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ISSUES IN PUBLIC HEALTH

Lenacapavir, pre-exposure prophylaxis demand and the efficacy-effectiveness gap in South African HIV prevention

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South Africa has launched a limited, phased roll-out of twice-yearly injectable lenacapavir pre-exposure prophylaxis (PrEP) for HIV prevention. Initially supported by donor funding, the medication is positioned as a turning point in the national HIV response. The launch reflects a recurring pattern in biomedical HIV prevention where high efficacy in randomised trials is quickly translated into expectations of population-level impact, before real-world effectiveness, sustained demand, affordability and long-term health-system capacity are demonstrated. While lenacapavir may address one limitation of oral PrEP by eliminating daily pill-taking, previous PrEP experience shows that uptake and continuation are shaped by stigma, mobility, gender power relations, access to services, changing risk perceptions and the social meanings attached to HIV prevention. Lenacapavir is likely to be most efficient where HIV incidence is high, risk is ongoing and follow-up systems are strong. However, its broader population-level impact depends on whether programmes can identify, reach and retain at-risk users without diverting scarce resources from interventions with already established epidemiological and economic returns. Lenacapavir is a relevant addition to the HIV prevention repertoire, but its health-system feasibility, affordability and opportunity cost must be assessed cautiously in the context of likely future donor decline.

S Afr Med J 2026;116(10):e5408. https://doi.org/10.7196/SAMJ.2026.v116i10.5408

On 5 June 2026, South Africa (SA)'s President and the Minister of Health announced the introduction of lenacapavir, a twice-yearly injectable pre-exposure prophylaxis (PrEP) medication, calling it a turning point in SA's HIV response.[1] The initial roll-out is phased across selected high-burden facilities, and is financed largely through external support.

The Global Fund and the Children's Investment Fund Foundation have committed nearly USD70 million, which, together with government funding, brings the roll-out investment to ZAR1.3 billion.[2,3] This follows registration by the South African Health Products Regulatory Authority (SAHPRA) in October 2025, which described the product as a game-changer, echoing global narratives of an epidemic transformation.[4,5] Cheaper generics are anticipated later.

While millions of dollars have been committed to the launch phase of lenacapavir, including support from multiple donors and agencies, a number of questions remain about the extent to which the drug will contribute to SA's overall prevention response. For example, SA's HIV Investment Case in 2023 considered PrEP scale-up, including oral pills or 2-monthly injectable cabotegravir PrEP, unaffordable, with condom provision highlighted as the only cost-saving intervention.[6] Antiretroviral treatment also remains fundamental to HIV prevention, with sustained viral suppression reducing onward transmission while preventing illness and death. Protecting and extending treatment coverage is therefore an essential consideration in investment decision-making for HIV prevention. It is also important to consider how much the emphasis on lenacapavir may overshadow a broader, epidemiologically rationalised, multifaceted and cost-effective HIV prevention strategy for the country. This includes assessing the risks of donor declines and opportunity costs, and the need for a sustainable HIV prevention response.

Trial efficacy v. real-world effectiveness

Efficacy v. effectiveness is a concern that immediately arises when 'game-changer' claims are made for any single product or approach. This relates directly to the risk of conflating efficacy in randomised controlled trial settings, such as the PURPOSE 1 trial, where no HIV infections were observed among participants receiving lenacapavir.[1]

The distinction was made explicitly within the scientific community when the trial results were shared. In an editorial in the *New England Journal of Medicine* accompanying the findings of the PURPOSE 1 trial, Walensky and Baden[7] argued that the real test of lenacapavir was its effectiveness, not its efficacy. They highlighted the fact that translating very high efficacy into epidemic impact depended on access, delivery and continuation rather than on the product itself. This distinction is well established in the global health literature, and has been repeatedly raised as a necessary caveat in reference to HIV trials.

According to UNAIDS, ~3.9 million people started oral PrEP in 2024, far short of the 2025 target of 21.2 million, despite more than a decade of donor investment in PrEP programmes.[8] This shortfall, alongside persistent HIV incidence, suggests that PrEP uptake and continuation are shaped by factors beyond product availability or promotion. Demonstration projects and trial-linked implementations have shown that PrEP can substantially reduce incidence among users. For example, a population-based programme in rural Kenya and Uganda reported 74% lower incidence among PrEP initiators than among matched controls.[9] However, successes remain localised and dependent on supervision, and, given limited coverage and persistence, there is little evidence that PrEP has

produced durable population-level declines in HIV incidence in eastern and southern Africa.[10]

Oral PrEP and cabotegravir were described as game-changers when trial results emerged, underscoring the risk of overestimating epidemic impact before implementation data were available.[11] While lenacapavir is an important advance, the added value of 6-monthly dosing does not overcome other constraints associated with PrEP uptake and sustained use.

