



PERSPECTIVE HIV AND AIDS

## Long-acting Antiretroviral Agents in the Prevention and Treatment of HIV/AIDS: A Review of Recent Advances in Sub-Saharan Africa

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### ABSTRACT

Long-acting antiretroviral (LAARV) agents have the potential to enhance treatment and prevention by eliminating the need for daily oral medications and increasing available options. This paper reviewed recent evidence on LAARVs and explores the opportunities and challenges of implementing these innovative prevention and treatment strategies in Sub-Saharan Africa (SSA). Several clinical trials and studies on the effectiveness, drug-drug interactions, and resistance of LAARVs in key populations in SSA are ongoing or recently completed. While the effectiveness, efficacy, and cost-effectiveness of LAARVs compared to existing oral therapies have been established, these products are not yet widely used in SSA. Significant logistical challenges in integrating LAARVs into clinic workflows under the poor health systems that are common in SSA necessitate a multi-sectoral, patient-centered approach, including the use of non-traditional healthcare delivery models.

**Keywords:** Acquired Immunodeficiency Syndrome, Africa, Antiretroviral Agents, Antiretroviral Therapy, Highly Active, HIV Infections

### INTRODUCTION

The introduction of long-acting antiretrovirals (LAARVs) for the prevention and treatment of HIV/AIDS represents a significant advancement in the delivery of antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP).<sup>[1]</sup> While these agents offer an alternative to daily oral medications, they bring both opportunities and challenges for implementation in Sub-Saharan Africa (SSA). SSA has been disproportionately burdened by the impact of HIV disease. Approximately 39 million people are living with HIV (PWH) in the world, and 67% of these individuals reside in SSA.<sup>[2]</sup> In 2023, approximately 630,000 HIV-related deaths were reported worldwide, and 390,000 (56%) of these cases were reported in SSA. The key drivers of the HIV/AIDS epidemic in this region include poverty, multiple concurrent sexual partnerships, recreational drug use, interpersonal violence, poor adherence to antiretroviral therapy, and testing and treatment resource constraints, among others.<sup>[3,4]</sup> In order to address this high disease burden in SSA and other HIV/AIDS epicenters in the world, the United Nations Joint Program on HIV/AIDS (UNAIDS) has proposed the attainment of ambitious 95–95–95 targets by 2030.

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The targets advocate for testing and diagnosis of 95% of people with HIV; 95% of people who have been diagnosed should receive sustained antiretroviral therapy; and 95% of the patients who are receiving treatment should have viral suppression (<1,000 copies/mL).<sup>[5]</sup> Overall, progress toward achieving these goals has been uneven across countries in SSA, and efforts to reduce new HIV infections in this region have been limited and below expectations.<sup>[5]</sup> Thus, there is an urgent need for innovative and high-yield prevention strategies to reduce the incidence of HIV infection in this region and effective programs to promote adherence to antiretroviral therapy. This paper reviewed the recent advances in LAARVs and the opportunities and challenges in the implementation of these innovative treatment and prevention approaches in SSA.

### ART USE IN SSA

Access to ART has increased significantly in SSA in the past two decades because of funding from international donors and initiatives such as the President's Emergency Plan for AIDS (PEPFAR) and the Global Fund to Fight AIDS.<sup>[6]</sup> Despite these huge investments aimed at preventing the spread of HIV disease and improving disease outcomes, many countries in SSA have not reached the UNAIDS recommended targets for testing, enrollment in treatment programs, adherence to antiretroviral therapy, and viral suppression.<sup>[6]</sup> While several factors, such as structural and social factors, have been known to affect the quality of life among PWH, empirical evidence has shown that treatment outcome is fundamentally predicated upon the patient's adherence to the prescribed daily medication regimen.<sup>[7]</sup>

Evidence has shown that poor adherence to ART can lead to severe consequences. Most patients who are non-adherent are likely to have a viral load rebound, and they are potentially at an increased risk of transmitting HIV disease because a higher viral load may increase the risk of disease transmission to others.<sup>[8]</sup> Additionally, nonadherence to ART can lead to drug resistance, increased risk of co-infections, increased healthcare costs, and increased HIV-related complications such as kidney disease and liver disease.<sup>[7,9,10]</sup> Given the impact that poor adherence could have on treatment outcomes and quality of life among people living with HIV, there is a growing interest in the use of injectable LAARVs to promote adherence. LAARVs are also thought to help lessen the stigma commonly linked to oral therapy for treatment and PrEP use.

Adherence to ART has been limited in SSA by several factors, including socioeconomic factors such as poverty and lack of education, fear of stigma, high pill burden, conflicting cultural beliefs, alcohol and substance abuse, and healthcare worker attitudes, among others.<sup>[11-13]</sup> Nonadherent patients are prone to having a weakened immune system and increased morbidity and mortality.<sup>[7]</sup> The use of long-acting

(LA) injectable ART may be a promising and innovative way of addressing the challenges that are associated with ART nonadherence in this region.

