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REVIEW

The Current and Future Impact of WHO Guidance on Global HIV Pre-Exposure Prophylaxis Programs: A Narrative Review

Fady Mishriky[1], Philip A Chan[2–4]

[1]Faculty of Medicine, Cairo University, Cairo, Egypt; [2]Department of Medicine, Brown University, Providence, RI, USA; [3]Rhode Island Public Health Institute, Providence, RI, USA; [4]Rhode Island Department of Health, Providence, RI, USA

Correspondence: Philip A Chan, Department of Medicine, Brown University, Providence, RI, USA, Tel +1401793-4859, Email Philip_Chan@brown.edu

Abstract: Pre-exposure prophylaxis (PrEP) is a cornerstone of HIV prevention and includes a daily oral pill, intermittent dosing, a vaginal ring, and long-acting injectables. This narrative review is based on recent literature through November 1, 2025 and the World Health Organization (WHO) PrEP guidance from 2012 to 2025. We review how WHO has shaped global PrEP policy and service delivery, and implementation priorities in low- and middle-income countries (LMICs) with a focus on long-acting injectables. We summarize the shift toward differentiated service delivery and the evolution of HIV self-testing to support PrEP initiation, retention, and adherence. Persistent gaps in PrEP care include access to healthcare, stigma, limited awareness, costs, transportation, and medication burden. The long-acting era of PrEP is exciting and offers significant opportunity for HIV prevention. Current long-acting injectable PrEP formulations are still limited in most LMICs but recent progress on access and implementation is encouraging. Other long-acting formulations are in development. Priorities for PrEP implementation should include securing funding for and improving access to PrEP medications including long-acting formulations; cross-sector partnerships among governments, community-based organizations, pharmacies, and medical providers; and pro-access licensing, regional manufacturing and transparent pricing to ensure affordability in LMICs. Implementing these priorities will facilitate population-level HIV prevention and accelerate progress toward reducing HIV incidence.

Keywords: pre-exposure prophylaxis, WHO, long-acting PrEP, differentiated service delivery, HIV self-testing, low- and middle-income countries

Introduction

As of 2024, an estimated 40.8 million people across the world were living with human immunodeficiency virus (HIV). While significant progress has been made toward addressing the HIV epidemic, 1.3 million people were still newly infected in 2024, highlighting the persistent challenges faced globally.[1] Pre-exposure prophylaxis (PrEP) first demonstrated significant efficacy in preventing HIV infection in 2010.[2,3] PrEP is a highly effective prevention tool by which HIV-negative individuals utilize an antiretroviral medication to significantly lower their chances of acquiring HIV.[2] The first PrEP formulation was the fixed dosed combination of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) which is taken orally once a day. Subsequent studies demonstrated efficacy with TDF/FTC as intermittent or event-driven PrEP[4] as well as an updated formulation with tenofovir alafenamide and emtricitabine (TAF/FTC).[5] More recently, long-acting injectable cabotegravir[6] and lenacapavir[7,8] have demonstrated efficacy as PrEP. PrEP is a significant scientific advancement and has the potential to address HIV worldwide.

The World Health Organization (WHO) made their first recommendations for the use of PrEP in key populations at risk of acquiring HIV in 2012.[9] PrEP uptake across the world has been increasing over time.[10] The WHO plays a crucial role in steering global health policy through its ability to develop international recommendations while stewarding countries towards a shared public health objective.[11] We review how WHO guidance has shaped the implementation of HIV prevention and PrEP worldwide, examine the key barriers to equitable PrEP access and explore the future of HIV prevention in light of newly-emerging long-acting formulations.

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Uptake of HIV Pre-Exposure Prophylaxis Across the World

At a global level, access to PrEP for HIV prevention has expanded rapidly but remains below targets. PrEP is a key component of public health approaches to address HIV and reduce HIV incidence. According to the AIDS Vaccine Advocacy Coalition (AVAC) Global PrEP Tracker, cumulative oral PrEP initiations increased from approximately 100,000 people in 2016 to nearly two million by 2021 and around eight million by late 2024.[12] The WHO's Global State of PrEP report, based on UNAIDS monitoring data, estimates that more than 3.5 million people received PrEP at least once in 2023 with over 75% of them in the WHO African Region. Although encouraging, this was still below the target of 10 million PrEP users by 2025.[10] The role of the WHO in guiding PrEP implementation efforts across the world is critical. The WHO is the main multilateral agency issuing globally endorsed clinical guidance on PrEP, and by 2023, 94% of countries had already incorporated WHO PrEP recommendations into national guidelines. This narrative review focuses on WHO guidance and its implementation in low- and middle-income countries.

