty of evidence)*

4. Rationale and supporting evidence: testing for long-acting injectable PrEP

4.1 Summary of review findings

WHO has existing recommendations on HIV testing strategies and algorithms and encourages countries to offer a strategic mix of approaches to maximize public health impact. For details see the *Consolidated guidelines on differentiated HIV testing services (64).*

Evidence was gathered from a systematic review that synthesized research findings on various testing approaches for injectable LA-PrEP delivery, with a focus on RDTs, HIV self-tests, laboratory-based testing and NAT techniques.

The systematic review included 22 studies (CAB-LA: 20 studies, LEN: 2 studies) involving 15 594 participants and spanning Africa, Asia, Europe and the Americas. Evidence included non-randomized comparator studies (n=7) and observational studies without a comparator group (n=15). There was limited information on continued HIV testing among those who discontinued injectable LA-PrEP.

Box 3 summarizes the key findings of the review. Web Annex D presents details.

Box 3

Evidence summary on testing for injectable LA-PrEP

The following findings relate to HIV RDT supported injectable LA-PrEP compared to NAT and/or laboratory-based HIV testing algorithms:

- Faster turnaround times providing the same diagnosis and more rapid ART initiation following HIV diagnosis *(65-68)* [1] *(very low certainty of evidence)*;
- Fewer delayed or missed injection visits *(65, 66) (very low certainty of evidence)*;
- May have lower test sensitivity, missing some cases, but with similar negative predictive values and positive predictive values across algorithms *(5, 6, 65, 66) (low certainty of evidence)*;
- May be no difference in the absolute number of missed or delayed HIV infections detected *(5, 6, 65, 66, 68) (low certainty of evidence)*;
- May be no difference in the detection of breakthrough HIV infections among those using injectable LA-PrEP *(5, 6, 65, 66) (low certainty of evidence)*;
- May be no difference in the prevention of integrase strand transfer inhibitor resistance associated mutations *(6, 65, 66) (low certainty of evidence)*;
- No difference in frequency of HIV testing among those taking injectable LA-PrEP *(59, 68)* [2] *(very low certainty of evidence)*;
- No effects on clinical or social harm such as consequences from misdiagnosis, anxiety or domestic violence *(5, 6, 59, 65, 66) (very low certainty of evidence).*

Evidence on the use of HIVST for injectable LA-PrEP was limited and focused on testing frequency and performance.[3] Studies reviewed indicated that there was very low certainty evidence that HIVST could increase testing frequency among those using injectable LA-PrEP.

Emerging data among adolescents receiving CAB-LA in Brazil suggest that HIVST and RDTs had good accuracy and demonstrated high sensitivity and specificity; both produced test results comparable with those of NAT *(96).* Further research is needed to more fully understand the potential role of HIVST as part of injectable LA-PrEP implementation.

1 Personal communications: Das M. Gilead Sciences. PURPOSE 1 and PURPOSE 2. 2024; Landovitz R, Geffen School of Medicine, HPTN083 study, 2024; Parikh U, University of Pittsburgh School of Medicine, CATALYST study, 2024.)

2 Personal communications: Dourado I, Universidade Federal da Bahia, PrEP1519, 2024; Dvora JD, Medicine and Epidemiology at University of California, CAB-PK in Pregnancy and Postpartum study, 2024; Fox J, King's College London, MOBILE MEN, 2024; Hoagland B, Instituto Nacional de Infectologia Evandro Chagas, ImPrEP CAB-LA Brasil study, 2024; Houssemini Mina, University of North Carolina, Project Malawi, Malawi Path to Scale, CAB-LA Implementation study, 2024; Langa N, Ministry of Health Zambia, Zimbabwe observational cohort, CAB-LA implementation, 2024; Martin C, Wits RHI, University of the Witwatersrand, Project PrEP, 2024; Mulenga L, Ministry of Health Zambia, Zambia observational cohort, CAB-LA implementation, 2024; Parikh U, University of Pittsburgh School of Medicine, CATALYST study, 2024; Saidi F, University of North Carolina, Project Malawi, PrIMO study, 2024; Tembo A, Ezintsha South Africa, Axis study, 2024; Zash R, Botswana Harvard Institute Boston, Tshireletso Study, 2024.

3 Personal communications: Dourado I, Universidade Federal da Bahia, PrEP1519, 2024; Fox J, King's College London, MOBILE MEN, 2024; Hoagland B, Instituto Nacional de Infectologia Evandro Chagas, ImPrEP CAB-LA Brasil study, 2024.

Additional modelling of the impact of using NAT, RDTs or HIVST in the context of CAB-LA also showed that, while NAT would detect HIV earlier, there would be no measurable difference in drug resistance because cases of acute infection or breakthrough infection remain very rare *(69)*. This modelling also shows that using lower sensitivity tests or missing or delaying a testing visit has minimal impact on drug resistance *(69)*.

4.2 Values and preferences

Through the systematic review (Web Annex D), the GDG assessed values and preferences concerning testing among PrEP providers and users. The GDG also considered values and preferences collected by WHO through an online survey and in-depth interviews for the development of the 2022 guidelines on CAB-LA *(70)*.

The systematic review found that users generally supported the use of HIV RDTs for injectable LA-PrEP service delivery. A study examining preferred settings to receive LA-PrEP among men who have sex with men (n=1076) found that 26% preferred receiving LA-PrEP at home, while 14% preferred obtaining it at a pharmacy *(71)*. These findings suggest that users favour options that reduce clinic visits and can facilitate decentralized service delivery options.

The 2022 WHO-led values and preferences process *(58, 70)* included survey responses from 1353 participants and in-depth interviews with 30 health workers. Findings indicated that HIV testing requirements were a concern. However, there was broad support from users and providers for RDTs as the standard testing strategy. There was also some interest in the potential use of HIVST. Previous WHO guideline processes and values and preferences assessments have had similar findings, which indicate that simplified testing through RDTs or self-tests is highly feasible and acceptable to providers and users *(64)*.

Key messages

- **Providers generally welcomed simplified testing strategies**, emphasizing the importance of rapid, same-day results to avoid delays in initiating or continuing injectable LA-PrEP).
- **End users favoured test methods that reduce clinic visits**, suggesting potential future roles for HIVST in injectable LA-PrEP delivery.
- **Further implementation research is needed** to fully determine the **role of HIVST** in delivering injectable LA-PrEP.

4.3 Resource use

Among other advantages, HIV RDTs cost less than most other HIV tests. The systematic review identified evidence on cost and resource use from five studies *(72-77)*.

One modelling study included HIV testing commodity costs ranging from US$ 0.17–4.00 for HIV RDTs, US$ 3–5 for HIVST, US$ 1.20–24.08 for laboratory-based antigen/antibody tests and US$ 8.80–85.10 for NAT. Additionally, data from one CAB-LA open-label extension study *(78)* indicated that detecting one additional case with NAT – missed by RDT at an earlier stage – would require testing at least 5305 individuals using NAT. Given available cost information, this would translate to costs ranging from US$ 46 684 to US$ 451 456 per case detected.

Another modelling study, of CAB-LA *(79)*, reported that using a standard HIV RDT was cost-effective compared with NAT, and there was no significant difference in reducing AIDS deaths (HIV RDT: mean 28 460 (9520–64 170) AIDS deaths per year compared with NAT: 21 840 (7630–47 300)) despite increased integrase inhibitor resistance, estimated at 5% by 2030, if CAB-LA were used, compared with 0.5% if no CAB-LA were used. The modelling also reported that NAT commodities were more expensive (average cost of US$ 22 per test) than HIV RDTs (US$ 4).

Overall, HIV RDTs and HIVST were found to cost less than NAT/RNA testing or other laboratory-based testing strategies (Web Annex D). Reviewers and the GDG considered all cost and resource use information to be conservative, as it did not include fully costs such as: expenses related to scale-up, supply, laboratory equipment, human resources, training and confirmatory assays. There continues to be only one commercially available NAT that is currently validated and has a diagnostic claim for use in those older than 18 months of age, further hindering access to more affordable NAT options.

Key messages

- **RDTs cost significantly less than NAT** and other laboratory-based testing.
- **Costly follow-up testing** for false positive NAT results adds to the financial burden of RNA-based testing in programmatic settings.

4.4 Equity and human rights

Equity and human rights considerations were informed by facilitated discussion among the GDG members. The GDG concluded that using an RDT-based testing algorithm and/or self-tests may increase equity by enabling more people to have access to and effectively use LA-PrEP *(80)*.

Key drivers of poor access to NAT testing, as well as laboratory-based testing, are the cost and complexities of service delivery. NAT and laboratory-based testing have high commodity costs and require highly skilled staff and infrastructure including refrigeration and electricity. WHO has previously reported that nearly all HIV testing in the world is done in primary care or community level with no clinical laboratories *(64)*. Given the unmet need for routine viral load monitoring among people with HIV who are receiving ART, any increased NAT capacity should be directed to supporting treatment services *(81)*.

The GDG concluded that requiring NAT/RNA testing or other laboratory-based HIV testing for initiation of injectable LA-PrEP would most likely limit its availability. The GDG also noted that, because of current gaps in the availability of NAT for viral load monitoring of people with HIV, it would not be appropriate to prioritize NAT over RDTs for PrEP initiation or continuation.

Key messages

- **Access to RDTs and HIV self-tests can improve equity** by reducing travel time, lowering financial barriers and supporting confidential testing.
- **Routine testing requiring NAT** or other laboratory-based testing would likely be infeasible in many countries, and, therefore, services might miss populations most in need of injectable LA-PrEP.