Recurring demand challenges for PrEP

Oral PrEP demand has been found to vary rather than reflect a stable individual preference. Among adolescent girls and young women in African settings, for example, uptake and continuation have been shaped by stigma, fear of side-effects, partner dynamics, travel and transport costs, health facility-related limitations and shifting perceptions of personal risk.[10] PrEP-related stigma, including being seen as sexually active, HIV-positive, or distrusted by a partner, is a recurring deterrent in its own right.[12] PrEP use often varies as relationships, mobility and economic pressures change, with many users moving on and off oral PrEP over time.[10] In programmes, these patterns are typically framed as adherence or behaviour challenges, rather than prompting the conclusion that daily oral PrEP may not fit well with a model of stable, continuous demand for biomedical HIV prevention.

While potential users in eastern and southern Africa generally prefer longer-acting injectable formulations over daily oral pills, implementation effectiveness is influenced by approaches to PrEP delivery.[13] Logistical demands include facility-based administration and rigorous follow-up by healthcare providers.[14] Provider capacity and sustainable financing must be considered, and costing data indicate that human and financial resource requirements are significant in high-burden settings.[15] The emerging lesson is that injectable PrEP can reduce the burden of pill-taking, but it does not necessarily overcome uptake, delivery and financing challenges or translate into sustained demand.

As lenacapavir implementation has proceeded with limited evidence from routine delivery settings, the specific barriers and challenges remain incompletely understood. While initial uptake may be driven by high-budget publicity, novelty and political launch effects, whether people at high and continuing HIV risk will return for the second injection on time, and remain engaged once the launch effect has faded, remains unknown. Over and above demand, the health-system requirements cannot be ignored. Lenacapavir implementation requires repeat HIV testing before each injection, clinical assessment, trained staff to administer the injection, appropriate storage and supply-chain management, recall and follow-up systems to bring people back every 6 months, and pharmacovigilance and data systems to monitor use.[16] These requirements are considerable when health facilities are expected to meet other diverse needs.

The assumed adherent user

A useful way to understand recurring demand problems is to consider the kind of user PrEP programmes are designed to support. Such programmes often work best for a person who can recognise and accept their HIV risk, view biomedical prevention as a relevant way to manage that risk, access a health facility, accept repeated HIV testing and monitoring, and incorporate visit schedules into everyday life. These assumptions fit some users, and lenacapavir may be valuable for people who prefer a twice-yearly injection. The difficulty is that people who meet epidemiological criteria for PrEP may not experience risk, HIV prevention, or health services in this way.

HIV vulnerability is often episodic, relational and socially mediated. It is shaped by partner dynamics, stigma, mobility, economic insecurity, access to services, gender power and concerns such as criminalisation.[10] Weak uptake or discontinuation may be the product of a lack of fit with the conditions in which HIV vulnerability is produced, rather than a lack of knowledge or motivation. While lenacapavir reduces the burden of frequent adherence, it still requires user initiation, testing, injection uptake, timely return and commitment to long-term linkage to a health facility. Demand is therefore not a latent opportunity for an innovative product; it is a process that requires a close understanding of complexity. Even with that understanding, alternative strategies for HIV prevention, including non-biomedical approaches, may be far more viable options for people who are vulnerable to HIV infection.[17]

Biomedical tools and biosocial prevention

Beyond the efficacy-effectiveness gap lies a deeper distinction between two ways of understanding HIV prevention. Dominant biomedical prevention frameworks often individualise HIV risk and locate intervention at the point of transmission. Within this view, biomedical tools and products are the appropriate means of prevention, and social factors enter mainly as barriers, risks, or behaviours to be managed in support of biomedical delivery.[17,18]

Social epidemiology begins from a different orientation, viewing epidemics such as HIV as biosocial phenomena produced through structural and sociocultural conditions such as poverty, gender power, mobility, inequality and uneven access to resources.[19] From this perspective, addressing these underlying conditions is itself an essential pathway for prevention. This does not displace biomedical tools. Rather, it positions them within a wider social response and holds them accountable to the conditions that drive exposure and vulnerability, rather than treating a product as the central means through which an epidemic is transformed. Population-level change in HIV epidemics has occurred without biomedical products available at scale, and southern Africa offers a clear example. In Zimbabwe, a synthesis of modelling, surveillance, survey, qualitative and programme data found that adult HIV prevalence fell from ~29% in 1997 to 16% in 2007, with incidence declines concentrated between roughly 1999 and 2003. These declines occurred before antiretroviral therapy reached meaningful coverage, with fewer multiple partnerships, awareness of high AIDS mortality, and economic factors representing the main behavioural and structural shifts.[20,21] These were supported by HIV prevention programmes including mass media, church and workplace-based programmes and interpersonal communication.