Narrative Review: Approach and Methodology

The review was based on literature indexed in PubMed and online including clinical guideless and WHO reports published through November 2025. Various search terms were used including combinations of the words: HIV, prevention, PrEP, pre-exposure prophylaxis, WHO, World Health Organization, long-acting injectable, low-income country, and middle-income country. The search strategy used an iterative process with different permutations of search terms. Reports and publications were limited to English language.

The Global Impact of WHO Guidance on PrEP

A primary role of the WHO includes setting evidence-based standards and supporting their uptake in countries, which gives the WHO a central role in shaping policy in many countries.[13] PrEP access and availability continue to be substantially lower in low- and middle-income countries (LMICs) compared to high-income settings.[14] The importance of the recommendations provided by the WHO is especially influential in many LMICs due to limited domestic HIV policy development. Therefore, many country public health entities rely on WHO recommendations when developing their own national policies.[15] This was evident for PrEP when following the WHO's pivotal recommendation in 2015.[16] At least thirty-five countries had formal PrEP policies introduced and five more had policies pending by June of 2018 following WHO recommendations in 2015 which included both high-income and low- and middle-income settings.[16,17] This number grew to 120 countries adopting the WHO PrEP Guidelines into their national policies by the end of 2019.[18] With these policy recommendations, the number of global PrEP users grew by approximately 69% from 2018 to 2019 alone.

Between 2010 and 2024, global HIV incidence dropped by about 40% and acquired immunodeficiency syndrome (AIDS)-related mortality declined to an estimated 630,000 deaths in 2024.[1] This decline in incidence and mortality reflect the combined impact of antiretroviral therapy as a form of treatment as prevention, together with expanded prevention tools such as PrEP and other WHO-endorsed combination prevention approaches.[16,19] Over a similar timeframe, HIV/AIDS dropped markedly as a cause of death worldwide, moving from the 7th leading cause of death globally in 2000 down to the 21st in 2021 while still remaining in the top 10 causes for low-income countries.[20] On a population level, multiple studies demonstrated the impact of PrEP implementation. A study on Scotland's national PrEP program showed new HIV diagnoses falling by 19.7% and recently acquired infections decreasing by 35.6%.[21] In New South Wales 12 months after high-coverage PrEP implementation, HIV diagnoses declined by 25% and recently acquired infections fell by 31.5%.[22]

While WHO guidance is an important step for PrEP scale-up, it does not on its own ensure rapid or equitable implementation in all settings. A scoping review of WHO guideline uptake found that many member states formally endorse WHO recommendations yet face challenges in financing, technical capacity, and monitoring systems, resulting in delayed or partial implementation at country level.[15] For PrEP specifically, global analyses show that adoption of WHO-aligned PrEP guidelines has not always translated into broad service coverage, with many countries offering PrEP only in a limited number of settings or through pilot programs.[18] For long-acting PrEP, WHO recommendations will most likely be implemented within health systems that still face gaps in resources and procurement difficulties, contributing to slower and uneven rollout in many LMICs.[23]

The Evolution of WHO Guidelines on PrEP

The WHO's recommendations for PrEP have evolved over time as more data has become available, transitioning from more cautious and targeted recommendations to a comprehensive public health strategy that encompasses multiple PrEP methods. The WHO made its initial yet conditional recommendation on PrEP in 2012 as a result of the landmark iPrEx trial, which demonstrated the efficacy of daily oral TDF/FTC among men who have sex with men (MSM).[2,9] In its first iteration of recommendations, the WHO recommended daily oral PrEP as a prevention option but limited its use in countries with higher HIV incidence between serodiscordant couples, MSM and transgender women while emphasizing the need for more demonstration projects and studies. In 2013, the WHO published a structured framework for PrEP demonstration projects to standardize the process for countries to ensure evidence for future scale-up efforts.[24] This evidence-gathering phase was further solidified in the 2014 consolidated guidelines, which reiterated PrEP as a valuable prevention tool specifically for vulnerable populations, which was expanded to include incarcerated individuals, sex workers and people who inject drugs.[25]