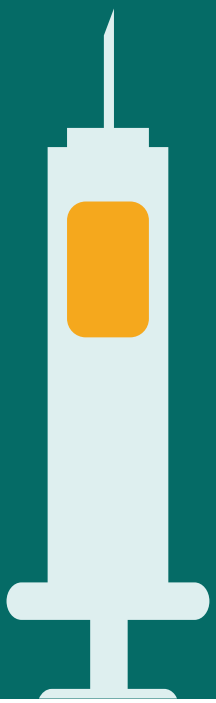
4.5 Rationale and recommendation

The GDG considered the overall benefits of RDT-based algorithms to outweigh the potential harms. This decision is based on observed advantages of RDT-based testing, including faster turnaround times compared with NAT, minimal variation in how people value rapid results, moderate-to-substantial cost savings, high feasibility and likely acceptability among stakeholders in the health system. RDT-based algorithms are expected to improve health equity by increasing access, particularly in resource-limited settings. By addressing barriers, including cost, infrastructure and human resources, RDT-based testing can potentially expand LA-PrEP accessibility in low- and middle-income countries where NAT capacity is often scarce. Importantly, the GDG emphasized that, despite current evidence gaps, implementation of RDT-based testing in LA-PrEP programmes should not be delayed. Reductions in resource use, feasibility and values and preferences in favour of RDTs were key factors that led the GDG to make a strong recommendation for the use of HIV RDTs despite very low certainty of evidence.

The GDG noted that HIVST may be an important implementation consideration in some contexts, increasing programme flexibility and testing frequency. However, there were insufficient data to make a formal recommendation. WHO plans to review emerging evidence as soon as it is available and to update guidance accordingly.

Recommendation [NEW]

Rapid diagnostic tests may be used for HIV testing for initiation, continuation and discontinuation of long-acting PrEP. *(strong recommendation, very low certainty of evidence)*



5. Implementation considerations and research gaps: lenacapavir for HIV prevention

5.1 Implementation considerations

The success of LEN implementation as an additional HIV prevention option will depend on political will and on an enabling environment for global scale-up. Ensuring equitable access among populations should be a priority during implementation. It is important that national programmes partner with communities of people affected by HIV and design and implement LEN integration into existing programmes with their meaningful participation. WHO will develop implementation guidance for countries to support adoption of LEN. (See Chapter 6 for implementation considerations and research gaps related to HIV testing in the context of LEN delivery.)

5.1.1 Dosing

The dosing strategy for LEN involves a mandatory oral loading dose of two 300 mg tablets given on each of days 1 and 2, beginning on the day of the first injection (total oral loading dose of 1200 mg). The injectable component is delivered subcutaneously as two 1.5 mL injections (total injectable dose of 927 mg). Follow-up injections are administered every 26 weeks.

> **The window for follow-up injections is from two weeks before to two weeks after the next scheduled appointment.**

Oral reloading is not needed for follow-up injections, provided users return on time to follow-up appointments (26 weeks +/− two weeks after the previous injection). Individuals who return after 28 weeks and wish to continue LEN will need to receive the same reloading dose with the oral tablets over two days.

Programmes and providers should support individuals to return on-time for follow-up injections to maintain protection. This support will include educating clients on the importance of receiving follow-up injections according to visit schedules and the importance of using other HIV prevention products or approaches if a follow-up injection is delayed or if LEN is stopped. Systems to remind and/or recall clients for follow-up injections may be of benefit. These systems may include automated reminders via digital interventions and mobile platforms.

As a long-acting product, LEN administered subcutaneously in a dose of 927 mg may remain in the body for at least 12 months after the last injection (known as a pharmacokinetic tail). However, after six months LEN concentrations in the body fall below the protective threshold, although they remain detectable and can contribute to HIV drug resistance if HIV acquisition occurs. For users who discontinue LEN, providers should support transition to other HIV prevention approaches to protect against HIV acquisition during the pharmacokinetic tail period.

Similarly, programmes should ensure continuity of supply and access and remove structural barriers to on-time administration of follow-up injections to reduce the risk of delayed or prematurely stopped LEN.

5.1.2 Service delivery

To date, evidence available on the delivery of LEN has been limited to highly controlled trial settings. However, experience with oral PrEP and CAB-LA provide relevant and important evidence for implementation of LEN. This experience suggests that differentiated service delivery options, including task sharing and delivery in community settings, are crucial to achieve scale-up and create person-centred, accessible and acceptable services.

LEN should be offered as part of a comprehensive person-centred service package tailored to the local context and the needs and preferences of individuals. Importantly, LEN may not suit the needs of every client. Clients should be offered a choice of PrEP products. Offering choice can increase PrEP uptake, coverage and persistence. In addition, flexibility while offering LEN is crucial, as over time some individuals may change their preferences for a specific product.

The service package for LEN may include the provision of other PrEP options (TDF-based oral PrEP, the DVR and/or CAB-LA) to support PrEP choice, condoms and lubricants, PEP, screening and treatment of STIs and viral hepatitis, sexual and reproductive health services (including contraceptive services), mental health support, services that prevent and protect against gender-based violence, gender-affirming care, and harm reduction services for people who use drugs (including for chemsex). People who may benefit from PrEP and service providers should be engaged in the design of PrEP services for LEN.

National programmes should look for opportunities for differentiated service delivery to support LEN access across diverse populations within countries. Some approaches for differentiated and simplified service delivery include:

- task sharing with nurses, pharmacists, community health workers and peers;
- delivery in community settings, such as pharmacies, mobile sites, community-based organizations and other types of community centres;
- leveraging virtual interventions and telehealth, including digital tools and delivery channels;
- integration with other services, including antenatal and postnatal services.

5.1.3 Hepatitis and other STIs

Following person-centred approaches, and to avoid missed opportunities to prevent and manage other infections, testing for hepatitis B virus (HBV) and/or hepatitis C virus (HCV) should be offered for people starting LEN and repeated annually for those who test negative. Vaccination for HBV should be offered for people who are negative to HBV. People with reactive results for HBV and HCV should follow national diagnostic algorithms for hepatitis and be referred to care if a diagnosis is confirmed. Individuals with HBV infection could consider TDF-based oral PrEP, given its dual effectiveness against HIV and HBV.

LEN is not contraindicated for individuals with HBV or HCV. However, it is important to note that LEN has not been extensively studied in people co-infected with HIV and active HBV or untreated HCV, and it has not been studied in individuals with severe hepatic impairment. Therefore, close monitoring is advisable when prescribing LEN to patients with HBV or HCV.

Testing for STIs such as gonorrhoea, chlamydia, syphilis and trichomoniasis should be offered to people starting or continuing LEN. The high incidence of STIs among PURPOSE 1 and PURPOSE 2 trial populations strongly suggests that regular STI testing should be part of LEN delivery to support broader STI control. WHO has produced an implementation tool that follows a step-wise approach to support the integration of STI control activities in HIV prevention programmes *(82)*.

While testing for hepatitis and STIs should be offered, their lack should not limit or delay access to LEN.

5.1.4 Toxicity and drug-to-drug interactions

The use of LEN has not been associated with nephrotoxicity or hepatotoxicity. Thus, no liver or kidney function testing and monitoring are required during LEN initiation or follow-up. No dose adjustment is required in individuals with mild, moderate or severe renal impairment (creatinine clearance ≥ 15 mL/min). LEN has not been studied in individuals with end-stage renal disease; thus, it should be used with caution in these individuals.

After administration, LEN undergoes minimal metabolism. Drugs affecting LEN metabolism include moderate and strong inducers of drug metabolizing enzymes like CYP3A4.
At the same time, LEN is a moderate inhibitor of CYP3A4 and, therefore, affects drugs metabolized by CYP3A4, particularly those that have a narrow therapeutic range *(28)*.
Upon discontinuation of LEN, residual concentrations of LEN may remain in the circulation for prolonged periods and could affect how other CYP3A4 substrates are metabolized, particularly those initiated within nine months after the last subcutaneous dose.

Table 1 summarizes interactions with selected key drugs. This information and management strategies may be updated as experience on LEN implementation increases and new data become available. Further interactions and management strategies may be found online at https://hiv-druginteractions.org; the list of medicines here is not exhaustive and is subject to change.

Table 1. Summary table of drug–drug interactions with lenacapavir used as PrEP

Drug class	Interaction and management
Antibiotics for treatment of tuberculosis (TB) Rifabutin Rifampicin Rifapentine	**Potential interaction, which requires dose adjustment** Induction of CYP3A4 can substantially reduce LEN concentrations which may result in loss of its prevention efficacy.
Anticonvulsants Carbamazepine Phenobarbital Phenytoin	**Potential interaction, which requires dose adjustment** Induction of CYP3A4 can substantially reduce LEN concentrations, which may result in loss of its prevention efficacy.
Illicit/recreational Ketamine	Potential interaction, which may persist after discontinuation of lenacapavir Ketamine concentrations may increase due to inhibition of CYP3A4 by LEN and may increase side-effects associated with ketamine, such as respiratory depression and hallucinations.
Erectile dysfunction Avanafil Sildenafil Tadalafil Vardenafil	Potential interaction, which may persist after discontinuation of lenacapavir Sildenafil, tadalafil and vardenafil concentrations may increase due to inhibition of CYP3A4 by LEN.
Gender-affirming hormones Estradiol Conjugated estrogens Ethinylestradiol Medroxyprogesterone Micronized progesterone Testosterone	No dose adjustment required. LEN is a moderate inhibitor of CYP3A4 and could potentially increase exposure of the gender-affirming hormone, although to an extent that does not require dose adjustment.
Hormonal contraceptives Ethinylestradiol Etonogestrel Levonorgestrel Medroxyprogesterone Norethisterone Norgestrel	No dose adjustment required. LEN is a moderate inhibitor of CYP3A4 and could potentially increase exposure of the contraceptive hormone, although to an extent that does not require dose adjustment.

