Realising long-acting ART as first-line treatment

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A fixed-dose combination of tenofovir alafenamide, emtricitabine, and bictegravir is considered a first-line therapy for HIV by the US Department of Health and Human Services and is widely prescribed in the USA and other high-income settings.[1] Long-acting antiretroviral therapy (ART) offers the promise of improved quality of life among people with HIV-1 who are burdened by daily pills. In *The Lancet HIV*, the SOLAR study, reported by Moti N Ramgopal and colleagues,[2] shows that injectable cabotegravir plus rilpivirine dosed every 2 months, following two loading doses, is non-inferior to daily bictegravir, emtricitabine, and tenofovir alafenamide among virally suppressed people with HIV who have received an integrase strand transfer inhibitor (INSTI)-based regimen in the previous 6 months.

Although the study moves the field forward with the comparison to this gold standard INSTI regimen, several of the findings deserve to be highlighted. 47% of participants in the study reported always struggling with a fear of disclosure, adherence anxiety, and daily reminders about HIV status. Previous studies have noted convenience and discretion as commonly cited reasons for preferring long-acting ART;[3] notably, 90% of those randomly assigned to receive long-acting cabotegravir plus rilpivirine in this study preferred the injection to the pill. Additionally, the study allowed individuals who became pregnant during the study to continue treatment. Although no conclusion could be drawn on drug safety owing to early termination by two individuals who became pregnant, we applaud the authors in making pregnant people a priority and encourage future clinical trials to do the same.

Despite efforts to enrol from multiple countries, participants enrolled in the study might not be representative of all individuals who benefit from long-acting ART. Only 31% of trial participants were non-White whereas 21% had a BMI of at least 30 kg/m^2. In the USA, 69% of new infections are among Black and Hispanic individuals,[4] and obesity rates, which strongly correlate with food insecurity in select regions,[5] are as high as 40%.[6] Furthermore, the study offers no data on any other similarly vulnerable populations, including individuals who inject drugs, have been homeless, or suffer serious mental health challenges.

Although virological failure remains infrequent in all clinical trials involving cabotegravir-based long-acting ART, failure does carry high stakes with the potential loss of INSTIs as a class. Previous studies have identified specific baseline risk factors including rilpivirine-associated resistance mutations, HIV subtype A6/A1, and BMI of at least 30 kg/m^2. Among people with obesity, use of a 5-cm needle has been proposed as one option to mitigate risk of failure in this population.[7] In this study, none of these baseline factors existed among those for whom long-acting cabotegravir plus rilpivirine every 2 months was unsuccessful. Further work is warranted in identifying additional risk factors for virological failure.

We now have ample evidence that cabotegravir plus rilpivirine is a promising option for virally suppressed people with HIV-1 without previous virological failure or chronic hepatitis B. However, bringing that promise to reality remains a serious challenge. In our clinic, we have encountered several implementation barriers that might challenge real-world scale up of long-acting ART. These include lack of consistent procurement due to widely discrepant coverage by third party payors and under-resourced clinical operations to ensure timely administration.

The heterogeneity of coverage by USA-based insurers, with some covering long-acting ART as a medical benefit and others covering it as a pharmacy benefit, results in the onus on clinics to navigate an intricate web of procuring supply of injectables for their patients. The pharmacy benefit might allow a more streamlined process by leveraging specialty pharmacies, particularly those with discount (340B) contracts, which can negotiate fair pricing. But with either type of plan, the risk of a burdensome cost-share for the patient remains concerning.[8,9]

Moreover, the challenges of daily adherence are replaced by new challenges of scheduling the injections within a narrow window and ensuring coverage with an oral regimen if people with HIV-1 are not able to adhere to that window. Ideally, at least one dedicated full-time equivalent staff member is needed to manage a growing list of patients and their scheduled doses, in the same way that a site coordinator would do in a clinical trial setting.

Identifying less frequently dosed long-acting ART options as clinically equivalent to first-line oral ART regimens is a remarkable endeavour. But the benefits of this promising therapy languish at the hands

of systems that are ill-prepared for such innovations in health-care delivery. Further investment is needed to understand and improve real-world implementation of long-acting ART, with particular attention to historically underserved populations.

JSC reports serving on a scientific advisory board for Merck in 2021. TV declares no competing interests.

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