In 2015, the WHO expanded their recommendations by moving away from focusing only on vulnerable populations to include daily oral PrEP as the prevention of choice for anyone at substantial risk of acquiring HIV, defined as populations with a clear incidence threshold of greater than three HIV infections per 100 person-years.[16] Additionally, this marked a pivotal shift in the WHO's stance on PrEP as a method of prevention as they transitioned from conditional to strong recommendations for oral PrEP. The 2016 guidelines provided the first comprehensive roadmap on the use of PrEP as prevention.[26] Recognizing the need to address specific populations, the WHO released a technical brief in 2017 confirming the safety of offering oral TDF/FTC to pregnant and breastfeeding individuals that remain at substantial risk of acquiring HIV.[27]

During this period, WHO also moved from developing clinical recommendations to implementation support for PrEP programs. The WHO developed a comprehensive PrEP implementation tool to guide countries from introduction to scale-up in 2017.[28] This 28-page practical toolkit was designed to help countries move from policy to delivery by providing frontline healthcare staff clear, actionable steps to start PrEP and monitor ongoing use as part of routine clinical services. The first module of the toolkit described the eligibility criteria and baseline assessments for daily oral TDF/FTC as well as follow-up and safety monitoring. This allowed programs to standardize clinical decision-making during rollout, monitoring, and evaluation. The eligibility included being HIV negative, no acute HIV symptoms present, and being at substantial risk of acquiring HIV without any drug allergies to TDF/FTC or renal impairment which was defined as creatinine clearance (CrCl) <60 mL/min. Baseline assessment recommendations covered both creatinine and HIV testing on the same day as initiation with routine follow-up testing for HIV every three months and creatinine monitoring every six months with more frequent testing if comorbid risks were present. The initial module also provided concrete counselling for starting and stopping PrEP that recommend utilizing an additional method of prevention for the first seven days of starting PrEP, and stopping 28 days after the last potential exposure with special advice on post-exposure prophylaxis (PEP) followed by a no-gap transition to PrEP in recent exposures while outlining options if acute HIV was suspected. The module further detailed special situations when PrEP could be offered or continued such as in pregnancy and breastfeeding when the risk still remains significant. The module also addresses hepatitis B virus (HBV) and hepatitis C virus (HCV) within the context of HIV prevention.

Responding to evolving evidence and the need for more flexibility to address barriers to adherence, the WHO updated its guidance in 2019 to include intermittent or event-driven PrEP as an alternative to daily dosing in MSM. These recommendations were expanded to include transgender women and people assigned male at birth later in 2022.[29,30] In 2021, the WHO made a conditional recommendation for the dapivirine vaginal ring, providing the first long-acting form of HIV prevention.[31] The dapivirine ring is self-inserted vaginally and worn continuously for 28 days, after which it should be replaced with a new ring.[32] In a study among 1959 cisgender women in Sub-Saharan Africa, the dapivirine ring lowered the incidence of HIV by 31% compared to placebo.[33] Later that year, new consolidated guidelines were released combining all post-2016 recommendations together into a single updated document.[19]

The momentum for long-acting PrEP options accelerated in 2022 with the WHO's recommendation for the first long-acting injectable medication (ie, cabotegravir) as an additional choice for people deemed at substantial risk for HIV.[34] Long-acting injectable cabotegravir is administered as a loading dose at baseline and one month, and then as a subsequent

intramuscular injection every two months thereafter. The efficacy of long-acting cabotegravir was demonstrated in two Phase 3 trials conducted on cisgender MSM, transgender women and cisgender women.[6,35] Long-acting injectable cabotegravir had a 66% reduction in incidence of HIV compared to daily oral TDF/FTC in MSM and transgender women and a 88% reduction among cisgender women, highlighting the advantage of this approach on adherence.[6,35] Importantly, this expanded options for people who prefer discreet, long-acting methods, and directly addressed adherence and stigma barriers observed with oral PrEP. In addition, no renal function tests are needed for people receiving cabotegravir which simplifies monitoring.[34]

