Treatment: Viral Fitness

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HIV can develop mutations that confer resistance to lenacapavir, but doing so comes at a cost to viral fitness. The long-acting HIV capsid inhibitor is approved as a component of treatment for people with multidrug-resistant HIV (Sunlenca) and as a single agent for pre-exposure prophylaxis (Yeztugo). Gilead scientists characterized resistance-associated capsid mutations in 40 HIV samples collected from people treated with lenacapavir in two clinical trials as well as 44 site-directed mutants (genetically altered virus). In laboratory tests, HIV with capsid mutations had various degrees of reduced susceptibility to lenacapavir. The mutations that conferred the most resistance also substantially impaired the virus's ability to replicate efficiently. The development of resistance to lenacapavir remains rare in clinical practice, but these findings underscore the importance of combining it with other active drugs for HIV treatment, using sensitive tests to rule out acute infection before starting PrEP and maintaining good adherence.