5.1.5 Other adverse events

While LEN is generally safe, side-effects have been reported, primarily ISRs. Few participants in the PURPOSE 1 and 2 trials were reported to discontinue use due to ISRs, and these became less frequent and less severe with time. However, participants in clinical trials are given incentives to keep using an investigational product. Programmes offering LEN should monitor discontinuation due to ISRs. Other adverse events, especially serious adverse events that are related to LEN and adverse events that lead to stopping use of LEN, should be documented, aggregated and reported to relevant stakeholders during implementation. Community-led information sharing can support monitoring of side-effects.

5.1.6 Surveillance and monitoring

Existing routine monitoring systems for PrEP can be adapted to incorporate LEN. However, they must be able to capture and accurately report the delivery and use of different products and formulations for both client and programme management and improvement. All available PrEP products and service delivery modes should be considered for monitoring, as this information can be used to improve access and uptake. In a reporting period, people may start, continue, stop and restart PrEP and switch between PrEP products. Longitudinal data systems capturing individual-level data are best suited to capture this information.

The PURPOSE 1 and PURPOSE 2 trials provided LEN to participants for a median of 12 months under clinical trial conditions. There are limited data on some adverse event outcomes that might occur during longer follow-up and no data on real-world implementation of LEN currently exist. Programmes offering LEN should include robust routine data systems to monitor LEN initiation and persistence, safety and adverse events, including during pregnancy and breastfeeding; seroconversions; and drug resistance. Adverse event monitoring is of particular importance.

Table 2 suggests a minimum set of individual-level data on PrEP to collect. Detailed information on these indicators can be found in WHO's *Consolidated guidelines on person-centred HIV strategic information (83)*.

Table 2. Recommended minimum dataset for PrEP for recording in national data systems

Intervention	Minimum dataset
Pre-exposure prophylaxis (PrEP)	Date PrEP prescribed (includes initial prescription and repeats) Date PrEP dispensed (if available from dispensing pharmacy or community distribution) PrEP product prescribed (for example, oral PrEP containing tenofovir, dapivirine vaginal ring (DPV-VR), CAB-LA or LEN) Volume of PrEP product prescribed/dispensed (for example, number of pills, number of devices) Date individual attends follow-up appointment

Source: WHO 2022 *(83)*.

5.1.7 Drug resistance

There is a risk of resistance to capsid inhibitors if a person with an undetected HIV infection starts LEN or if a person acquires HIV during LEN use or after discontinuation. Programmes implementing LEN should build in surveillance of drug resistance among people with a history of LEN use who are diagnosed with HIV. In well-resourced settings, there may be benefit in conducting population-level assessments of drug resistance to capsid inhibitors in persons newly diagnosed with HIV.

5.1.8 Use in pregnancy and breastfeeding

Due to its infrequent administration, high efficacy and safety profile, LEN could be an acceptable and convenient PrEP option during pregnancy and breastfeeding. It is important that women of reproductive potential do not face barriers to use and benefit from LEN. While the data available on LEN use during pregnancy and breastfeeding suggest that it is safe, robust systems need to be in place to monitor adverse pregnancy and infant outcomes (for example, stillbirth, birth defects, neonatal mortality), particularly for uncommon and rare adverse events, through large-scale surveillance, PrEP programmes and/or ARV pregnancy registries.

Antenatal and postnatal care services offer an opportunity to offer PrEP products such as LEN to women at risk of HIV, but more operational experience and research are needed to understand the unique needs and challenges of this population and how best to address them. A WHO toolkit to facilitate and support the inclusion of pregnant and breastfeeding women in clinical studies of ARVs may help addressing these gaps *(84)*. Services delivering LEN should ensure that contraceptive services are available for women who do not desire pregnancy and that linkages to antenatal care are available for women who become pregnant while receiving PrEP.

5.1.9 Training and support for providers

National programmes should furnish providers with appropriate training, technical support and operational tools, including job aids and decision-support algorithms aimed at a range of providers. Providers have a critical role in supporting choice, facilitating safe and effective choice of, and switching between, PrEP products and other prevention approaches. Providers also have a role supporting individuals who choose LEN to start and continue using it safely and effectively. The focus of this support should be on return for follow-up injections on time to ensure coverage and protection. Individuals who choose LEN should be equipped to start, use and stop LEN safely and effectively.

Training of LEN providers should include:

- discussing HIV prevention needs and preferences with clients, including their HIV prevention and sexual health goals;
- supporting choice among different HIV prevention options such as LEN, oral PrEP, the DVR and/or CAB-LA and condoms, considering relative efficacy and comparative advantages and disadvantages;
- correct dosing and administration of LEN, including oral and injectable components and proper injection technique;
- support for safe and effective use, including the importance of returning for follow-up injections on time;
- drug–drug interactions, safety and toxicity;

- guidance on testing strategies following a reactive HIV test result, including linkages to care and treatment;

- provision of other sexual and reproductive health services based on individual needs, and linkages to mental health services and harm reduction programmes as needed.

Providers should also be trained to offer respectful and inclusive services that are free of discrimination and help to reduce stigma. This includes recognizing and responding to the range of health, social and emotional needs of people who may benefit from PrEP.

During implementation, particularly in the context of differentiated service delivery, there may need to be additional specific training, registration, accreditation or policy support for task sharing and to address the evolving needs of different cadres of providers.

5.1.10 Creating awareness and generating demand

As it is a new HIV prevention option, many communities and providers may have limited or no knowledge about LEN. Countries anticipating LEN introduction should launch campaigns to increase awareness and create demand; these campaigns should be tailored to communities and providers before and during product introduction, enabling people to make informed HIV prevention decisions. One reason that HIV programmes engage and partner with networks of people who could benefit from PrEP is to better understand and respond to people's concerns about a new product. Broad awareness and acceptance within communities is important also to minimize stigma and discrimination and increase acceptability, thereby supporting uptake and effective use.

5.1.11 Engaging communities

Meeting the needs of people who may benefit from PrEP and other HIV prevention services and providing LEN requires the full participation of communities in designing, implementing and monitoring programmes.

The following are good participatory practices that apply to services for all priority and key populations:

- Recognize the leadership and resilience of priority and key populations in addressing the HIV epidemic at both the local and global levels and sustain their participation through adequate funding and support for community-led organizations.

- Strengthen the capacity of community-based organizations to educate and train their communities about all PrEP and HIV prevention options.

- Promote and expand community-based services, especially services led by members of priority and key populations.

- Ensure that any PrEP option is offered as a choice, free of coercion and with access to other prevention strategies that individuals at substantial risk may prefer.

- Increase political commitment to rights, including the rights of priority and key populations, by decriminalizing consensual sexual activity, gender expression, sex work and drug use.

5.1.12 Adolescents, key populations and other vulnerable populations

There is currently no programmatic implementation experience for LEN with adolescents or key populations. However, both PURPOSE 1 and PURPOSE 2 trials included adolescents among the participants. Subanalyses from PURPOSE 1 data found no differences in LEN safety and efficacy in adolescents ages 16 and 17 compared with participants who were 18 years or older (85), suggesting no need for dose adjustments.

However, evidence from other HIV prevention programming emphasizes the importance of person-centred services that are available, accessible and acceptable and that communities are involved with designing and implementing (see section 5.1.9).

Members of key populations and adolescents typically experience greater legal and social challenges to accessing PrEP services, including stigmatization, discrimination and criminalization. Adolescents may face additional age-related legal, policy, regulatory and social barriers as well, including age of consent laws that limit access to HIV prevention and/or testing services and additional challenges with logistics and expenses associated with attending a physical PrEP service. Reducing these barriers will be important to the success of LEN implementation. For example, delivery within family planning services may be beneficial for adolescent girls and young women.

LEN may also be an important option for partners of people living with HIV, particularly among those newly diagnosed with HIV, and partners of members of key populations. LEN providers should be sensitive to the needs and challenges of marginalized populations and conscious of intersecting risks for HIV – for example, drug use, displacement and homelessness, as these may influence decisions about LEN suitability and other health and support needs.

5.1.13 Costs and impact

As part of planning LEN introduction, national programmes will want to consider the relative costs and benefits (direct, indirect, financial and other) of introducing LEN as an additional HIV prevention option. Countries may engage in modelling of the costs and potential impacts of LEN introduction under different scenarios to evaluate the best strategies. The limited modelling available to date suggests that LEN may have the greatest impact when it increases overall prevention coverage and that, while highly targeted provision may be most cost–effective approach, there is a trade-off between focus and overall impact. Evaluating the feasibility of any introduction approach will also be critical. Generic manufacture of LEN, at high volumes, is likely to contribute to cost savings. Nonetheless, negotiating lowest possible prices in the short-term will be crucial for all low- and middle-income countries.

5.2 Research gaps

Implementation science will inform decisions on the implementation and scale-up of LEN as it is rolled out. However, the GDG stressed that further research should not delay programmatic implementation in countries.

PURPOSE 1 and PURPOSE 2 provided LEN to participants for a median of 12 months under clinical trial conditions. There is a gap in real-world implementation experience and limited evidence on, for example, the optimal HIV testing strategies, the best strategies to support access, adherence to the dosing schedule, persistence of use, product switching and stopping, as well as provision as part of differentiated service delivery models and across populations and geographies.

5.2.1 Alternative injection sites and dosing

Additional research to support the safety, effectiveness, acceptability and feasibility of alternative injection sites is needed, especially where these may support scale-up through differentiated service delivery models, including self-care models. A Phase I study found thigh and upper arm injections provided similar or higher drug exposures than abdominal injections, but this has not been evaluated in trials *(86)*. There is also insufficient evidence on variations in dosing schedules, including strategies for managing delayed or missed doses.

5.2.2 Service delivery

Programmatic rollout and implementation science will play an important role in collecting evidence to support differentiated service delivery models for LEN, including delivery through task sharing with different cadres of providers and provision in a variety of community settings, virtual models and self-care models. Implementation science should also aims to collect evidence on strategies to support access, uptake and persistent use by different populations − for example, adolescents, members of key populations and pregnant or breastfeeding women. Investigation should include exploring efficient approaches to recall clients for on-time injections.