The recommendation for long-acting injectable cabotegravir was followed by the release of simplified guidelines for PrEP administration with the most up-to-date provider handbook being released in 2024 detailing clinical guidelines for all PrEP forms approved at that time including those not covered in the previous 2017 version.[30,32] Finally, the WHO most recently recommended the twice-yearly injectable lenacapavir citing the safety and efficacy showcased in the two most recent PURPOSE trials, further expanding the prevention toolkit and making long-acting injectable PrEP programs more feasible to implement.[7,8,36] Long-acting injectable lenacapavir is a significant advancement in HIV prevention and is administered every six months. Additionally, a Phase 1 study indicates that yearly dosing of lenacapavir may also be feasible.[37] A tabular summary of forms of PrEP currently recommended by the WHO is shown in Table 1 and the key changes and recommendations done by WHO are summarized in Table 2.

Barriers to PrEP Uptake in Low- and Middle-Income Countries

According to UNAIDs, access to PrEP in LMICs is still lower than 10% of the projected 2025 target.[38] Structural barriers in many LMICs limit sustained availability and program scale-up. Health-system and supply-chain requirements such as procurement, inventory reporting, and clinic logistics are the most recurrent bottle-necks, with reports of drug stockouts and space or workflow complaints impeding delivery in some settings in Africa.[23,39,40] Financing remains a key hurdle. In Kenya's first year of public sector scale-up across clinics, 69% of total costs were medications, with training and

Table 1 "Summary of WHO PrEP Recommendations by Formulation, Dosing Schedule, and Target Population"

PrEP Type	Dosing	Frequency	Population	WHO Recommendation Timeline	Reference
Daily Oral PrEP (TDF-based)	One tablet of TDF/FTC or TDF/lamivudine	Daily	Anyone at substantial risk	2012 (Conditional) 2015 (Strong)	[9,16,19]
Event-Driven Oral PrEP (ED-PrEP or "2+1+1")	Two tablets 2–24 hours before sex, then one tablet daily until two days after the last sexual exposure	As needed	MSM and transgender women	2019	[29,30]
Dapivirine Vaginal Ring	One 25 mg dapivirine-impregnated silicone ring inserted into the vagina	Worn continuously for one month and then replaced with a new ring	Cisgender women	2021	[31,33]
Long-Acting Injectable Cabotegravir	600 mg gluteal intramuscular injection	An initial injection, a second injection one month later, and then one injection every two months thereafter	Anyone at substantial risk	2022	[6,34,35]
Long-Acting InjectableLenacapavir	Initial 927 mg subcutaneous injection with an oral loading dose, followed by maintenance injections of 927 mg	Twice a year (every 6 months)	Anyone at substantial risk	2025	[7,8,36]

Table 2 "Summary of the Evolution of WHO Recommendations on HIV PrEP"

Year (Month)	Key Changes	Populations Affected/Addressed	References
2012	First conditional recommendation for daily oral TDF/FTC PrEP	Serodiscordant couples, men who have sex with men, transgender women	[2]
2013	Framework published to guide national PrEP demonstration projects	Clinicians	[24]
2014	PrEP is incorporated into consolidated HIV guidelines for key vulnerable populations	Sex workers, people who inject drugs, incarcerated individuals	[25]
2015	PrEP broadened to anyone at substantial risk of HIV; daily oral TDF-based PrEP given a strong recommendation	All people at substantial risk of HIV (>3 infections per 100 person-years)	[16]
2016	First comprehensive roadmap for the use of PrEP for HIV prevention	Clinicians	[26]
2017 (July)	Support of the use of daily oral TDF/FTC PrEP in pregnant and breastfeeding individuals at substantial risk of HIV	Pregnant and breastfeeding individuals at substantial risk	[27]
2017 (July)	Release of the first oral PrEP implementation tool	Clinicians	[28]
2019	Updated recommendations to include event-driven (2+1+1) oral PrEP as an alternative to daily dosing	Men who have sex with men	[29]
2021 (January)	Conditional recommendation for the dapivirine vaginal ring as an additional PrEP option for cisgender women	Cisgender women at substantial risk of HIV	[31]
2021 (July)	Updated consolidated HIV guidelines integrating oral PrEP and the dapivirine ring into a single document	Clinicians	[19]
2022 (July)	Recommendation that the 2+1+1 oral PrEP regimen can also be used by transgender women and people assigned male at birth	Transgender women and people assigned male at birth	[30]
2022 (July)	Recommendation of long-acting injectable cabotegravir as an additional PrEP option	Men who have sex with men, transgender women, cisgender women	[34]
2024	Updated provider module combining clinical guidance for oral PrEP, dapivirine ring, and CAB-LA in one handbook	Clinicians	[32]
2025	Recommendation of twice-yearly injectable lenacapavir as a new long-acting PrEP option	People at substantial risk of HIV	[36]

