Managing complex antiretroviral regimens

Westend61 via Getty Images

Published Online
February 25, 2026
https://doi.org/10.1016/
S0140-6736(26)00364-8

See Online/Articles
https://doi.org/10.1016/
S0140-6736(26)00307-7

The practice of switching antiretroviral therapy (ART) in people with HIV who have reached and maintained virological suppression is an important component of contemporary HIV care. Advances in ART pharmacology, tolerability, and the expanding availability of simplified, single-tablet regimens have shifted treatment goals beyond viral suppression alone towards long-term safety, durability, adherence optimisation, and improved quality of life.[1,2]

Most people with HIV who have been in care since the early days of ART have been treated with multiple regimens over the decades. Regimens during the 1990s and early 2000s were less potent and resulted in regimen failure, often associated with mutations conferring resistance to existing antiretroviral drugs. As such, many people with HIV today are on complex, multi-tablet ART regimens designed to cover the resistance-conferring mutations generated by previous regimens. Over the past decade, several new high-potency drugs from different ART classes have been developed that create the opportunity to simplify complex regimens to single-tablet, once-daily ART.[1,2]

In *The Lancet*, Chloe Orkin and colleagues evaluate the efficacy and safety of a novel single-tablet regimen, bictegravir–lenacapavir, versus continuing a complex, multi-tablet, albeit successful, regimen among people with HIV who have extensive ART experience.[3] In this randomised, open-label, phase 3 clinical trial, individuals on complex regimens were randomly assigned to either continue their current ART or switch to a single, daily oral bictegravir–lenacapavir (75 mg/50 mg) tablet. The primary endpoint, designed to establish whether bictegravir–lenacapavir was non-inferior to continuing the current successful regimen, was the proportion of participants with an HIV-1 RNA viral load of 50 copies per mL or higher at week 48 of therapy. During the first 9 months in 2024, 557 participants (100 [18%] were assigned female at birth, 97 [17%] were Black, and 122 [22%] were Hispanic or Latine) were randomly assigned and received at least one dose of treatment: 371 were assigned to bictegravir–lenacapavir and 186 were assigned to remain on their current, successful, complex, multi-drug regimen. At week 48, three (1%) of those receiving bictegravir–lenacapavir had an HIV-1 RNA viral load of 50 copies per mL or higher compared with two (1%) who had continued their current regimen (–0·3% difference; 95·002% CI –2·3 to 1·8), meeting the criterion of non-inferiority (4%). Six (2%) of those on bictegravir–lenacapavir discontinued treatment versus one (<1%) in the control group, although no significant difference in adverse events was reported and overall satisfaction was better in the bictegravir–lenacapavir group.

These results are similar to several other randomised switch studies performed over the past decade, which included adults with HIV-1 RNA viral loads below 50 copies per mL for at least 4 months on stable antiretroviral regimens, with no documented resistance mutations to the study regimens.[4–10] Each of these studies demonstrated non-inferiority of the study regimen versus control using the same criteria (proportion with HIV-1 RNA ≥50 copies per mL using a 4% non-inferiority threshold) as the bictegravir–lenacapavir study.

A major difference, however, is the liberal inclusion criteria used in the current study.[3] Mimicking real-world scenarios, where the majority of patients who are trying to maintain adherence with their complex, multi-tablet regimens are highly ART-experienced, older, have multiple comorbid conditions, and/or are experiencing some degree of kidney dysfunction, Orkin and colleagues' study evaluated participants with a median HIV treatment duration of 28 years (IQR 22–32) and a median age of 60 years (range 22–84), who were taking a median of three ART pills per day (range 2–11; 218 [39%] of 557 were taking ART medications twice daily), and had on average two or more concomitant medical conditions, including dyslipidaemia (377 [68%]), hypertension (280 [50%]), diabetes or hyperglycaemia (133 [24%]), and/or chronic kidney disease (78 [14%]). However, individuals with hepatitis B co-infection were excluded owing to the absence of a regimen component active against hepatitis B.

