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Commentary

Advances in Long Acting Antiretroviral Therapies for HIV Management

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DESCRIPTION

The management of HIV has undergone a remarkable transformation over the past four decades, progressing from a fatal diagnosis to a manageable chronic condition thanks to the development and optimization of combination antiretroviral therapy (ART). However, conventional ART regimens typically require daily oral administration, which can pose significant challenges in terms of adherence, especially in marginalized populations, younger patients or individuals experiencing stigma or mental health issues. Poor adherence not only compromises viral suppression but also contributes to drug resistance and transmission risk. In response to these challenges, long acting antiretroviral therapies (LA-ART) have emerged as a groundbreaking innovation with the potential to redefine HIV management by improving treatment adherence, reducing pill burden, and enhancing overall quality of life for people living with HIV.

Long acting formulations are designed to maintain therapeutic drug levels over extended periods, ranging from weeks to months, with a single administration. The most advanced LA-ART products include injectable formulations of cabotegravir and rilpivirine, approved for monthly or bimonthly use. Clinical trials such as ATLAS, FLAIR, and ATLAS-2M have demonstrated that these agents are as effective as standard daily oral ART in maintaining viral suppression in patients who are already virologically stable. These trials also report high levels of patient satisfaction and preference for injectables over oral regimens, citing greater convenience, discretion, and reduced anxiety associated with daily reminders of HIV status.

Beyond injectables, other delivery platforms are being explored, including subdermal implants, long acting oral tablets, and transdermal patches. Subdermal implants, similar in concept to contraceptive implants, provide the promise of sustained drug delivery for six months or more. Early studies on tenofovir alafenamide (TAF) implants and islatravir-based implants have shown promising pharmacokinetic profiles, although safety, scalability, and cost-effectiveness remain critical concerns. Furthermore, nanoparticle-based drug carriers and *in-situ* forming depots are being investigated for their ability to extend drug half-life and enhance targeted delivery to reservoir sites.

The development of LA-ART also opens new doors for differentiated care models, especially in low-resource settings. By reducing the frequency of clinic visits required for medication refills and viral load monitoring, long acting therapies can ease the burden on overstrained healthcare systems. This is particularly relevant in sub-Saharan Africa and parts of Eastern Europe where healthcare infrastructure may not support intensive follow-up. In these contexts, community-based injection programs and mobile health clinics could be leveraged to improve ART coverage and retention.

Despite these advantages, several challenges must be addressed before LA-ART can become a universal standard. Injection site reactions, although generally mild and self-limiting, can affect patient compliance. Moreover, the long pharmacokinetic tails of some agents raise concerns about subtherapeutic drug levels that could facilitate the development of resistance in the event of missed doses. Managing missed injections, transitioning between formulations, and dealing with drug-drug interactions in patients with comorbidities also require carefully crafted clinical guidelines. Additionally, the cost of LA-ART remains significantly higher than that of generic oral regimens, posing barriers to widespread adoption in economically constrained healthcare systems.

Importantly, ethical and logistical considerations must be accounted for to ensure equitable access. Populations with limited autonomy, such as incarcerated individuals or those facing housing instability, may especially benefit from long acting options. However, they must be fully informed and consent to treatment without coercion. Pharmacovigilance systems must also be strengthened to monitor long-term safety and resistance patterns in real-world settings. Moreover, attention must be given to integrating LA-ART into existing national HIV programs and electronic health records to optimize patient tracking and follow-up.

In Greece and other European countries with concentrated epidemics among men who have sex with men (MSM), migrants,

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and people who inject drugs (PWID), LA-ART offers a promising tool to address both clinical and social dimensions of HIV care. National HIV plans are increasingly recognizing the need to tailor services to specific risk groups, and long acting therapies align well with this personalized approach. The Greek healthcare system, despite its financial constraints, is exploring pilot programs to assess the feasibility of LA-ART in public health settings, particularly in urban centers like Athens and Thessaloniki where prevalence rates remain significant.

In conclusion, advances in long acting antiretroviral therapies represent a paradigm shift in the management of HIV, offering a more patient-centered, adherent-friendly, and potentially scalable treatment modality. While current data support their efficacy and acceptability, ongoing research and strategic implementation will be essential to overcome remaining barriers. For countries like Greece striving to meet UNAIDS 95-95-95 targets, integrating LA-ART into national HIV strategies could substantially improve long-term outcomes and move us closer to epidemic control. As innovation continues, the ultimate goal remains unchanged an HIV-free future where every person receives effective, acceptable, and accessible care.