administrative supplies comprising 26% of recurring non-drug costs.[41] Costs include not only medications but staff, laboratory testing, and other infrastructure for successful PrEP delivery.

On an individual-level, the PrEP care continuum can help guide implementation efforts and describe the steps needed to achieve successful PrEP outcomes.[42] The steps of the PrEP care continuum include identifying individuals at highest risk, increasing HIV-risk awareness, enhancing PrEP awareness, facilitating access, linking to PrEP care, prescribing, initiating PrEP, adhering to PrEP and retaining individuals in PrEP care. Disengagement from PrEP can occur at any step and adherence and retention in care are frequently the most faced bottlenecks as the final two stages. This stage-based strategy helps clarify where care shortcomings arise and helps prioritize targeted individual-level interventions in LMICs programs.

Multiple individual-level barriers can hinder the initiation of PrEP among key populations at risk including stigma, lack of awareness, limited availability of services, travel costs and distance to service-providing clinics.[43] These barriers may vary from country to country and among specific populations. Across LMICs, especially in Sub-Saharan Africa, a systematic review identified low PrEP awareness, perceived low HIV risk, PrEP-related stigma, fear of side effects, out-of-pocket costs, and lack of user-friendly services as recurrent barriers to initiating PrEP.[44] Among sex workers in Sub-Saharan Africa as well, a 2024 systematic review found that uptake and adherence varied depending on the delivery

model, concluding that community-based approaches might mitigate continuity barriers and highlighting how uptake challenges are context-dependant.[45] A global systematic review of trials and implementation studies further concludes that non-adherence is commonly driven by stigma, low-risk perception, side effects during initiation, and regimen burden, compounded by socioeconomic and policy constraints that are particularly apparent in LMIC settings.[46] A 2024 meta-analysis also found that system-level events could impede uptake and resistance as was the case with 21% of PrEP users reporting disruption in their access to PrEP during the COVID-19 pandemic, citing social barriers, financial constraints, and coverage issues as the major culprits.[47] Collectively, these data also point to system-level barriers such as providers with limited clinical training or comfort with PrEP and fragmented service delivery.[45,46]

Among pregnant women and women in the postpartum period, a meta-analysis highlighted PrEP barriers related to medication side-effects, stigma, lack of access to resources and knowledge gaps as some of the key impediments to uptake.[48] A quantitative cohort in South Africa showed early side-effects such nausea, vomiting and dizziness were commonly reported especially in the first and second trimester, and were associated with decreased adherence compared to unaffected individuals.[49] Another study conducted on the same group in Kenyan Maternal and Child Health (MCH) clinics concluded that side-effects, along with low perceived risk, were among the leading causes for early discontinuation of PrEP.[50] At the same time, a 2024 systematic review and meta-analysis found no increase in perinatal outcomes with antenatal exposure to PrEP while noting the lack of pregnancy data for cabotegravir, highlighting knowledge gaps for long acting injectables.[51]

Among MSM, Zhao et al noted that lack of supportive policy, stigma, limited health system investment and challenges to accessibility accounted for disparities in PrEP uptake among LMICs compared to high-income countries (HICs).[52] A global systematic review and meta-analysis found that even though PrEP awareness has increased over the years, it remained low among key populations. Proposed solutions included investments in PrEP education and HIV risk perception to improve engagement.[53] Adherence to PrEP is also a challenge. A global meta-analysis identified low perceived risk, side-effects such as long-term toxicity concerns, pill-burden, selection of other prevention methods, and relocation as the most commonly reported reasons for PrEP discontinuation.[54] For MSM specifically, another meta-analysis found poorer adherence with the presence of depressive symptoms and substance use while reporting improved adherence with a higher educational level.[54] Implementation reviews further highlight structural barriers for MSM such as lack of transportation, lower income, lack of insurance, and not having a primary care provider as the main causes that impede both PrEP uptake and persistence.[55]