5.2.3 Product choice and switching

Studies such as SEARCH *(59)* and programmatic implementation in countries such as South Africa *(87)* have demonstrated the importance of offering choice to increase uptake and coverage, given the variability in individual preferences for HIV prevention. Evidence from the systematic review of values and preferences (Chapter 3) suggests that there will be a considerable preference for LEN across populations and geographies. Implementation science is needed to further evaluate the impact of providing LEN as an additional choice alongside other PrEP and HIV prevention options. An individual's HIV prevention needs and preferences are expected to change over time, and there is currently no real-world evidence for how long an individual may choose to stay on LEN. Research should explore patterns of LEN use, including persistence and optimal strategies for supporting on-time injections.

Individuals using LEN may need or want to stop its use and change PrEP products. Currently, best practices for switching from LEN to other PrEP products (oral PrEP, CAB-LA and the DVR) are not known; they should be explored as part of implementation studies that offer PrEP product choice. When switching between products, providers should ensure continuous HIV prevention coverage during the transition period. This may may result in a short overlap between PrEP products. No drug–drug interactions are expected between LEN and other PrEP products; in fact, antiretrovirals are often prescribed in combination as ART *(88)*. Co-administration of long-acting antiretrovirals is taking place as part of trials and studies of long-acting treatment; more data are expected soon *(89)*.

As LEN is a new PrEP option, there is limited evidence on values and preferences for LEN. The systematic review found limited information about providers' perspectives on LEN, and none is available outside the USA. Providers reported concerns including potential costs, HIV testing requirements, adherence to the injection schedule, drug resistance, additional burden on health care providers, as well as product-specific efficacy, side-effects and drug-drug interactions. Studies should collect additional information on acceptability, concerns and feasibility from different cadres of health care providers and geographies to support quality implementation, including training.

5.2.4 Adolescents, key populations and other vulnerable populations

Neither PURPOSE 1 nor PURPOSE 2 explicitly included or reported on people who inject drugs. LEN is expected to be efficacious for parenteral, as well as sexual, exposure. Research now underway is expected to yield specific direct evidence on its safety and efficacy, with results expected in mid-2027.

Evidence should be collected, as part of implementation science or routine monitoring and evaluation, to support PrEP and specifically LEN service delivery improvements for adolescents, members of key populations and other vulnerable populations, including those experiencing displacement or homelessness, as well as during pregnancy and breastfeeding to ensure equitable access and uptake of LEN as a new prevention option.

Importantly, more evidence is needed on service delivery models for LEN in people who use injectable drugs, sex workers and people in prisons and other closed settings.

5.2.5 Costs and impact

There is a need for additional country-specific modelling, including modelling for concentrated epidemics (such as in Latin America and in the Asia–Pacific region), to support decision-making for LEN introduction in low- and middle-income countries. Modelling will be important to provide insights into the potential impacts and costs of adding LEN into a country's HIV prevention response. It can also provide insights at both the country and global level about the overall coverage (or volume) of LEN needed to drive epidemics into the elimination phase. Such models should be aligned with realistic assumptions about programmatic scale-up, such as the feasibility of highly targeted approaches to eligibility and fully loaded cost considerations. Models also will be needed in the future to look at the scale-up of LEN for PrEP and any associated drug resistance.

6. Implementation considerations and research gaps: testing for long-acting injectable PrEP

6.1 Implementation considerations

HIV testing to support PrEP should be planned and implemented using a public health approach. Simplified and affordable testing approaches, including HIV RDTs and self-tests, are important to ensure access to and uptake of PrEP services among those who may benefit. Individuals and programmes may use a range of different PrEP options, such as oral TDF/FTC, the DVR and other long-acting products such as CAB-LA and LEN.

WHO recommends that RDTs be routinely used for LA-PrEP initiation and continuation. NAT and laboratory-based HIV testing should not be required nor prioritized for PrEP delivery, including for injectable LA-PrEP. Among RDTs, antibody/antigen RDTs do not appear preferable to antibody-only RDTS, which are less expensive (Box 4).

Testing programmes need to be standardized and simple to support interchangeability and user choice across PrEP options. National programmes should continue efforts to adopt and implement simple and low-cost HIV testing strategies and algorithms as recommended by WHO.

Box 4

Summary of evidence on antibody/antigen HIV RDTs

Acute HIV infection is the earliest stage when HIV can be detected. A rapid diagnostic test capable of identifying HIV at this stage could enable earlier diagnosis and treatment. In the context of injectable LA-PrEP, this could help prevent missed HIV cases and reduce the risk of unintended consequences such as drug resistance.

Antibody/antigen RDTs have been available for about a decade, but they are not widely used in resource-constrained settings due to higher costs and complexities compared with standard antibody-only RDTs. In 2024 WHO conducted a systematic review to understand the ability of antibody/antigen HIV rapid diagnostic tests to detect acute HIV infection, including among PrEP users. This review found that antibody/antigen HIV rapid diagnostic tests had a pooled sensitivity during acute HIV infection of 50% (95% CI: 35–64) and specificity of 99% (95% CI: 96–100). Additionally, during acute HIV infection, among PrEP users, sensitivity and specificity was found to be 25% (95% CI: 13–44) and 94% (95% CI: 64–99) *(90-92)*. This indicates that antigen/antibody RDTs may not substantially increase detection of acute HIV cases in this context.

WHO continues to provide standard guidance to use quality-assured HIV rapid tests and self-tests, such as those that are WHO prequalified *(93)*. These should be used in testing algorithms achieving at least 99% positive predictive value (that is, fewer than one false positive per 100 diagnoses). There is no evidence supporting the prioritization of antigen/antibody RDTs over antibody-only RDTs.

Countries are encouraged to use the WHO toolkit *(94)* to optimize HIV testing strategies and product selection based on their setting and population needs.

6.1.1 HIV testing services for initiating LA-PrEP

HIV testing is required before initiating injectable LA-PrEP. Individuals who have a reactive test and are diagnosed with HIV according to the national testing strategy and algorithm should be immediately referred to and offered treatment.

Only individuals who have an HIV-negative test result should be started on PrEP, including injectable LA-PrEP. An individual who has an inconclusive test result (initial test reactive, followed by a negative test) should be referred for further testing in 14 days to rule in or rule out seroconversion. Screening tools to address suspected acute infection can be effective *(95)*, and they can be considered according to a country's national guidelines. After retesting 14 days later, any individual with persistent inconclusive results should be considered HIV-negative and started on PrEP, including injectable LA-PrEP.

Flexible testing options are important. Programmes offering HIVST for initiating oral PrEP or DVR should continue to offer HIVST. However, individuals with a negative self-test result should also be offered rapid testing by the provider before initiating injectable LA-PrEP. Some programmes, such as those in Brazil, advise clients to self-test before coming to the facility for their first LA-PrEP injection *(60)*. More studies are expected to report results on HIVST as part of injectable LA-PrEP delivery and will be reviewed by WHO as an urgent priority.

6.1.2 HIV testing services for continuing LA-PrEP

HIV testing is an important part of PrEP continuation, including for injectable LA-PrEP. It is practical for individuals taking PrEP to receive testing at their refill or injection visit. Depending on the PrEP option used, testing schedules may differ – for example, every two months for CAB-LA and every six months for LEN. However, it is important to provide clients and programmes with the flexibility to support effective PrEP use. More, or less, frequent testing intervals may be considered where warranted and based on available resources. Self-tests can be a potential option where needed and considered beneficial by the client or provider.

Individuals with a negative HIV test result should continue PrEP, including injectable LA-PrEP, according to their preference and national guidance. Anyone taking injectable LA-PrEP who has a reactive HIV test result, including a self-test result, should receive further testing, according to the national testing strategy and algorithm, to confirm the diagnosis. Upon confirmation of a diagnosis, ART should be initiated promptly, in accordance with local clinical protocols, to minimize risks of drug resistance. If available, drug resistance testing should be done to inform public health impact.

Individuals with an inconclusive HIV test status while taking injectable LA-PrEP should be retested in 14 days, using the national testing algorithm, to rule in or rule out seroconversion. NAT should not be used to resolve these cases because, among those taking injectable LA-PrEP, HIV may not be adequately detected and there could be a greater likelihood of false positives *(97)*. If the serology profile remains inconclusive, the person receiving injectable LA-PrEP is considered HIV-negative, and LA-PrEP can be continued. If the serology profile evolves and an individual is diagnosed with HIV according to the national algorithm, they should be immediately referred for care and treatment according to national guidelines. All people with a confirmed HIV diagnosis should be linked to ART and HIV care services, ideally on the same day as diagnosis or as soon as possible thereafter.

Each suspected breakthrough infection should be evaluated individually. All individuals with a reactive result or inconclusive result that needs further testing and follow-up should be counselled to ensure that they understand their test results. They should be encouraged to continue PrEP until more information and a final diagnosis are available, and they should consider taking precautions to prevent potential onwards transmission of HIV, such as the use of condoms during sex.

6.1.3 HIV testing services following discontinuation of LA-PrEP

Individuals taking PrEP, including injectable LA-PrEP, should be advised of the importance of HIV testing if they decide at any point to discontinue or transition to another PrEP option.

It is important to provide people using PrEP, including injectable LA-PrEP, with education and simple messages about testing after PrEP discontinuation. General messages should encourage clients who discontinue PrEP, including injectable LA-PrEP, to retest if risk behaviour takes place after they stop, or take a long break from, using PrEP. Also, individuals taking PrEP, including injectable LA-PrEP, should be informed that HIV detection might be delayed because of their PrEP use. Self-testing after PrEP discontinuation should be discussed with current PrEP users and provided for those who discontinue PrEP. Clients should be informed of the benefits of disclosing their past PrEP use to future HIV testing providers, as it may help provide an accurate HIV diagnosis; this information may be important for interpreting results and encouraging follow-up retesting.

