Lenacapavir Resistance Comes at a Cost to HIV Fitness

HIV can evolve to evade the long-acting antiretroviral, but such mutations impair its ability to replicate efficiently.

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HIV can develop capsid mutations that confer resistance to lenacapavir, but doing so can come at a cost to viral fitness, according to a study results published in Science Translational Medicine. These findings have implications for lenacapavir use for HIV treatment and pre-exposure prophylaxis (PrEP).

“As [lenacapavir] moves into broader use for both PrEP and treatment, these findings highlight the importance of maintaining fully active companion drugs during HIV treatment, improving access to resistance testing and surveillance, and accelerating development of next-generation capsid inhibitors,” Manish Choudhary, PhD, and Jonathan Li, MD, of Brigham and Women’s Hospital and Harvard Medical School, wrote in an accompanying commentary.

Lenacapavir, Gilead Sciences’ first-in-class HIV capsid inhibitor, was first approved in 2022, under the brand name Sunlenca, as a component of combination therapy for heavily treatment-experienced people with multidrug-resistant HIV. Because it works differently from other antiretrovirals—disrupting the cone-shaped shell that surrounds HIV’s genetic material and essential enzymes—lenacapavir remains active against virus that has developed resistance to other drug classes.

The CAPELLA trial showed that most people who were unable to maintain an undetectable viral load on their previous regimen achieved viral suppression after switching to a combination containing lenacapavir injections every six months. The CALIBRATE trial showed that lenacapavir is also effective as a component of first-line treatment.

Lenacapavir was also approved last June for PrEP, under the brand name Yeztugo, after two large trials showed that it dramatically reduced the risk of HIV acquisition for young women in Africa (PURPOSE 1) and for gay and bisexual men and gender-diverse people in the United States and six other countries (PURPOSE 2). While lenacapavir alone is adequate for HIV prevention, it must be combined with other antiretrovirals—or potentially with broadly neutralizing antibodies—for treatment in order to limit the emergence of drug resistance.

Even when lenacapavir is used in combination therapy, however, HIV can sometimes evolve mutations in its capsid protein that lead to resistance. This can occur, for instance, if other drugs in a regimen aren't potent enough or if adherence is suboptimal. This may also happen if someone uses lenacapavir alone for PrEP when they have undiagnosed acute infection. But these mutations can impair the virus's ability to replicate efficiently, according to the new study.

Nina Pennetzdorfer, PhD, of Gilead Sciences, and colleagues characterized potential resistance-associated capsid mutations in 40 HIV samples collected from people treated with lenacapavir in the CAPELLA and CALIBRATE trials as well as 44 site-directed mutants (genetically altered virus). Some CAPELLA participants initially added lenacapavir to a failing regimen, and some had virus so resistant that they did not have enough remaining drugs to build a fully active background regimen.

In laboratory tests, HIV clones with capsid mutations had various degrees of decreased susceptibility to lenacapavir. Structural analysis showed that the mutations altered the drug's ability to bind to the virus, which was associated with reduced potency. However, the mutations that conferred the most resistance also led to substantial impairment of viral replication. One change, dubbed M66I, reduced replication capacity to below 20% of that of nonmutated virus. This suggests that HIV without the mutations would likely outcompete mutant versions, which may have been the case for several CAPELLA participants who regained viral suppression on lenacapavir despite resistance without changing their background regimen.

"These findings provide insights into lenacapavir-resistance mechanisms and underscore the unusually high fitness costs associated with treatment-emergent capsid mutations," the study authors concluded.

Reassuringly, the development of resistance to lenacapavir is "rare," Gilead senior vice president Jared Baeten, MD, PhD, told Fierce Biotech, but the findings underscore the importance of combining lenacapavir with other active agents, maintaining good adherence and ongoing surveillance for resistance mutations.

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