Across LMICs, PrEP adherence has remained a major challenge despite the increase in uptake and availability.[56,57] This is particularly important as PrEP efficacy is tightly coupled to adherence, underscoring why even minor lapses can translate to reduced protection in real-world settings.[58] A meta-analysis focused on adolescents and young adults, a group that is heavily represented in African cohorts, found only 64% met study-defined adherence thresholds overall, with disproportionately lower adherence in young cisgender women (46%) than young MSM (65%), pointing to gendered barriers such as stigma and risk perception.[59] Among female sex workers in sub-Saharan Africa, a 2024 systematic review concluded that the delivery models themselves shaped adherence.[45] For MSM, a recent meta-analysis quantified suboptimal adherence and found that it was significantly more common in the Global South (41%) than it is in the Global North (29%), noting alcohol use and depressive symptoms being the most consistently linked to lack of adherence as well as factors that interact with structural barriers like stigma and limited mental-health services in LMICs.[57]

WHO Recommendations and Innovations to Reduce Barriers to PrEP Care

Specific WHO policies and recommendations have tried to address many implementation barriers and highlight successful models in LMICs demonstrating PrEP policies in action. Many studies have attempted to correlate the effect of WHO guidance or national frameworks co-developed with the WHO on PrEP outcomes. For example, PrEP implementation efforts at Kenyan HIV clinics where they operationalized WHO's PrEP recommendations found a 24x increase in PrEP initiation with high adherence and a low HIV incidence rate.[60] WHO's 2022 technical brief reframed PrEP as a person-centered service and recommended differentiated service delivery (DSD) models that best serve the people receiving PrEP. The WHO Brief recommended community initiation, task-sharing, streamlined follow-up, and multi-month dispensing to improve uptake, adherence and persistence.[30] The updated 2024 Provider Module of the PrEP Implementation Tool builds on that and operationalizes these steps for oral PrEP, the dapivirine ring, and long-acting cabotegravir.[32] In parallel, WHO's differentiated HIV testing guideline was released in the same year and integrates HIV

self-testing (HIVST) into PrEP for either initiation, re-start, and continuation, with recommended testing every 2–3 months depending on the medication.[61]

These new HIV testing recommendations were particularly important for LMICs with limited resources. Randomized implementation trials done in Sub-Saharan Africa show that HIVST integrated with PrEP care is efficient.[62,63] Studies have demonstrated that semiannual dispensing of PrEP with interim HIVST maintained non-inferior 12-month outcomes in studied cohorts and reduced visit burden compared to quarterly visits. A 2024 network meta-analysis found that a combined strategy centered on HIVST plus adherence counseling significantly improved adherence compared to standard care. This reinforces the WHO's emphasis on DSD models rather than visit-intensive models.[64] Consistent with the WHO's push to move services closer to people who use them, task-sharing and decentralization have also moved from guidance to implementation, and demonstrated efficacy in real-world settings. A nurse-facilitated, pharmacy-based model for adolescent girls and young women (AGYW) conducted in Kenya achieved high PrEP initiation and planned continuation with participants citing convenience, privacy and reduced stigma as the most common reasons why.[65] Another regional scoping review in Sub-Saharan Africa documented how mobile and community-based models improved linkage from testing to PrEP uptake in both men and AGYW.[66]

The Future of WHO Guidance

With various options now available for PrEP and with ongoing research, the future looks promising for HIV prevention. Looking forward, the WHO's next refinements are likely to consolidate long-acting guidance and specifically for lenacapavir and other long-acting formulations that may be available in the future. Studies are still needed to harmonize testing methods and product-specific testing windows for both lenacapavir and cabotegravir while preserving the same person-centered, DSD model that was codified in the 2024–2025 guidance.[36] The pharmaceutical company responsible for lenacapavir (ie, Gilead Sciences) has reported an equitable-access plan to help provide lenacapavir in high-incidence at-cost, as well as facilitate partnerships to enable near-simultaneous rollout across both LMICs and HICs.[67] As a key component of its equitable access strategy, Gilead Sciences has established royalty-free, non-exclusive voluntary licensing agreements with six pharmaceutical companies. These licenses are designed to facilitate the production of quality-assured generic lenacapavir for 120 resource-limited countries, forming a critical part of the company's plan to ensure a sustainable global supply. On September 24, 2025, two Indian generic manufacturers officially announced agreements, backed by Unitaid, CHAI, and Wits RHI, to supply twice-yearly lenacapavir for PrEP at $40 USD per person-year beginning in 2027.[68] Broader long-acting access will also depend on generic pathways for cabotegravir. The medicines patent pool's voluntary license with ViiV (the maker of cabotegravir) will be a key enabler for cabotegravir scale-up in eligible countries, helping to address earlier constraints in supply for injectable PrEP.[69,70]

