Lenacapavir in first-line therapy

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Where are we now with long-acting therapy? Based on an extensive registrational trial programme, long-acting injectable cabotegravir and rilpivirine is the first complete regimen to be recommended for the treatment of HIV-1 infection.[1–3] The regimen is indicated for the treatment of virally suppressed individuals without hepatitis B co-infection who meet other virological suitability criteria.[2] It is not yet universally available.

Lenacapavir is the second long-acting injectable treatment for HIV-1 infection to receive a license.[4] It is a potent, first-in-class capsid inhibitor that is active at multiple points in the viral lifecycle, with a flexible pharmacokinetic profile that facilitates subcutaneous injection every 6 months with potential for weekly oral therapy.[5] The licensed indication for lenacapavir is different from long-acting injectable cabotegravir and rilpivirine. Lenacapavir has been licensed by the European Agency for the Evaluation of Medicinal Products for the treatment of individuals with HIV-1 with extensive treatment experience and for whom it is otherwise impossible to construct a viable regimen.[4] The CAPELLA study[5] in heavily treatment-experienced individuals showed that when lenacapavir is combined with an optimised backbone, impressive levels of viral suppression over 52 weeks are possible, as is significant immune restoration. Injection site reactions were frequent but mild and there were very few resulting discontinuations. Capsid inhibitor resistance occurred in eight participants, almost all of whom were either non-adherent to the optimised backbone or had no other active agents.

In *The Lancet HIV*, Gupta and colleagues present the primary endpoint of the CALIBRATE study—the first study to evaluate long-acting ART for first-line therapy.[6] This is an ongoing phase 2, open label study including 183 adult participants through 52 weeks of therapy. Participants were randomised (2:2:2:1) to one of four groups further stratified by viral load (≤100 000 or >100 000 copies per mL). After oral loading dosing, groups 1 and 2 received lenacapavir (927 mg) subcutaneously every 26 weeks. For the first 28 weeks lenacapavir was provided within a three-drug regimen (together with oral daily emtricitabine plus tenofovir alafenamide), after which it was prescribed as a two-drug regimen with either oral daily tenofovir alafenamide (group 1) or bictegravir (group 2). Group 3 received oral daily lenacapavir with emtricitabine and tenofovir alafenamide. Group 4 received oral bictegravir, emtricitabine, and tenofovir alafenamide.

Of the 182 participants who received treatment, 22 did not complete the study, 21 of whom were in the lenacapavir groups, 17 in the subcutaneous groups. Efficacy was on a par with modern oral first-line therapy studies: by week 28, 94% (147 of 157) in the lenacapavir groups (groups 1, 2, and 3) were virally suppressed (HIV-1 RNA <50 copies per mL). At week 54, 90% were virally suppressed (47 of 52 patients) in group 1, 85% (45 of 53) in group 2, and 85% (44 of 52) in group 3, compared with 92% (23 of 25) in group 4. Six participants met the protocol-defined virological failure criteria and were tested for resistance. Capsid inhibitor resistance occurred in two participants dosed (one subcutaneously, one orally) with lenacapavir.

Headache and nausea were the most frequent non-injection site reaction adverse events. No serious adverse events related to study treatment occurred. The most common lenacapavir-related injection site reactions were mild or moderate and were characterised as erythema (27%, 28 of 105), swelling (23%, 24 of 105), and pain (19%, 20 of 105). Three participants discontinued subcutaneous lenacapavir because of grade 1 injection-site reactions.

These are undoubtedly promising results; however, lenacapavir needs a long-acting partner if it is to deliver on the promise of being part of a complete long-acting regimen. With the development of islatravir slowed by unexpected immunological findings,[7] the identity of this partner is far from clear.

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The case for pre-exposure prophylaxis in prison settings

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Prison settings concentrate key populations who are at high risk for HIV, and this risk increases further as a result of consensual or coerced unprotected sexual intercourse and sharing of inadequately sterilised needles or grooming equipment.[1–3] Furthermore, HIV-related stigma and punitive laws criminalising HIV exposure prevent disclosure of risky behaviours to prison officials. In response, pre-exposure prophylaxis (PrEP) is recommended as an additional prevention choice as part of combined HIV prevention approaches by WHO.[4] Implementing PrEP in prison facilities might be challenging due to the multiple reported barriers preventing optimum HIV prevention programmes.

In *The Lancet HIV*, Brianna Lindsay and colleagues[5] conducted a cross-sectional study describing PrEP implementation in 16 Zambian prison facilities. The study showed high rates of PrEP uptake among all age groups of men and women who are incarcerated. Of those who tested HIV negative and were eligible for PrEP (using a Ministry of Health guideline for high-risk behaviour), more than 90% initiated PrEP use. Lindsay and colleagues have provided the first evidence globally on the feasibility of PrEP implementation—despite the known challenges from similar settings[6,7]—and they provide a blueprint to be followed by prison facilities in the region. The article also highlighted the dearth of literature on PrEP implementation in many countries. Only two studies, both from outside sub-Saharan Africa, assessed willingness to choose PrEP as a HIV prevention option.[8,9]

The study by Lindsay and colleagues also shows the high acceptance of HIV prevention modalities within this population, suggesting that there is continued exposure to HIV while incarcerated, despite Zambia having a very conservative society, and condoms not being permitted for distribution in criminal justice facilities. This high rate of PrEP uptake highlights a very important issue of condom provision in prison facilities. Only 30% of nations around the world report condom provision in the prison system,[10] and even in countries that provide condoms, implementation is not consistent and condoms are often provided without lubricant. Yet, condom provision is one of the most effective harm reduction interventions to control sexually transmitted infections (including HIV/AIDS and viral hepatitis) in prisons.

In keeping with the reluctance of officials to admit to any additional HIV risks, in Lindsay and colleagues' study, a national tool was used to determine who was at high risk of HIV. Although this tool can identify those at high risk for HIV in general populations, it might be necessary to adapt such a tool with characteristics that could be more relevant in a prison setting. There is a very high uptake of PrEP in the young age group (15–24 years), which might indicate a higher perception of risk among this group. However, the risk assessment did not include young age as a criterion.

The cyclical nature of prison facilities and communities—with individuals moving in and out—warrants emphasis on continuation of care. If PrEP use is initiated in prison settings and follow up for completion is conducted in communities post-release, HIV transmission is likely to be interrupted. Future longitudinal studies are needed to assess completion and incident HIV infections in these settings and communities, post-release.

Although the population of women who are incarcerated in Zambian prison facilities is small (<5%), as is common in all criminal justice settings, studies have shown a higher prevalence of HIV among women living in prison than men living in prison.[1,3] Lack of access to HIV prevention due to known factors such as gender inequality, stigma, and poverty contribute to such disproportionate HIV prevalence. Strategies to prevent HIV transmission are particularly necessary for