6.2 Research gaps

Evidence on HIV testing for injectable LA-PrEP was of very low certainty. There are several research gaps that, if filled, could guide improved programming and public health impact.

6.2.1 Optimizing the frequency and flexibility of HIV testing services

Understanding the best time to offer HIV testing services for clients and for public health impact is critical. More flexible testing services can improve users' experiences, remove barriers and reduce requirements. Implementation science to understand how to promote testing services across PrEP, including injectable LA-PrEP, is also needed.

6.2.2 HIV self-test and self-care models

The potential role of self-testing to support current and future LA-PrEP options merits further exploration. It is important to understand whether and how self-testing increases programme efficiency, decentralization, access, affordability and flexibility and helps with scale-up and impact. Self-testing may be particularly important to mitigate risks after PrEP discontinuation or transition to other agents and formulations, including injectable LA-PrEP.

6.2.3 Address and mitigate HIV drug resistance concerns

HIV acquisition in the context of PrEP, including injectable LA-PrEP is very rare and even more rarely can be linked with development of resistance to HIV drugs. While some programmes have screening tools that might help identify those with acute infection or with long acting early viral inhibition, evidence on their feasibility and impact are limited. Programmatic tools, as well as simple and affordable point-of-care diagnostics, that can further assist with early diagnosis, prompt linkage to ART and reduce the risk of drug resistance important. However, existing diagnostics and tools remain expensive; efforts to simplify and reduce costs are a priority.

7. Updating and dissemination

These guidelines and the evidence presented to the GDG (Web Annexes A through G) are being launched as a web-based product. These guidelines will also be incorporated into the periodic updates of the WHO consolidated guidelines on HIV, which is updated in full or in part when regular scoping exercises of available evidence and experience from country implementation trigger and guide the need for new guidance. As the evidence base or users' needs change, WHO will consider producing technical updates such as a document on specific subjects.

WHO will update implementation guidance on PrEP to include LEN, including considerations for programmatic delivery and specific populations, and to reflect additional relevant evidence as it becomes available. As evidence emerges on the use of HIVST for injectable LA-PrEP, WHO will prioritize its review.

WHO headquarters will work closely with WHO regional and country offices, national ministries of health and implementing partners to plan for dissemination, adaptation and implementation of these new recommendations. Key steps in the dissemination will include presenting the recommendations at international conferences; conducting workshops to support regional and country adaptation; rapidly developing adaptation tools to help countries set priorities for resource allocation so as to facilitate full implementation over time; and conducting briefings and joint planning for dissemination with international and national implementing partners.

Monitoring of implementation will rely on the Global AIDS Monitoring indicators framework and the National Commitments and Policy Instrument, which is an annual reporting system for country-level information on policy adoption and programmatic delivery of HIV services. Qualitative monitoring will include tracking adoption of LEN as an additional PrEP product in national guidelines. Quantitative monitoring will include the number of people using PrEP at least once in a year, disaggregated by product type.

References

1. 2024 global AIDS report — the urgency of now: AIDS at a crossroads. Geneva: Joint United Nations Programme on HIV/AIDS; 2024 (https://www.unaids.org/en/resources/documents/2024/global-aids-update-2024, accessed 1 April 2025).

2. WHO implementation tool for pre-exposure prophylaxis of HIV infection: provider module for oral and long-acting PrEP. Geneva: World Health Organization; 2024 (https://www.who.int/publications/i/item/9789240097230, accessed 1 April 2024).

3. WHO handbook for guideline development. 2nd ed. Geneva: World Health Organization; 2014 (https://iris.who.int/handle/10665/145714, accessed 1 April 2025).

4. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A et al. Going from evidence to recommendations. BMJ. 2008;336:1049-51. doi: 10.1136/bmj.39493.646875.AE

5. Bekker LG, Das M, Abdool Karim Q, Ahmed K, Batting J, Brumskine W et al. Twice-yearly lenacapavir or Daily F/TAF for HIV prevention in cisgender women. N Engl J Med. 2024;391:1179-92. doi: 10.1056/NEJMoa2407001

6. Kelley CF, Acevedo-Quinones M, Agwu AL, Avihingsanon A, Benson P, Blumenthal J et al. Twice-yearly lenacapavir for HIV prevention in men and gender-diverse persons. N Engl J Med. 2024. doi: 10.1056/NEJMoa2411858

7. Jamieson L M-RG, Johnson L. Lenacapavir: preliminary impact, cost effectiveness and cost threshold for South Africa. Unpublished preliminary results. 2024.

8. Wu L, Kaftan D, Wittenauer R, Arrouzet C, Patel N, Saravis AL et al. Health impact, budget impact, and price threshold for cost-effectiveness of lenacapavir for HIV pre-exposure prophylaxis in eastern and southern Africa: a modelling analysis. Lancet HIV. 2024;11:e765-e73. doi: 10.1016/S2352-3018(24)00239-X

9. Kaftan D SM, Resar D, Milali M, Mudimu E, Wu L, et al. Health impact and cost threshold for emerging long-acting PrEP products in Eastern and Southern Africa: a mathematical modeling study. 2024.

10. van de Vijver D vKJ, Dimtrov D, Janamnuaysook R, Wongsa A, Phanuphak N. Impact of lenacapavir on the HIV epidemic among MSM in Thailand: a modelling study. Unpublished preliminary results. 2025.

11. Link JO, Rhee MS, Tse WC, Zheng J, Somoza JR, Rowe W et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature. 2020;584:614-8. doi: 10.1038/s41586-020-2443-1

12. Margot N, Vanderveen L, Naik V, Ram R, Parvangada PC, Martin R et al. Phenotypic resistance to lenacapavir and monotherapy efficacy in a proof-of-concept clinical study. J Antimicrob Chemother. 2022;77:989-95. doi: 10.1093/jac/dkab503

13. Margot NA, Naik V, VanderVeen L, Anoshchenko O, Singh R, Dvory-Sobol H et al. Resistance analyses in highly treatment-experienced people with human immunodeficiency virus (HIV) treated with the novel capsid HIV inhibitor lenacapavir. J Infect Dis. 2022;226:1985-91. doi: 10.1093/infdis/jiac364

14. Margot NA, Jogiraju V, Pennetzdorfer N, Naik V, VanderVeen LA, Ling J et al. Resistance analyses in heavily treatment-experienced people with HIV treated with the novel HIV capsid inhibitor lenacapavir after 2 years. J Infect Dis. 2025. doi: 10.1093/infdis/jiaf050

15. Watts DH. Teratogenicity risk of antiretroviral therapy in pregnancy. Curr HIV/AIDS Rep. 2007;4:135-40. doi: 10.1007/s11904-007-0020-y

16. Bekker L-G, Moodley D, Harkoo I, Kigozi G, Louw CE, Malahleha M et al. Inclusion of pregnant and lactating people in the PURPOSE 1 study: efficacy, safety, and pharmacokinetics. 13th International AIDS Society Conference on HIV Science; 12–17 July; Kigali, Rwanda, 2025.

17. Erlwanger A, Rocroi I, Kirtley S, Hemelaar J. Perinatal outcomes associated with pre-exposure prophylaxis for HIV prevention during pregnancy: a systematic review and meta-analysis. EClinicalMedicine. 2024;70:102532. doi: 10.1016/j.eclinm.2024.102532

18. Naidoo M, Naidoo KL, Lombard C, Desmond AC, Clark R, Rooney JF et al. In-utero exposure to tenofovir disoproxil fumarate pre-exposure prophylaxis and growth metrics in HIV unexposed breastfed infants in South Africa: a post hoc analysis of the CAP 016 PrEP in pregnancy RCT. Front Pediatr. 2024;12:1447173. doi: 10.3389/fped.2024.1447173

19. Mugwanya KK, Hendrix CW, Mugo NR, Marzinke M, Katabira ET, Ngure K et al. Pre-exposure prophylaxis use by breastfeeding HIV-uninfected women: a prospective short-term study of antiretroviral excretion in breast milk and infant absorption. PLoS Med. 2016;13:e1002132. doi: 10.1371/journal.pmed.1002132

20. Kistan G, Sebitloane M, Lombard C, Godlwana Z, Desmond AC, Clark R et al. Tenofovir disoproxil fumarate/emtricitabine prophylaxis has no effect on bone mineral density and bone mineral content in African breastfeeding women receiving pre-exposure prophylaxis for HIV. J Acquir Immune Defic Syndr. 2024. doi: 10.1097/qai.0000000000003563

21. Reddy K, Naidoo KL, Lombard C, Godlwana Z, Desmond AC, Clark R et al. In-utero exposure to tenofovir-containing pre-exposure prophylaxis and bone mineral content in HIV-unexposed infants in South Africa. J Int AIDS Soc. 2024;27:e26379. doi: 10.1002/jia2.26379

22. Noguchi LM, Owor M, Mgodi NM, Gati Mirembe B, Dadabhai S, Horne E et al. Safety and drug quantification of the dapivirine vaginal ring and oral pre-exposure prophylaxis in breastfeeding mother-infant pairs (MTN-043): a phase 3B, open-label, randomised trial. Lancet HIV. 2025. doi: 10.1016/S2352-3018(24)00306-0

23. Makanani B, Balkus JE, Jiao Y, Noguchi LM, Palanee-Phillips T, Mbilizi Y et al. Pregnancy and infant outcomes among women using the dapivirine vaginal ring in early pregnancy. J Acquir Immune Defic Syndr. 2018;79:566-72. doi: 10.1097/QAI.0000000000001861

24. Baeten JM, Palanee-Phillips T, Mgodi NM, Mayo AJ, Szydlo DW, Ramjee G et al. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. Lancet HIV. 2021;8:e87-e95. doi: 10.1016/S2352-3018(20)30304-0

25. Bunge K, Balkus JE, Fairlie L, Mayo AJ, Nakabiito C, Mgodi N et al. DELIVER: A safety study of a dapivirine vaginal ring and oral PrEP for the prevention of HIV during pregnancy. J Acquir Immune Defic Syndr. 2024;95:65-73. doi: 10.1097/QAI.0000000000003312

26. Delany-Moretlwe S, Hanscom B, Guo X, Nkabiito C, Mandima P, Nahirya PN et al. Evaluation of long-acting cabotegravir safety and pharmacokinetics in pregnant women in eastern and southern Africa: a secondary analysis of HPTN 084. J Int AIDS Soc. 2025;28:e26401. doi: 10.1002/jia2.26401

27. Delany-Moretlwe S VE, Said F. Initial evaluation of injectable cabotegravir (CAB-LA) safety during pregnancy in the HPTN 084 open-label extension. 25th International AIDS Society Conference; Munich, Germany, 22–26 July (https://www.natap.org/2024/IAS/IAS_50.htm, accessed 2 April 2025).