### LONG-ACTING ANTIRETROVIRALS AND RECENT ADVANCES IN SSA

Although the availability of oral antiretroviral therapy has made HIV a manageable chronic illness, several countries in SSA have not been able to attain the UNAIDS-recommended targets for viral suppression due to nonadherence to dosing regimens and other structural challenges.<sup>[14]</sup> Fortunately, emerging evidence has shown that long-acting regimens may improve treatment outcomes because they address challenges that are associated with lifelong daily pill taking, such as stigma, violence from family members, and pill fatigue from daily dosing.<sup>[14]</sup> There are five Antiretrovirals (ARVs), namely, cabotegravir (CAB), rilpivirine (RPV), lenacapavir (LEN), ibalizumab (IBA), and dapivirine (DPV), that are currently available in a limited number of countries as LA options for preventing and treating HIV. While research has been conducted in the developed world to demonstrate the efficacy and effectiveness of LAARVs for the treatment of people with HIV, only a limited number of patients from SSA have been included in the study samples, and the generalizability of study outcomes to this region is not known.<sup>[14]</sup>

Several ongoing and recently completed studies have examined the effectiveness of long-acting antiretroviral therapy in SSA.<sup>[15,16]</sup> Notably, the Improving HIV Outcomes in Africa with Long-acting Antiretrovirals (IMPALA) study is being conducted in Kenya, Uganda, and South Africa. The study is a phase 3 randomized clinical trial that is recruiting 540 virologically suppressed patients who have had a detectable viral load in the past two years or who are not currently in HIV care.<sup>[14]</sup> The study compares the effectiveness and efficacy of LA cabotegravir and LA rilpivirine relative to the existing oral therapy. It utilizes qualitative and quantitative approaches to elicit information on the cost-effectiveness of this treatment modality from patients, healthcare workers, and other stakeholders who are engaged in HIV patient care.<sup>[15]</sup> The overall objective of the study is to generate data that will enhance access to LAARVs in SSA. Furthermore, the HIV Prevention Trials Network (HPTN) 083 and 084, with participants from across seven countries in SSA (Botswana, Kenya, Malawi, South Africa, Eswatini, Uganda, and Zimbabwe), reported that LA cabotegravir (CAB-LA) for HIV-1 prevention was superior to daily oral tenofovir/emtricitabine (TDF/FTC) for PrEP in cisgender men and transgender women (TGW) who have sex with men and cisgender women. HPTN 083 revealed a 66% reduction in HIV-1 transmission in participants taking CAB-LA compared to those taking oral PrEP, while HPTN 084 reported an 89% risk reduction.<sup>[16]</sup> Regulatory submissions are currently in progress in the countries participating in the HPTN 083

and 084 studies. However, Botswana and Zimbabwe are the only African nations that have approved LA cabotegravir plus rilpivirine for treatment. LA injectable cabotegravir PrEP has been recently recommended by the World Health Organization (WHO) as an additional option for HIV prevention in SSA.<sup>[17]</sup> In a model study aimed at projecting the health benefits and risks of cabotegravir-PrEP introduction in settings in SSA, it was reported that its introduction is likely to result in net reductions in AIDS deaths and disability-adjusted life years in addition to reductions in HIV incidence and to be cost-effective when compared to the cost of oral-PrEP.<sup>[17]</sup>

## CHALLENGES AND IMPLEMENTATION CONSIDERATIONS

There are several barriers that could affect the implementation of long-acting antiretroviral therapy in SSA, including a number of research gaps, issues regarding resistance, and understudied populations. First, health system challenges, such as lack of infrastructure for the monitoring of treatment failure, limited staff training and capacity, cold chain requirements, and medical supply shortages, could impede program implementation.<sup>[18]</sup> Second, patient-level factors, including medical mistrust, fear of injection, stigma, and perceived medication effectiveness, can affect a patient's willingness to participate in treatment programs.<sup>[14,18]</sup> Finally, the cost of instituting long-term antiretroviral therapy would be higher than the administration of traditional therapies. This could limit accessibility to this treatment regimen in resource-constrained settings such as SSA. In order to improve long-term ART acceptance and uptake in SSA, health administrators would have to address these challenges.

## PUBLIC HEALTH IMPLICATIONS

LAARVs could play a significant role in reducing HIV transmission rates in the SSA by improving adherence and reducing viral loads more consistently. Their introduction could complement existing HIV initiatives, like community-based ART delivery models, by providing more adaptable treatment options for patients struggling with daily medication adherence. LAARVs could be especially beneficial for high-risk groups in SSA, such as sex workers, men who have sex with men, and adolescents, who often encounter additional challenges to daily adherence due to stigma, mobility, or criminalization.

## CONCLUSION AND GLOBAL HEALTH IMPLICATIONS

LAARVs have the potential to revolutionize HIV care in SSA, where the HIV burden is disproportionately high, by enhancing treatment adherence, reducing stigma, alleviating pressure on the healthcare systems, and aiding in the overall control of

the HIV epidemic. However, their long-term effectiveness and affordability will be crucial in determining their widespread adoption and impact in the region. It is also important to address the series of health systems and patients' levels of implementation challenges identified. SSA must utilize a multi-sectoral approach that will involve, among others, laboratory capacity building for monitoring patients and the adoption of non-traditional healthcare delivery models for LAARVs.

## Key Messages

1. Long-acting antiretroviral agents have the potential to enhance treatment and prevention by eliminating the need for daily oral medications and increasing available options for people with human immunodeficiency virus (HIV) and at risk of HIV.
2. Although several ongoing and recently completed studies have examined the effectiveness, efficacy, and cost-effectiveness of long-acting antiretroviral therapy, these products are not yet widely used in Sub-Saharan Africa (SSA).
3. Significant logistical challenges in integrating long-acting antiretrovirals (LAARVs) into clinic workflows under the poor health systems that are common in SSA necessitate a multi-sectoral, patient-centered approach, including the use of non-traditional healthcare delivery models.

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## COMPLIANCE WITH ETHICAL STANDARDS

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