Lenacapavir plus two bNAbs: feasible, with some caveats

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Antiretroviral therapy (ART) has reached very high levels of efficacy, tolerability, and convenience.[1] Combining oral drugs in a single pill once daily is the current gold standard for ART. As HIV cure remains elusive, the simplification of therapy is desired for many people with HIV.[2] We know that a combination of at least two drugs is needed: monotherapy, even with potent and high-genetic barrier drugs such as boosted protease inhibitors or dolutegravir, has led to an increased risk of virological failure, with potential for class resistance mutations, particularly in the case of dolutegravir.[1] Generic dolutegravir-based regimens are currently used by more than 22 million people worldwide[3] and the risk of resistance so far is low but might increase in the future.[4]

Any information about new classes of medications with dose intervals greater than once a day attracts a lot of attention from physicians and people with HIV. In *The Lancet HIV*, Joseph J Eron and colleagues[5] report the results of a proof-of-concept, randomised, phase 1b study in adults with virologically suppressed HIV who had their oral therapy switched to 927 mg subcutaneous lenacapavir plus an oral loading dose given with two broadly neutralising antibodies (bNAbs): 30 mg/kg intravenous teropavimab, and 10 mg/kg or 30 mg/kg intravenous zinlirvimab. Participants resumed previous therapy by the end of week 26.

As the study is a phase 1 trial, the primary endpoint was safety. Although there were no serious adverse events, there were some important safety limitations of this treatment regimen. Injection-site reactions were reported in 17 of 20 participants. One participant had injection-site cellulitis, which required parenteral and oral antibiotic treatment. This adverse event is particularly worrisome for such a small group of people who received only a single dose of study drugs. It is also remarkable that eight participants developed treatment-emergent anti-drug antibodies (ADAs; four participants had ADAs to one of the baseline broadly neutralising antibodies [bNAbs] and four participants had ADAs to both bNAbs). The proportion of participants affected with ADAs after a single dose makes me suspect that repeated doses might affect almost all people given treatment. Although the potential long-term consequences derived from these emerging ADAs are unknown, it should be noted that the participant with virological failure had developed ADAs.

There are some other noteworthy limitations potentially affecting the implementation of this regimen. The sample included highly selected participants who had HIV RNA of less than 50 copies per mL for at least 18 months, with a CD4 count nadir of at least 350 cells per µL and a current CD4 count of at least 350 cells per µL, and who were on their first ART regimen for at least 2 years. Therefore, as the authors acknowledge, the results might not be generalisable to other people with HIV. In addition, this strategy would require baseline bNAbs phenotypic susceptibility testing on HIV DNA, which would need additional laboratory work and cost to be implemented. Less than 50% of potential candidates tested met the bNAb sensitivity criteria at baseline, thus substantially reducing the potential applicability of these drugs. Even with such a carefully justified and planned design, one of 20 participants had low-level virological failure (HIV RNA 155 copies per mL and the repeat test was 534 copies per mL; zinlirvimab 10mg/kg group) with unsuccessful genotypic and phenotypic amplification despite having their plasma concentration of lenacapavir, teropavimab, and zinlirvimab within the range of other participants of the same dose group and at levels predicted to be therapeutic. The fact that virological failure might appear despite having plasma concentrations of lenacapavir in the target range is one of the most unexpected facts of long-acting therapy with lenacapavir.[6] Long-acting regimens need drugs with high genetic barriers to resistance, which does not seem to be the case with these bNAbs and is also uncertain with lenacapavir.[7]

This proof-of-concept strategy demonstrates for the first time that it is feasible to maintain HIV suppression for 26 weeks with a single administration of a complete long-acting antiretroviral regimen, with some caveats. Although it might not be the ideal definitive long-acting regimen, the regimen used in this study paves the way for advancements in achieving more optimised regimens that allow doses to be spaced every several months without trade-offs of more cost, complexity, or toxicity with respect to the current standard of treatment.

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