

Viewpoint

Will Long-Acting Antiretroviral Therapy be a Game Changer Globally?

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Antiretroviral therapy has transformed HIV prevention and treatment, but current life-long daily dosing poses challenges. Overton et al.¹ show that a combination ART formulation administered intramuscularly every 8 weeks is as safe and efficacious as 4-week dosing. Efforts must now focus on ensuring global access.

INTRODUCTION

Effective antiretroviral therapy (ART) has improved the quality of life of people living with HIV and is a key component in HIV prevention strategies. However, a significant challenge is that HIV treatment is life-long, with current oral dosing formulations requiring stringent daily adherence to maintain viral suppression and prevent clinical disease progression and emergence of drug resistant variants. Although many patients have succeeded with daily dosed ART, in others it can lead to treatment fatigue and adherence can be negatively impacted by socio-behavioral factors such as stigma. Frequent dosing may also be more vulnerable to supply chain failures occasioned by inadequate health systems and individual or societal instability, such as that presented by the current COVID-19 pandemic. Consequently, there has been a concerted effort over the past decade to develop long-acting antiretroviral drug formulations that would simplify dosing and thereby amplify the impact of ART globally.

In a Phase 3 study by Overton et al.,¹ 1,045 participants were randomized to long-acting intramuscular (IM) injection of cabotegravir (an integrase strand transfer inhibitor) and rilpivirine (a non-nucleoside reverse transcriptase inhibitor) either every 8 weeks or every 4 weeks. Participants were on average 42 years old, and majority (73%) were male (n = 765) and white (n = 763). Over 48 weeks of

follow-up, cabotegravir and rilpivirine dosed intramuscularly every 8 weeks was at least as safe and efficacious as the 4-week dosing. This is the first Phase 3 study to provide evidence that an injectable long-acting ART formulation administered every 2 months can be a safe and efficacious alternative to daily oral or monthly injectable long-acting ART dosing regimens.

For individuals living with HIV, this study will provide hope of access to long-acting injectables, and potentially numerous benefits (Table 1) as many prefer this formulation as an alternative to daily oral ART.² This innovation may lead to substantial improvement in adherence to ART medication since less frequent dosing may mitigate against some of the factors that contribute to non-adherence such as stigma, fear of inadvertent disclosure of HIV status, comorbidities, and daily dosing fatigue.^{3,4} At the public health level, long-acting ART may be a game changer for improvement of both HIV prevention and treatment efforts. Currently, despite significant progress in the roll-out of antiretroviral therapy, the global response to the HIV epidemic is characterized by uneven outcomes across geographic areas, both at a global and local scale.⁵ Recent data suggest that despite widespread roll-out of ART, only an estimated 59% of people living with HIV globally are on effective

ART.⁶ Improved adherence rates through long-acting ART injectables may result in better overall suppression of population viral loads, improving the quality of life and health outcomes for people living with HIV. This in turn has the potential to be a major boost for the goal of achieving universal viral suppression ("undetectable equals untransmissible" or U = U), a key pillar in the HIV elimination strategy. However, long-acting antiretrovirals are only likely to have significant global impact if these interventions are accessible to individuals and communities in heavily burdened low- and middle-income countries (LMICs).

The current study builds on previous findings that monthly injections of cabotegravir plus rilpivirine were non-inferior to daily oral ART for HIV-1 suppression⁷ and will therefore likely accelerate the transition to long-acting injectable ART. However, several challenges remain before this innovation can be truly transformative for global public health (Table 1). Antiretroviral agents, including long-acting injectables may have detrimental health consequences, such as disturbances in lipid metabolism, obesity, and mitochondrial dysfunction.⁸ Monitoring of patients will therefore be required to ensure long-term safety and ability to switch regimens or manage cases of virologic failure or adverse events, although the 48 weeks follow-up data

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Table 1. A summary of some of the benefits and challenges that may be associated with long-acting injectable antiretroviral therapies

Direct and indirect benefits	Challenges and remaining questions
(1) Less frequent dosing	(1) Cost and affordability
(2) Potential reduction of stigma	(2) Increased visits to health facilities for injections
(3) Less fear of inadvertent disclosure of HIV status	(3) Impact of biological factors such as viral subtypes, human genetic factors and comorbidities
(4) Reduced risk of non-adherence due to forgetfulness, individual patient circumstances, fatigue	(4) Formulations for vulnerable groups such as children, pregnant women, and those with comorbidities
(5) More efficient viral suppression because of better adherence	(5) Compatibility with ART-based HIV prevention approaches that contain similar or identical antiretroviral agents
(6) Better health outcomes for people living with HIV	(5) Less frequent dosing formulations
(7) Lower population viral loads and therefore reduced risk of HIV transmission	(6) Health system infrastructure and preparedness

from this study is reassuring. The hope that a long-acting ART combination will work in individuals with adherence challenges still requires formal testing, as it may turn out that the same stresses that impede adherence to oral ART make it difficult for patients to regularly attend injection appointments. Additional areas that require further investigations include formulations for pediatric and other vulnerable populations such as pregnant women and those with comorbidities that require additional medications, and innovations to further reduce dosing frequencies.