Looking ahead, several innovations could influence future WHO guidance and recommendations. Phase 1 study data supports higher-concentration suspensions of long-acting injectable cabotegravir intended for once yearly dosing and self-administration, promising results that this could be a possibility in the future.[71] Another phase 1 trial found islatravir subdermal implants showed promising pharmacokinetics and tolerability for sustained delivery, offering another potential approach to administering PrEP.[72] A Phase 2 trial of the same medication, islatravir, found that once monthly oral dosing was safe, tolerable and achieved potentially effective levels of protection.[73] Moreover, multipurpose vaginal rings that combine both dapivirine and levonorgestrel show early acceptability and are advancing with favorable safety and tolerability profile.[74,75]

Future WHO updates and guidelines will need to revolve around the current and future formulations of long-acting injectable PrEP. This is especially true given the WHO lenacapavir guidance in 2025 explicitly flags research gaps and implementation considerations that require further real-world research to resolve. This is an example how future research can help guide WHO recommendations with increased focus on lenacapavir and cabotegravir.[36]

Recommendations

Countries should align national policies with WHO guidance if possible and scale person-centered, differentiated service delivery as resources allow. This includes task sharing for nurses and trained providers, multi-month dispensing, and routine use of HIV self-testing to support initiation and adherence. Programs should deliver PrEP through pharmacy-based and community-led delivery, mobile and outreach models, and integration within primary care. As long-acting

forms of PrEP expand, testing algorithms and usage guidelines should be in line with the WHO's most up-to-date guidelines. To facilitate PrEP implementation, governments should prioritize sustainable financing for PrEP and its delivery. This requires partnerships and collaborations across both the private and public sector among ministries of health, organizations, pharmacies, and providers to expand reach and reduce access barriers. Most importantly, industry partners should commit to strategies that would increase access for LMICs such as voluntary licensing, regional manufacturing, at-cost pricing and streamlined product delivery. Finally, we recognize the need for future studies to assess continued safety, efficacy and drug-resistance while fine-tuning product specific retesting timeline.

Conclusion

In summary, WHO guidance and recommendations have evolved as PrEP has transformed from a single medication to multiple formulations and dosing approaches. Current WHO recommendations include oral TDF-based PrEP, event-driven dosing for MSM and transgender women, the dapivirine ring, and long-acting injectable cabotegravir and lenacapavir, with implementation guidelines that make these policies actionable in both clinical and community settings. Short-term priorities are to solidify access to longer-acting formulation, update the testing algorithms for long-acting PrEP, sustain resistance surveillance during scale-up, and to invest in DSD models that support adherence, especially in LMICs where service access remains uneven and where decentralized delivery can help close the gaps. Ensuring that WHO guidance is put into practice through person-centered, WHO-aligned PrEP delivery, including differentiated service models and equitable access to long-acting injectables especially in LMICs, will be essential for closing current prevention gaps and sustaining progress in global HIV control.

Abbreviations

HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TAF/FTC, tenofovir alafenamide and emtricitabine; WHO, World Health Organization; AVAC, AIDS Vaccine Advocacy Coalition; MSM, men who have sex with men; CrCl, creatinine clearance; PEP, post-exposure prophylaxis; HBV, hepatitis B virus; HCV, hepatitis C virus; LMICs, low- and middle-income countries; AIDS, acquired immunodeficiency syndrome; MCH, maternal and child health; CAB-LA, cabotegravir; HICs, high-income countries; DSD, differentiated service delivery; HIVST, HIV self-testing; AGYW, adolescent girls and young women.

Disclosure

The authors report no conflicts of interest in this work.

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