Lenacapavir for HIV-1 — Potential Promise of a Long-Acting Antiretroviral Drug

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As we walk through the lobby of a modern clinic for the treatment of patients with human immunodeficiency virus (HIV) infection or review antiretroviral regimens in the electronic medical record, it is easy to forget the days when managing multidrug-resistant HIV-1 was routine. Although the advent of protease inhibitors has saved lives,[1] many patients already had resistance mutations to then-available nucleoside reverse-transcriptase inhibitors (NRTIs). For these patients and for others who contracted HIV infection with primary resistance, the subsequent iterative availability of new drug classes, including non-NRTIs and integrase-strand transferase inhibitors, essentially offered functional monotherapy against a background of complex resistance mutations. These patients continue to be among the most challenging to treat, even in well-resourced settings. At worst, treatment options may be exhausted; even if a suitable regimen can be designed, survival and quality of life are often compromised.[2] Globally, among adults in whom non–NRTI-based first-line antiretroviral therapy has failed, 50 to 97% have evidence of resistance to these drugs.[3]

In this issue of the *Journal*, Segal-Maurer and colleagues[4] describe a potentially new option for addressing this topic in the CAPELLA trial. Lenacapavir is a first-in-class capsid inhibitor with several important characteristics. First, it has two mechanisms of action at separate stages of the viral life cycle, thus posing a barrier to resistance that may be intrinsically higher. Second, it can be administered subcutaneously in infrequent injections up to every 6 months, which minimizes the pill burden and may improve adherence. Third, adverse events appear to be uncommon except for the formation of injection-site nodules or indurations in the small number of patients who have been evaluated. Finally, although resistance to lenacapavir was noted in 8 of 72 patients in the CAPELLA trial (mainly in those with M66I mutations), such resistance largely occurred early in the trial, and half these patients had poor adherence to their optimized background therapy. The early timing is reassuring because emergence of late resistance poses greater challenges to monitoring of the efficacy of antiretroviral therapy, especially in resource-limited settings. Moreover, some patients had viral suppression while continuing to receive lenacapavir, which suggests that reduced replication capacity of these mutants may translate into less fitness in maintaining infection.

Segal-Maurer et al. enrolled a highly treatment-experienced group of patients who had a median CD4+ count of 150 cells per cubic millimeter. The population notably included persons who are not always embraced in trials of new agents: adolescents (≥12 years of age) and patients with a relatively high body-mass index. The investigators used a rigorous definition of multidrug resistance and a two-cohort design that provided the opportunity to study lenacapavir in patients who were receiving different regimens. Cohort 1 included 36 patients who had stable viremia (i.e., a decrease of <0.5 $\log_{10}$ copies per milliliter between the screening and cohort-selection visits) and an HIV-1 RNA level of 400 copies or more per milliliter. These patients were randomly assigned in a 2:1 ratio to receive oral lenacapavir or matching placebo for the first 14 days, with the initiation of subcutaneous lenacapavir on day 15 and day 29, respectively. Cohort 2 included 36 patients (3 with reduced viremia and 33 who were enrolled after cohort 1 had been closed) who all received open-label oral lenacapavir with optimized background therapy on day 1 and started to receive subcutaneous lenacapavir once every 6 months on day 15. Follow-up occurred through week 52. Finally, the patients included an ethnically and racially diverse group that was representative of patients with HIV-1 infection — notably, 25% were women, 38% were Black, and 21% were Hispanic or Latinx. However, representation from Africa and Asia was limited.

The majority of patients in both cohorts had suppression of viremia, which was defined as a reduction of at least 0.5 $\log_{10}$ copies per milliliter in plasma HIV-1 RNA by day 15 (the primary efficacy end point measured at the end of the

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functional monotherapy period) and a viral load of less than 50 copies per milliliter and less than 200 copies per milliliter at week 26 after the initiation of subcutaneous lenacapavir. By day 15 in cohort 1, viral suppression had occurred in 88% of the patients in the lenacapavir group as compared with 17% of those in the placebo group. In cohort 2, the patients also had similar viral suppression, with a mean change from baseline in viral load of –2.49 $\log_{10}$ copies per milliliter by 26 weeks. Finally, lenacapavir treatment resulted in a least-squares mean increase from baseline in the CD4+ count of 75 cells per cubic millimeter in cohort 1 and 104 cells per cubic millimeter in cohort 2.

Although the number of patients in this trial was small, the CAPELLA trial offers support for HIV-1 treatment with long-acting agents with mechanisms of action that may minimize the development of resistance mutations. Equally exciting is the potential for the use of such agents as HIV-1 preexposure prophylaxis, for which lenacapavir is currently being evaluated. That said, several challenges remain — most notably, obstacles to establishing the safety and efficacy of very long-acting products in women of reproductive age (15 to 49 years) who are pregnant, are breast-feeding, or wish to become pregnant.[5,6] The number of such women was projected to increase by 54% between 2015 and 2030 in sub-Saharan Africa, where the incidence of HIV-1 infection remains unacceptably high and access to modern contraceptives remains subpar.[7] Nearly half of all infants born to women with HIV infection have resistance to one or more non-NRTIs.[3] To truly change the trajectory of the global HIV pandemic, we must ensure expanded access to safe and effective life-changing medications for all patients.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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