Perhaps the most important remaining question is whether injectable long-acting ART will improve the health of people living with HIV and reduce transmission in LMICs. Only 27% and 18% of participants in this study were female and of

Black race, respectively, a notable limitation considering that these demographic groups are disproportionately infected with HIV worldwide. Furthermore, there was underrepresentation of participants from sub-Saharan Africa, where the need for such an intervention is greatest. It is unknown whether differences in health systems and biological factors such as viral subtypes, population genetics, and comorbidities, which are different in sub-Saharan Africa, will alter the effectiveness of long-acting ART. Modeling studies from low-income countries suggest that long-acting ART will be cost effective and advantageous compared with oral ART,⁹ but it remains to be seen whether this will be in the case in diverse real-world settings. The additional costs of rolling out long-acting ART are likely to be onerous, with patients likely requiring more visits to health facilities for injections. Moreover, the success of novel biomedical interventions is often dependent on extrinsic factors such as cost, distribution capacity, medical insurance, and preparedness of health systems.¹⁰ Overall, although the era of long-acting injectable ART has now arrived, research will be needed to address biological and health system factors that may stand in the way of maximum benefits particularly for those most in need- the marginalized, stigmatized, and poor people living with HIV in LMICs.

In summary, this study represents a significant advance and could potentially usher in a new era of long-acting ART for the management of HIV infection. Questions remain regarding long-term health consequences, affordability, preparedness, and access for heavily burdened countries and communities. Efforts must now shift toward ensuring equitable access to enable improvements in global public health.

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DECLARATION OF INTERESTS

The author declares no competing interests.

- Overton, E.T., Richmond, G., Rizzardini, G., Jaeger, H., Orrell, C., Nagimova, F., Bredeek, F., Garcia Deltoro, M., Swindells, S., Andrade-Villanueva, J.F., et al. (2021). Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet* 396, 1994–2005.
- Dandachi, D., Dang, B.N., Lucari, B., Swindells, S., and Giordano, T.P. (2020). Acceptability and preferences for long-acting antiretroviral formulations among people with HIV infection. *AIDS Care*, 1–9. Published online May 14, 2020. <https://doi.org/10.1080/09540121.2020.1764906>.
- Akinwunmi, B., Buchenberger, D., Scherzer, J., Bode, M., Rizzini, P., Vecchio, F., Roustand, L., Nachbaur, G., Finkielstein, L., Chounta, V., and Van de Velde, N. (2021). Dose-related and contextual aspects of suboptimal adherence to antiretroviral therapy among persons living with HIV in Western Europe. *Eur. J. Public Health*, ckaa229. Published online January 18, 2021. <https://doi.org/10.1093/eurpub/ckaa229>.
- Rueda, S., Mitra, S., Chen, S., Gogolishvili, D., Globerman, J., Chambers, L., Wilson, M., Logie, C.H., Shi, Q., Morassaei, S., and Rourke, S.B. (2016). Examining the

- associations between HIV-related stigma and health outcomes in people living with HIV/AIDS: a series of meta-analyses. *BMJ Open* 6, e011453.
5. Cuadros, D.F., Li, J., Mukandavire, Z., Musuka, G.N., Branscum, A.J., Sartorius, B., Mugurungi, O., and Tanser, F. (2019). Towards UNAIDS Fast-Track goals: targeting priority geographic areas for HIV prevention and care in Zimbabwe. *AIDS* 33, 305–314.
 6. UNAIDS (2021). Global HIV & AIDS statistics — 2020 fact sheet. https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf.
 7. Rizzardini, G., Overton, E.T., Orkin, C., Swindells, S., Arasteh, K., Górgolas Hernández-Mora, M., Pokrovsky, V., Girard, P.M., Oka, S., Andrade-Villanueva, J.F., et al. (2020). Long-Acting Injectable Cabotegravir + Rilpivirine for HIV Maintenance Therapy: Week 48 Pooled Analysis of Phase 3 ATLAS and FLAIR Trials. *J. Acquir. Immune Defic. Syndr.* 85, 498–506.
 8. Bourgi, K., Wanjalla, C., and Koethe, J.R. (2018). Inflammation and Metabolic Complications in HIV. *Curr. HIV/AIDS Rep.* 15, 371–381.
 9. Culhane, J., Sharma, M., Wilson, K., Roberts, D.A., Mugo, C., Wamalwa, D., Inwani, I., Barnabas, R.V., and Kohler, P.K. (2020). Modeling the health impact and cost threshold of long-acting ART for adolescents and young adults in Kenya. *EClinicalMedicine* 25, 100453.
 10. Kanazawa, J.T., Saberi, P., Saucedo, J.A., and Dubé, K. (2020). The LAIs Are Coming! Implementation Science Considerations for Long-Acting Injectable Antiretroviral Therapy in the United States: A Scoping Review. *AIDS Res. Hum. Retroviruses*. Published online December 7, 2020. <https://doi.org/10.1089/AID.2020.0126>.