Figure 2 in Orkin and colleagues' paper depicts the vast diversity of the complex regimens participants were receiving upon entry to the trial.[3] Over three-quarters were on a protease inhibitor-containing regimen, the majority either paired with an integrase strand transfer inhibitor (INSTI) alone (166 [30%] of 557) or an INSTI along with dual nucleos(t)ide reverse transcriptase inhibitors (135 [24%]). The remainder

of study entry regimens were a smattering of three-drug and four-drug regimens, representative of drug combinations used in clinics worldwide. Taken together, Orkin and colleagues' study is unique among switch studies in the use of liberal entry criteria for age, duration of HIV treatment history, diversity of regimens at baseline, and comorbid conditions.

A weakness of the study is the number of study sites used to conduct the study across the globe. The study used 90 sites across six continents to screen 729 potential participants, ultimately enrolling 561 for randomisation. Most study participants were from North America (269 [48%] of 561), Europe (185 [33%]), and Australia (37 [7%]), leaving only 70 (12%) participants coming from Asia, Africa, and South America. The effort, time, and cost required to establish a study site, including protocol review, approval for research involving humans, site training, and site monitoring, can be prohibitive for both the site and the sponsor. From a scientific perspective, however, concerns are raised regarding consistency of implementation and study protocol compliance when only one or two participants are enrolled at a single study site, not to mention inequity at the site when only a few participants are enrolled while others are excluded owing to insufficient capacity of the trial. Although the sponsor tried to make the study more generalisable by attempting to include participants from sub-Saharan Africa, only six were enrolled in the study; a separate study is required to address the effectiveness of bictegravir–lenacapavir in areas with more limited resources and higher concentrations of individuals with HIV.

Overall, however, this study represents a major advance in expanding the options of ART for highly treatment-experienced people with HIV who are struggling to remain on complex regimens. In the case of managing individuals who are highly ART-experienced, the majority would rather switch to a simpler single-tablet ART regimen than continue to fight the battle of adhering to complex, multidrug regimens to maintain their HIV treatment success. Based on the results of Orkin and colleagues' study, many people with HIV and their medical providers could now switch to a new oral single-tablet regimen. Further research comparing oral bictegravir–lenacapavir with other more convenient treatment options, such as long-acting, injectable ART agents, is warranted.

I am Vice Chair of the Data Safety Monitoring Board for the RECOVER Study (for which the US National Institutes of Health and RTI International are the sponsor and administrator, respectively) and Member and Chair of the Board of Directors of the International Antiviral Society-USA (IAS-USA), a not-for-profit organisation whose mission is the provision of advanced, well balanced medical education.

Michael S Saag
msaag@uabmc.edu

Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, AL 35294, USA

1 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf (accessed Feb 16, 2026).

2 Gandhi RT, Landovitz RJ, Sax PE, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2024 recommendations of the International Antiviral Society–USA Panel. *JAMA* 2025; **333:** 609–28.

3 Orkin C, Ruane PJ, Hedgcock M, et al. Switch to single-tablet bictegravir–lenacapavir from a complex HIV regimen (ARTISTRY-1): a randomised, open-label, phase 3 clinical trial. *Lancet* 2026; published online Feb 25. https://doi.org/10.1016/S0140-6736(26)00307-7.

4 Llibre JM, Hung CC, Brinson C, et al. Phase III SWORD 1 & 2: switch to dolutegravir plus rilpivirine maintains virologic suppression. *Lancet* 2018; **391:** 839–49.

5 van Wyk J, Ajana F, Bisshop F, et al. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose 2-drug regimen vs continuing a tenofovir alafenamide-based 3- or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus type 1: phase 3, randomized, noninferiority TANGO study. *Clin Infect Dis* 2020; **71:** 1920–29.

6 Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet* 2021; **396:** 1994–2005.

7 Sax PE, Rockstroh JK, Luetkemeyer AF, et al, and the GS-US-380–4030 Investigators. Switching to bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with human immunodeficiency virus. *Clin Infect Dis* 2021; **73:** e485–93.

8 Daar ES, DeJesus E, Ruane P, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2018; **5:** e347–56.

9 Colson AE, Mills AM, Ramgopal MN, et al. Switch to fixed-dose doravirine (100 mg) and islatravir (0·25 mg) once daily in virologically suppressed adults with HIV-1 on bictegravir, emtricitabine, and tenofovir alafenamide: 48-week results of a phase 3, multicentre, randomised, controlled, double-blind, non-inferiority trial. *Lancet* 2026; **407:** 611–21.

10 Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. *N Engl J Med* 2020; **382:** 1124–35.