

Picking the lock, paying the price: HIV's costly escape from a twice-yearly HIV drug

By Oliver Wolff

Twice a year. That's it. One injection, and a drug called lenacapavir keeps HIV suppressed for six months at a time, no daily pills required. For people who've spent decades juggling complicated regimens, it's one of the biggest advances in HIV treatment in years. But HIV has a reputation: give it any opening, and it will eventually find a way through. So, a team led by researchers at Gilead Sciences set out to answer an uncomfortable but necessary question: when HIV does slip past lenacapavir, what does that escape actually cost the virus?

Lenacapavir doesn't attack HIV the way most HIV drugs do. Instead of targeting the machinery the virus uses to copy its genes, it targets the capsid: the protein shell that protects HIV's genetic cargo as it breaks into a cell and heads for the nucleus. Lenacapavir wedges itself into a tiny pocket on this shell, like a key jammed into the wrong lock, and the whole structure falls apart. It's a clever, hard-to-dodge target. Still, in a large clinical trial of people who had run out of other treatment options, resistance emerged in about 1 in 5 participants after two years. The researchers wanted to know exactly how the virus was managing this, and whether it was paying a price for it.

To find out, the team collected HIV samples from patients whose virus had picked up mutations in the capsid gene during lenacapavir treatment. They rebuilt these mutant viruses in the lab, alongside dozens of hand-built variants carrying every combination of the suspect mutations, and put them through a battery of tests: how well did lenacapavir still work against them, and how well could the mutant virus actually reproduce without any drug around at all? They also used computer modelling to zoom into the capsid's drug-binding pocket at the atomic level, to see exactly how each mutation was jamming the lock.

One mutation, nicknamed M66I, turned out to be the virus's best move: it reshaped the binding pocket enough to make lenacapavir up to 1,000 times less effective. But it came at a brutal cost. Viruses carrying M66I alone could only replicate at 13-17% of the strength of ordinary HIV, a badly crippled competitor. The virus's next move was telling: in some patients, it layered on second and third mutations that clawed back some of that lost fitness, restoring replication to 30-45% of normal, enough, in a few real cases, for viral loads to rebound. Every other resistance route told a similar story of trade-offs; more resistance almost always meant a weaker virus, and the few mutations that dodged the drug cheaply were only mildly resistant to begin with.

Resistance comes at a cost

Relative replication capacity of HIV carrying lenacapavir resistance mutations.
Wild-type virus is normalised to 100%.

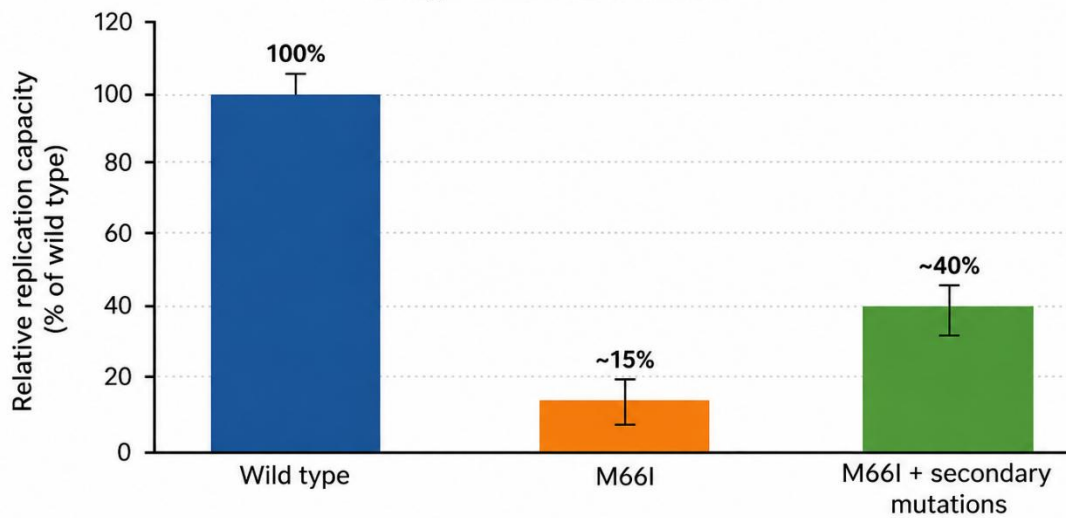


Figure 1. Relative replication capacity of HIV carrying lenacapavir resistance mutations. The M66I mutation greatly reduces viral fitness despite conferring high resistance. Additional compensatory mutations partially restore replication, but the virus remains substantially less fit than wild-type HIV.

This is a genuine arms race, but one where evolution has to pay its debts. HIV can pick a lock, but picking it seems to break the key it needs for its own survival, at least for now. The practical lesson from the paper is a familiar one in HIV medicine: never let lenacapavir fight alone. Paired with other active drugs, the virus never gets the room it needs to find, and then afford, its way around this remarkable new lock.