Uganda's epidemic decline in the early 1990s followed a similar logic. Political leadership and a multisectoral, community-based response primarily reduced multiple partnerships, supported by high awareness and social communication about HIV.[22,23] Condom programming has also been effective. For example, social marketing programmes in sub-Saharan Africa increased condom use with non-marital partners and complemented public-sector distribution.[24] Epidemiological impacts have been demonstrated for key populations, and mathematical models support their relevance for epidemic control.[25]

These examples demonstrate that non-biomedical approaches have produced substantial population-level epidemiological change, yet they have been progressively decentred by the emphasis on biomedical prevention. In the early 2010s, the concept of combination prevention gained currency, valuing biomedical, behavioural and

structural approaches together. Some programmes have drawn on this framework, but more recent framing tends to situate structural and social conditions as barriers or challenges to be addressed to improve access to biomedical prevention, rather than as prevention approaches in their own right.[26]

Demand, opportunity cost and prioritisation

Demand cannot be separated from opportunity cost. In a constrained health system, the relevant question is not only whether some users will prefer lenacapavir or whether the product can be delivered during a donor-supported introduction phase. Rather, the questions are whether sustained use can be supported among people at high and continuing risk; whether the health system has the long-term capacity to deliver repeated testing, injection, counselling, pharmacovigilance and follow-up; and whether scale-up would remain affordable as external HIV financing contracts.[27]

In a *Lancet Global Health* commentary, Granich[27] argues that enthusiasm for lenacapavir has been accompanied by insufficient attention to prioritisation. This includes considering unresolved treatment gaps, constrained budgets and competing health-system needs in contexts where the product is being written into national plans before opportunity cost, system capacity and sustainability have been adequately examined.

These delivery requirements have implications for cost-effectiveness, particularly as the number of person-years of prophylaxis needed intersect with declining HIV incidence. Some existing approaches already have clearer evidence of population-level effect and cost-effectiveness. Antiretroviral treatment remains foundational to epidemic control, preventing illness and death while reducing onward transmission through sustained viral suppression.[28] Closing gaps in diagnosis, treatment initiation, retention and viral suppression should therefore remain central to prevention investment decisions. Condom programming is demonstrably effective and, in SA's own investment case, the most cost-effective and cost-saving intervention available.[29] Yet SA's condom distribution programme has declined dramatically since 2018.[30]

Lenacapavir's scale-up needs to be considered alongside interventions with established outcomes, as evidence accumulates on its programmability and relevance. What must be avoided is framing the product as a game-changer when its epidemiological value is unknown at the outset, without comparative analysis against well-established approaches, and without opportunities to integrate lower-cost structural and sociocultural approaches that have historically been marginalised.

Conclusion: Implications for SA HIV prevention

Lenacapavir's contribution to epidemic control will depend on sustained demand, effective delivery and epidemiological value relative to established approaches. High clinical efficacy alone does not establish its population-level impact, or justify its prioritisation over other approaches.

While donor priorities strongly influence the introduction and establishment of a market for lenacapavir, it does not follow that long-acting injectable PrEP should dominate the HIV prevention response. The choices to be made must remain focused on a sustainable vision for the HIV response in SA that reflects its sovereign priorities and extends beyond the immediate promise of donor support and imperatives.

Policy and practice points

- Avoid positioning lenacapavir as a whole-of-prevention response. Prioritise lenacapavir in settings and populations where HIV incidence is high, risk is ongoing and reliable follow-up can be supported through acceptable, non-stigmatising delivery models. Assess lenacapavir alongside established interventions, particularly antiretroviral treatment and viral suppression, condom provision and social and structural approaches that have demonstrated contributions to HIV prevention.
- Prioritise assessment of the full delivery burden, including HIV testing, counselling, injection visits, recall systems, pharmacovigilance, data systems, healthworker time and supply-chain requirements.
- Lenacapavir roll-out should be evaluated based on continuation of use, including timely return for the second injection, and subsequent use patterns among people at high and continuing HIV risk.
- Test lenacapavir modelling assumptions and projections against emerging implementation and epidemiological evidence before expanding scale.
- Plan for affordability at the outset, taking into account that donor support is time-limited and the opportunity costs of domestic financing in a constrained health system include a range of cost and impact efficiencies.

Acknowledgements. None.

Author contributions. Sole author.

Funding. None.

Conflicts of interest. None.

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Received 10 June 2026; accepted 23 June 2026.