28. Lenacapavir [package insert]. Foster City, CA: Gilead Sciences; 2024. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/.

29. Clement M, Wang Z, Fichtenbaum C, Thomas S, Bazan J, Richardson P et al. Pre-exposure prophylaxis product choice of participants in HPTN 083. 25th International AIDS Society Conference; 22–26 July; Munich, Germany, 2024.

30. Delany-Moretlwe S, Hanscom B, Angira F, Dadabhai S, Gadama D, Mirembe B et al. Initial PrEP product choice: results from the HPTN 084 open-label extension. 12th International AIDS Society Conference on HIV Science; 23–26 July; Brisbane, Australia, 2023.

31. Keddem S, Thatipelli S, Caceres O, Roder N, Momplaisir F, Cronholm P. Barriers and facilitators to long-acting injectable HIV pre-exposure prophylaxis implementation in primary care since its approval in the United States. J Acquir Immune Defic Syndr. 2024;95:370-6. doi: 10.1097/qai.0000000000003370

32. Kerrigan D, Mantsios A, Grant R, Markowitz M, Defechereux P, La Mar M et al. Expanding the menu of HIV prevention options: a qualitative study of experiences with long-acting injectable cabotegravir as PrEP in the context of a phase II trial in the United States. AIDS Behav. 2018;22:3540-9. doi: 10.1007/s10461-017-2017-x

33. Khan T, Liu A, Perlotto S, Nelson KL, Stassek L, Fang J et al. Overcoming challenges integrating injectable PrEP into care: key strategies from the PILLAR study. 5th HIV Research for Prevention Conference; 6-10 October; Lima, Peru, 2024.

34. Meyers K, Rodriguez K, Brill AL, Wu Y, La Mar M, Dunbar D et al. Lessons for patient education around long-acting injectable PrEP: findings from a mixed-method study of phase ii trial participants. AIDS Behav. 2018;22:1209-16. doi: 10.1007/s10461-017-1871-x

35. Psaros C, Landovitz R, Rice W, Kelley C, Oyedele T, Coelho L et al. Understanding participant experiences and preferences in an injectable PrEP trial: a qualitative sub-study of barriers, facilitators and preferences for PrEP use among MSM and TGW. J Int AIDS Soc. 2021;24:30-1.

36. Richmond T, Dunn M, Bernard M, Urbaityte R, Sutton K, Sutherland-Phillips D. Engaging black women on cabotegravir la for PrEP by optimizing novel implementation strategies (EBONI) study: provider perceptions of appropriateness of cabotegravir LA for PrEP for cis-and-trans black women. Open Forum Infect Dis. 2023;10.

37. Tolley EE, Bula A, Chitukuta M, Ndimande-Khoza N, Etima J, Namey E et al. Preferences for oral and injectable PrEP among qualitative sub-study participants in HPTN 084. PLoS One. 2024;19:e0309811. doi: 10.1371/journal.pone.0309811

38. Eger WH, Bazzi AR, Valasek CJ, Vera CF, Harvey-Vera A, Strathdee SA et al. HIV pre-exposure prophylaxis programmatic preferences among people who inject drugs: findings from a discrete choice experiment. Addict Sci Clin Pract. 2024;19:81. doi: 10.1186/s13722-024-00505-2

39. Beckham SW, Sanchez T, Fowler R, Zlotorzynska M, Rai M, Sullivan P et al. Variation in preferences for long-acting injectable pre-exposure prophylaxis among US men who have sex with men: a latent class analysis. AIDS Patient Care STDS. 2023;37:495-503. doi: 10.1089/apc.2023.0109

40. Footer KHA, Lim S, Rael CT, Greene GJ, Carballa-Diéguez A, Giguere R et al. Exploring new and existing PrEP modalities among female sex workers and women who inject drugs in a U.S. city. AIDS Care. 2019;31:1207-13. doi: 10.1080/09540121.2019.1587352

41. Gutierrez J, Minnis A, T. P-P, Ndlovu N, Zulu S, Reddy K et al. Identifying preferred product attributes of long-acting implantable and injectable pre-exposure prophylaxis among men enrolled in the South African male user research on acceptability of implants and injections (SAMURAI) study. 5th HIV Research for Prevention Conference; 6–10 October; Lima, Peru, 2024.

42. Hill-Rorie J, Biello KB, Quint M, Johnson B, Elopre L, Johnson K et al. Weighing the options: which PrEP (pre-exposure prophylaxis) modality attributes influence choice for young gay and bisexual men in the United States? AIDS Behav. 2024;28:2970-8. doi: 10.1007/s10461-024-04384-1

43. Hsu JH, Ku SW, Chen TW, Li CW, Huang P, Wu HJ et al. Preferences for long-acting pre-exposure prophylaxis among gay, bisexual and other men who have sex with men in Taiwan: findings from the 2021 HEART Survey. J Int AIDS Soc. 2023;26:e26163. doi: 10.1002/jia2.26163

44. John SA, Zapata JP, Dang M, Pleuhs B, O'Neil A, Hirshfield S et al. Exploring preferences and decision-making about long-acting injectable HIV pre-exposure prophylaxis (PrEP) among young sexual minority men 17-24 years old. Sci Rep. 2023;13:5116. doi: 10.1038/s41598-023-32014-8

45. Little KM, Hanif H, Anderson SM, Clark MR, Gustafson K, Doncel GF. Preferences for long-acting PrEP products among women and girls: a quantitative survey and discrete choice experiment in Eswatini, Kenya, and South Africa. AIDS Behav. 2024;28:936-50. doi: 10.1007/s10461-023-04202-0

46. Minnis AM, Atujuna M, Browne EN, Ndwayana S, Hartmann M, Sindelo S et al. Preferences for long-acting pre-exposure prophylaxis (PrEP) for HIV prevention among South African youth: results of a discrete choice experiment. J Int AIDS Soc. 2020;23:e25528. doi: 10.1002/jia2.25528

47. Montgomery ET, Atujuna M, Krogstad E, Hartmann M, Ndwayana S, O'Rourke S et al. The invisible product: preferences for sustained-release, long-acting pre-exposure prophylaxis to HIV among South African youth. J Acquir Immune Defic Syndr. 2019;80:542-50. doi: 10.1097/QAI.0000000000001960

48. Odongpiny EL, Nakate V, Onzia A, Bagaya I, Manabe YC, Melendez JH. Willingness to use injectable PrEP among people at risk of HIV accessing services in community pharmacies in Kampala, Uganda. 5th HIV Research for Prevention Conference; 6–10 October; Lima, Peru, 2024.

49. Parsons JT, Rendina HJ, Whitfield TH, Grov C. Familiarity with and preferences for oral and long-acting injectable HIV pre-exposure prophylaxis (PrEP) in a national sample of gay and bisexual men in the U.S. AIDS Behav. 2016;20:1390-9. doi: 10.1007/s10461-016-1370-5

50. Patel RR, Crane JS, López J, Chan PA, Liu AY, Tooba R et al. Pre-exposure prophylaxis for HIV prevention preferences among young adult African American men who have sex with men. PLoS One. 2018;13:e0209484. doi: 10.1371/journal.pone.0209484

51. Rael CT, Lopez-Ríos J, McKenna SA, Das D, Dolezal C, Abascal E et al. Transgender women's barriers, facilitators, and preferences on tailored injection delivery strategies to administer long-acting injectable cabotegravir (CAB-LA) for HIV pre-exposure prophylaxis (PrEP). AIDS Behav. 2021;25:4180-92. doi: 10.1007/s10461-021-03357-y

52. Restar A, Wilson-Barthes MG, Dusic E, Operario D, Galárraga O. Using stated preference methods to design gender-affirming long-acting PrEP programs for transgender and nonbinary adults. Sci Rep. 2024;14:23482. doi: 10.1038/s41598-024-72920-z

53. Rodriguez A, Horvath KJ, Dowshen N, Voss R, Warus J, Jacobs M et al. Awareness and utilization of pre-exposure prophylaxis and HIV prevention services among transgender and non-binary adolescent and young adults. Front Reprod Health. 2023;5:1150370. doi: 10.3389/frph.2023.1150370

54. Schmidt H, Ong J, Chan C, Cassell M, Phanuphak N, Green K. Awareness and willingness to use a 6 monthly long-acting injectable PrEP among gay and other men who have sex with men and transgender women in Asia. 5th HIV Research for Prevention Conference; 6–10 October; Lima, Peru, 2024.

55. Schwartz S, Bula A, J H, Chilongosi R, Hoege D, Nyirenda R. Pre-exposure prophylaxis (PrEP) modality and service delivery preferences among diverse populations in Malawi: results from a discrete choice experiment. 5th HIV Research for Prevention Conference; 6–10 October; Lima, Peru, 2025.

56. Tagliaferri Rael C, Giguere R, Bryndza Tfaily E, Sutton S, Horn E, Schieffer RJ et al. The global impact of diversifying PrEP options: results of an international discrete choice experiment of existing and potential PrEP strategies with gay and bisexual men and physicians. AIDS Res Hum Retroviruses. 2024;40:591-605. doi: 10.1089/AID.2023.0120

57. Torres T, Torres da Silva M, Coutinho C, Hoagloand B, Jalil E, Cardoso S. Long-acting PrEP preference among Brazilian sexual and gender minorities: Key influencing factors. 13th International AIDS Society Conference on HIV Science; 13–17 July; Kigali, Rwanda, 2025.

58. Henderson M, Schmidt HA, Chitembo L, Peralta H, Alaama AS, Johnson C et al. The future of pre-exposure prophylaxis (PrEP) for HIV prevention: a global qualitative consultation on provider perspectives on new products and differentiated service delivery. AIDS Behav. 2023;27:3755-66. doi: 10.1007/s10461-023-04093-1

59. Kamya MR, Balzer LB, Ayieko J, Kabami J, Kakande E, Chamie G et al. Dynamic choice HIV prevention with cabotegravir long-acting injectable in rural Uganda and Kenya: a randomised trial extension. Lancet HIV. 2024;11:e736-e45. doi: 10.1016/s2352-3018(24)00235-2

60. Dourado I, Dezanet L, Magno L, Westin M, Soares F, Massa P et al. PrEP15-19 choices: an implementation study protocol of HIV prevention with oral and long-acting injectable cabotegravir PrEP in real-word settings among sexual and gender minority adolescents in Brazil. BMJ Open. 2025;15:e083146. doi: 10.1136/bmjopen-2023-083146

61. Grinsztejn B, Torres TS, Hoagland B, Jalil EM, Moreira RI, O'Malley G et al. Long-acting injectable cabotegravir for HIV preexposure prophylaxis among sexual and gender minorities: protocol for an implementation study. JMIR Public Health Surveill. 2023;9:e44961. doi: 10.2196/44961

62. Yeo Y-R WK, Takarinda K, Sithole N, Gwavavy E, Khabo BB, et al. Cost-effectiveness of different risk-group targeting across 3 types of PrEP in Zimbabwe. Conference on Retroviruses and Opportunistic Infections; 9–12 March; San Francisco, California, 2025.

63. Braithwaite RS CD, Yeo Y-R, Jeetoo M, Su, J. Allocative efficiency research to meet EHE 2030 goals: long-acting PrEP preliminary results. Unpublished preliminary results. 2025.

64. Consolidated guidelines on differentiated HIV testing services. Geneva: World Health Organization; 2024 (https://www.who.int/publications/i/item/9789240096394, accessed April 1 2025).

65. Delany-Moretlwe S, Hughes JP, Bock P, Ouma SG, Hunidzarira P, Kalonji D et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet. 2022;399:1779-89. doi: 10.1016/s0140-6736(22)00538-4

66. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med. 2021;385:595-608. doi: 10.1056/NEJMoa2101016

67. Luo R, Fong Y, Boeras D, Jani I, Vojnov L. The clinical effect of point-of-care HIV diagnosis in infants: a systematic review and meta-analysis. Lancet. 2022;400:887-95. doi: 10.1016/S0140-6736(22)01492-1

68. Macdonald P. Use of HIV rapid detection tests when initiating long-acting cabotegravir for HIV prevention, within an implementation science project (FASTPrEP). 5th HIV Research for Prevention Conference; 6-10 October; Lima, Peru, 2024.

69. van de Vijver D, van Kampen J, Wongsa A, Janamnuaysook R, Mesplede T, Matrajt L et al. Evaluating HIV testing strategies to reduce drug resistance during CAB-LA rollout in Thailand. A modelling study. 13th International AIDS Society Conference on HIV Science; 13–17 July; Kigali, Rwanda, 2025.

70. Henderson M. Web Annex F. Perspectives and preferences regarding long-acting injectable cabotegravir for HIV prevention among pre-exposure prophylaxis (PrEP) providers: a global survey and in-depth interviews. In: Guidelines on long-acting injectable cabotegravir for HIV prevention. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240054097, accessed 2 April 2025).

71. Glick JL, Nestadt DF, Sanchez T, Li K, Hannah M, Rawlings MK et al. Location preferences for accessing long-acting injectable pre-exposure prophylaxis (LA-PrEP) among men who have sex with men (MSM) currently on daily oral PrEP. J Int Assoc Provid AIDS Care. 2024;23:23259582241293336. doi: 10.1177/23259582241293336

72. Brogan AJ, Davis AE, Mellott CE, Fraysse J, Metzner AA, Oglesby AK. Cost-effectiveness of cabotegravir long-acting for HIV pre-exposure prophylaxis in the United States. Pharmacoeconomics. 2024;42:447-61. doi: 10.1007/s40273-023-01342-y

73. Paranhos J, Castilho M, Klein HE, Miranda C, Perin FS, Passoni P et al. Costs of implementing long-acting injectable cabotegravir as HIV prophylaxis in Brazil. Physis: Revista de Saúde Coletiva. 2023;33:e33021.

74. Cox SN, Wu L, Wittenauer R, Clark S, Roberts DA, Nwogu IB et al. Impact of HIV self-testing for oral pre-exposure prophylaxis scale-up on drug resistance and HIV outcomes in western Kenya: a modelling study. Lancet HIV. 2024;11:e167-e75. doi: 10.1016/S2352-3018(23)00268-0

75. Walensky RP, Jacobsen MM, Bekker LG, Parker RA, Wood R, Resch SC et al. Potential clinical and economic value of long-acting preexposure prophylaxis for South African women at high-risk for HIV infection. 2016;213 (10): 1523-31.

76. Smith J, Bansi-Matharu L, Cambiano V, Dimitrov D, Bershteyn A, van de Vijver D et al. Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study. Lancet HIV. 2023;10:e254-e65. doi: 10.1016/S2352-3018(22)00365-4

77. Jamieson L, Johnson LF, Nichols BE, Delany-Moretlwe S, Hosseinipour MC, Russell C et al. Relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis in South Africa based on the HPTN 083 and HPTN 084 trials: a modelled economic evaluation and threshold analysis. Lancet HIV. 2022;9:e857-e67. doi: 10.1016/S2352-3018(22)00251-X

78. Tieosapjaroen W, Williams, E, Johnson, CC, Baptista Da Silva, C, Barr-DiChiara, M, Siegfried, et al. Balancing accuracy, accessibility, and cost: HIV testing strategies for long-acting injectable PrEP: a systematic review of rapid, laboratory-based immunoassay and nucleic acid testing strategies. [Poster presentation]. Asia Pacific AIDS & Co-Infections Conference; 12–14 June 2025; Tokyo, Japan.

79. Smith J, Bansi-Matharu L, Cambiano V, Dimitrov D, Bershteyn A, van de Vijver D et al. Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study. Lancet HIV. 2023;10:e254-e65. doi: 10.1016/s2352-3018(22)00365-4

80. Kennedy CE, Yeh PT, Johnson C, Baggaley R. Should trained lay providers perform HIV testing? A systematic review to inform World Health Organization guidelines. AIDS Care. 2017;29:1473-9. doi: 10.1080/09540121.2017.1317710

81. 2024 HIV Market Report, Issue 15, December 2024. Boston: Clinton Health Access Initiative; 2024 (https://www.clintonhealthaccess.org/report/2024-hiv-market-report/, accessed 15 June 2025).

82. WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. Module 13. Integrating STI services. Geneva: World Health Organization; 2023 (https://iris.who.int/bitstream/handle/10665/362227/9789240057425-eng.pdf?sequence=1, accessed 2 April 2025).

83. Consolidated guidelines on person-centred HIV strategic information: strengthening routine data for impact. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/360948, accessed 10 June 2025).

84. Antiretrovirals in pregnancy research toolkit [webpage]. Geneva: World Health Organization; 2025 (https://www.who.int/tools/antiretrovirals-in-pregnancy-research-toolkit, accessed 1 April 2025).

85. Gill K, Ndlovu N, Brumskine W, Jaggernath M, Zwane Z, Zhao Y et al. Lenacapavir pharmacokinetics, safety, and efficacy in adolescents and adults in PURPOSE 1. Conference on Retroviruses and Opportunistic Infections; 9–12 March; San Francisco, California, 2025.

86. Lat AK KA, Zhang H, Lin S, Mortensen E, Palaparthy R, Singh R. Impact of subcutaneous administration sites on the clinical pharmacokinetics of lenacapavir, a long-acting HIV capsid inhibitor: does body site matter? Open Forum Infect Dis. doi: 10.1093/ofid/ofad500.1377

87. Subedar H. Implementing PrEP choice: experiences from South Africa - update on PrEP (including long-acting products) South Africa. 5th HIV Research for Prevention Conference; 6–10 October; Lima, Peru, 2024.

88. Interactions with lenacapavir. Liverpool: University of Liverpool; 2024 (https://liverpool-hiv-hep.s3.amazonaws.com/prescribing_resources/pdfs/000/000/276/original/Lenacapavir_2024_Oct.pdf?1730389168 accessed 10 June 2025).

89. Gandhi M, Hill L, Grochowski J, Nelson A, Koss CA, Mayorga-Munoz F et al. Case series of people with HIV on the long-acting combination of lenacapavir and cabotegravir: call for a trial. Open Forum Infect Dis. 2024;11:ofae125. doi: 10.1093/ofid/ofae125

90. Delaugerre C, Antoni G, Mahjoub N, Pialoux G, Cua E, Pasquet A et al. Assessment of HIV screening tests for use in preexposure prophylaxis programs. J Infect Dis. 2017;216:382-6. doi: 10.1093/infdis/jix297

91. Fransen K, de Baetselier I, Rammutla E, Ahmed K, Owino F, Agingu W et al. Performance of serological and molecular tests within acute HIV infection. J Clin Virol. 2017;93:81-4. doi: https://doi.org/10.1016/j.jcv.2017.03.010

92. Livant E, Heaps A, Kelly C, Maharaj R, Samsunder N, Nhlangulela L et al. The fourth generation AlereTM HIV Combo rapid test improves detection of acute infection in MTN-003 (VOICE) samples. J Clin Virol. 2017;94:15–21. doi: https://doi.org/10.1016/j.jcv.2017.06.006

93. Prequalified in vitro diagnostics [webpage]. Geneva: World Health Organization; 2023 (https://extranet.who.int/prequal/vitro-diagnostics/prequalified-vitro-diagnostics, accessed 1 April 2025).

94. Toolkit to optimize HIV testing algorithms [webpage]. Geneva: World Health Organization; 2025 (https://www.who.int/tools/optimizing-hiv-testing-algorithms-toolkit, accessed 14 April 2025).

95. Ong JJ, Coulthard K, Quinn C, Tang MJ, Huynh T, Jamil MS et al. Risk-based screening tools to optimise HIV testing services: a systematic review. Curr HIV/AIDS Rep. 2022;19:154-65. doi: 10.1007/s11904-022-00601-5

96. Oliveira Leite B, Magno L, Soares F, Zeballos D, Dezanet L, Ferreira O et al. Equivalent performance of HIV oral fluid self-testing and rapid testing compared to nucleic acid amplification test in screening adolescents for long-acting injectable cabotegravir in Brazil. 13th International AIDS Society Conference on HIV Science; 13–17 July; Kigali, Rwanda, 2025.

97. Landovitz RJ, Delany-Moretlwe S, Fogel JM, Marzinke MA, Piwowar-Manning E, Richardson P et al. Features of HIV infection in the context of long-acting cabotegravir preexposure prophylaxis. N Engl J Med. 2024;391:1253-6. doi: 10.1056/NEJMc2402088

98. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66:726-35. doi: 10.1016/j.jclinepi.2013.02.003

Annex. Process for developing the guidelines

A1.1 Overview

These guidelines were developed in accordance with procedures established by the WHO Guidelines Review Committee. The recommendations in these guidelines are based on the GRADE approach to reviewing evidence and formulating recommendations. Consistent with previous WHO guidelines, these guidelines employ a public health approach that considers effectiveness, acceptability, feasibility and resource needs across a variety of settings.

All external contributors to the guidelines, including members of the Guideline Development Group (GDG) and the External Review Group (ERG), completed a WHO declaration of interests form in accordance with WHO policy for experts (Web Annex A).

The systematic reviews on lenacapavir for HIV prevention and on HIV testing strategies for injectable long-acting PrEP followed research questions in population, intervention, comparator, outcome (PICO) format.

The systematic review findings and evidence-to-decision-making tables were prepared in accordance with the GRADE process, and they were shared in advance and presented at the GDG meetings, where an independent methodologist facilitated the discussions.

The following sections detail each aspect of the guideline development process.

A1.2 Establishing the groups to develop the guidelines

The guideline development process involved the formation of five main groups to guide and implement the process. Each group played a specific role, as described below. The members of these groups and other contributors are listed in the Acknowledgements section.

1. **WHO Guideline Steering Group (GSG).** The WHO GSG, which is responsible for the overall coordination of the guideline development process, was led by the Testing, Prevention and Population Unit within the WHO Department of Global HIV, Hepatitis and STI Programmes. Participants included staff members from other units in this department as well as from the Department of Regulation and Prequalification and the Department of Sexual and Reproductive Health and Research. This group also included WHO technical staff from all WHO regions.

2. **Guideline Development Group (GDG).** This group formulated the new WHO recommendations, including implementation and service delivery considerations. The group also reviewed and approved the final content of this guidelines document. It consisted of 19 members, with a balanced representation of geographic regions, gender and backgrounds, including academia and research, programme implementation and policy, and community organizations and networks. WHO selected the group members in coordination with the WHO GSG and WHO country and regional offices. The WHO GSG reviewed curricula vitae, declarations of interest and confidentiality agreements. WHO technical staff posted the proposed membership list for public review and comment and then finalized it.

3. **External Review Group (ERG).** ERG members were responsible for peer review of these guidelines. WHO technical staff selected this group in consultation with the WHO GSG to assure geographic and gender balance. It comprised 20 peer reviewers from academia, policy and research, programme implementation and community organizations, including networks of key and vulnerable populations.

4. **External guideline contributors, led by an independent methodologist**. With oversight by the guideline methodologist and with input from members of the WHO GSG and GDG, an independent team of experts conducted systematic reviews and mathematical modelling. Additionally, all review teams compiled and summarized evidence on values and preferences, feasibility and cost–effectiveness.

5. **External partners and observers**. Representatives of the Children's Investment Fund Foundation, the Gates Foundation; the Global Fund to Fight HIV, Tuberculosis and Malaria; the Joint United Nations Programme on HIV/AIDS (UNAIDS); the National Department of Health of South Africa and Unitaid attended the GDG meeting as observers. These organizations are potential donors and implementers of the proposed guidelines and have a long history of collaboration with the WHO Department of Global HIV, Hepatitis and STI Programmes. The Acknowledgements section lists the names of the observers who attended the GDG meeting.

All members of the GDG, non-WHO staff participating in meetings or guideline development and external peer reviewers submitted declarations of interest and confidentiality statements to the WHO secretariat. The WHO secretariat and the GSG reviewed all declarations and found no conflicts of interest sufficient to preclude any GDG member from participating fully in the development of the guidelines. Web Annex A provides a full compilation and a summary of these declarations of interests.

A1.3 Scope of the guidelines

To assess the need for these guidelines, WHO convened expert consultations and scoping meetings in August and September 2024. Based on the outcomes of these meetings, the GSG developed the scope for these guidelines on lenacapavir and HIV testing for long-acting PrEP between October and November 2024. The GSG also provided support with peer review of documents.

A1.4 Development of the guidelines

To support the development of these guidelines, WHO commissioned systematic reviews of available evidence on:

- lenacapavir for HIV prevention
- HIV testing for long-acting PrEP.

WHO also commissioned mathematical modelling to further assess the effects of HIVST-supported PrEP delivery.

The GSG, along with WHO technical staff, developed the PICO questions. The GDG then finalized these questions and defined the outcomes and stratifications of interest. GDG members prioritized outcomes using an electronic survey to rank the importance of each outcome on the GRADE rating scale of 1–9 (0–3: not important; 4–6: important; 7–9: critical). Once the PICO question and priority outcomes were agreed, external researchers, supported by the WHO team, conducted the systematic reviews.

Each systematic review team developed a protocol to review the relevant scientific evidence. The independent methodologist assessed and reviewed the protocol, as did the GDG, the WHO GSG and the WHO secretariat. In conjunction with the WHO technical team, review teams developed search strategies.

The methodologist advised the review teams on analytical decisions, risk of bias and quality appraisal, as well as the synthesis and grading of evidence. Each review team also summarized values and preferences and resource use, using information identified as an additional component of the systematic review. The web annexes present details on each systematic review.

WHO subsequently convened a virtual technical consultation (January 2025) with the GDG. The independent methodologist facilitated the GDG discussion and formulation of the recommendations. Based on the evidence reviewed and presented at this consultation, the GDG made new recommendations regarding lenacapavir for HIV prevention and HIV testing for long-acting injectable PrEP. External peer review was then completed in March 2025.

A1.5 Additional evidence

All recommendations were developed according to the WHO-endorsed GRADE evidence-to-decision-making process, which addresses the following questions:

- Is the problem a priority?
- How substantial are the benefits?
- How substantial are the harms?
- What is the overall certainty of evidence?
- What is the balance between benefits and harms?
- Is there important variability or uncertainty in patient preferences regarding the key outcomes?
- How large are the resource requirements (costs)?
- Is the intervention cost–effective?
- What would be the impact on health equity?
- Is the intervention acceptable to all stakeholders?
- Is implementation of the intervention feasible?

Under the WHO guideline development process, the GDG formulates the recommendations guided by the certainty of available evidence. The GRADE approach specifies four levels of certainty of evidence, as described in Table A1. Other factors – values and preferences, costs and feasibility, acceptability, and equity and human rights – are taken into consideration when determining the direction and strength of the recommendation *(98)*. These factors are not weighted, and, when formulating recommendations, the GDG is asked to consider these factors together. The strength of the recommendation is more likely to be strong when certainty is high and other factors are supportive. When certainty is low, or there is wide variability or uncertainty in values and preferences or acceptability, for example, a conditional recommendation is more appropriate.

Table A1. Interpretation of the four GRADE levels of evidence

Certainty of evidence	Rationale
High	We are very confident that the true effect lies close to the estimate of effect.
Moderate	We are moderately confident in the estimate of effect. The true effect is likely to be close to the estimate of effect but could be substantially different.
Low	Our confidence in the estimate of effect is limited. The true effect may be substantially different from the estimate of effect.
Very low	We have very little confidence in the estimate of effect. Any estimate of effect is very uncertain.

A1.6 Developing the recommendations

The GDG meeting included a presentation of final systematic review findings and supportive evidence. The independent methodologist facilitated the meeting. At the beginning of the meeting, the GDG agreed that the goal for decision-making would be to reach consensus, defined as agreement of the group, but that, if consensus could not be reached, a vote would be taken. Consensus was reached for all decisions, and no voting was required.

During the meeting the GDG discussed the findings of the systematic reviews and supplemental evidence, such as mathematical modelling. Following this discussion, the GDG reached consensus on the direction, strength and wording of the recommendation.

WHO then drafted the full guidelines and circulated them electronically to the GDG, the GSG and the ERG for comments and feedback. All responses were considered and addressed as appropriate in the final draft.

This targeted update to the guidelines is available on the WHO website (https://www.who.int/publications/i/item/9789240111608) and disseminated to member states. The final guidelines will also be published and disseminated in July 2025.

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