# Rukobia Still Effective at Five Years for People With Highly Resistant HIV

The HIV attachment inhibitor led to sustained viral suppression and CD4 cell gains in people with extensive prior treatment.

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Rukobia (fostemsavir) plus an optimized background regimen maintained durable viral suppression and CD4 T-cell recovery at five years in heavily treated people with multidrug-resistant HIV, according to recent studies. What's more, the regimen led to improvements in biomarkers associated with comorbidities and mortality.

Rukobia is a novel type of entry inhibitor that prevents HIV from attaching to host cells. It binds to the gp120 envelope protein on HIV's outer surface, preventing the virus from attaching to CD4 receptors to gain entry into cells.

The Food and Drug Administration approved Rukobia in July 2020 for people with highly resistant HIV who have tried several previous antiretroviral medications and whose current regimen is not working due to resistance, intolerance or safety issues. An estimated 6% of HIV-positive adults fall into this category, including some long-term survivors who used less effective regimens early in the epidemic, leaving them with few treatment options.

The approval was based on findings from the international Phase III BRIGHTE trial (NCT02362503), which evaluated Rukobia for highly treatment-experienced people with multidrug-resistant HIV who were unable to build an effective regimen using existing drugs. Initially, 272 participants were randomly assigned to add either twice-daily Rukobia or a placebo to their existing regimen for eight days. Then everyone received Rukobia plus an optimized background regimen, which had to include at least one fully active drug. In addition, a nonrandomized cohort of 99 people with no remaining fully active approved drugs could include other experimental agents in their background regimen.

About three quarters of the study participants were men, most were white and around half were over age 50, reflecting the population with highly resistant HIV. Nearly a third had a high viral load at baseline. Median CD4 counts were low, indicating advanced immune suppression; 30% had a fewer than 20 cells.

As previously reported, 54% of Rukobia recipients in the randomized cohort and 38% of those in the nonrandomized cohort had an undetectable viral load (below 40) at 48 weeks. A year later, the proportion with viral suppression rose to 60% in the randomized cohort and remained stable, at 37%, in the in the nonrandomized cohort at 96 weeks. At that point, participants had gained an average of 205 CD4 cells in the randomized cohort and 119 cells in the nonrandomized cohort.

As described in Infectious Diseases and Therapy, Judith Aberg, MD, of Mount Sinai Health System, and colleagues evaluated the long-term safety and efficacy of Rukobia at 240 weeks. Josep Llibre, MD, PhD, of Hospital Universitari Germans Trias I Pujol in Barcelona, and colleagues also presented study results at the recent European AIDS Conference (EACS 2023).

Overall, viral suppression rates were "generally stable," according to the researchers. At five years, 45% in the randomized cohort and 22% in the nonrandomized cohort had a viral load below 40 in an intention-to-treat analysis. In an analysis that excluded participants who discontinued Rukobia or had missing data (some due to missed study visits during the COVID-19 pandemic), 82% and 66%, respectively, had an undetectable viral load.

Most cases of virological treatment failure occurred during the first two years. Between 96 and 24 weeks, 6% of people in the randomized cohort and 4% in the nonrandomized cohort experienced new virological failure. Fewer than half of randomized participants and about two-thirds of nonrandomized participants had viral mutations associated with Rukobia resistance (primarily S375N or M426L), but five had decreased susceptibility without any known resistance mutations. Some people who developed resistance stayed on Rukobia and regained viral suppression without changing their regimen, perhaps thanks to improved adherence.

Mean CD4 cell gains at five years were 296 in the randomized cohort and 240 in the nonrandomized cohort, and CD4-to-CD8 cell ratios continued to increase. In fact, people with the greatest immune suppression at baseline saw the largest gains. At five years, 74% of people in the randomized cohort and 46% in the nonrandomized cohort who started with less than 50 CD4 cells had a count of 200 or more, putting them above the threshold for an AIDS diagnosis. The mean change from baseline was nearly as high in the nonrandomized cohort, which "suggests that the observed immunologic effects primarily reflect the action of fostemsavir rather than the optimized background regimen," the authors wrote. What's more, improvements in CD4 counts and CD4-to-CD8 ratios occurred even among participants without viral suppression, the researchers noted, suggesting that Rukobia might protect T cells by other mechanisms.

At IDWeek 2023, Alftan Dyson, PharmD, of ViiV Healthcare, presented additional data showing that Rukobio worked well across subgroups based on sex, age, race/ethnicity and geographic region. In the randomize cohort, the likelihood of viral suppression was similar in people with one or two fully active drugs in their background regimen, but those with a high baseline viral load had a lower response rate. All subgroups demonstrated "robust and continuous" increases in CD4 cell counts.

In another presentation at the EACS conference, Antonella Castagna, of Vita-Salute San Raffaele University in Milan, and colleagues described results of an exploratory biomarker analysis at 240

weeks. Participants treated with Rukobia plus an optimized background regimen showed improvements in biomarkers of coagulopathy (abnormal blood clotting) and inflammation associated with increased risk of non-AIDS comorbidities and mortality in people with HIV. Durable virological suppression “resulted in sustained improvement in immune activation and inflammation,” the researchers concluded, suggesting that Rukobia’s unique mechanism of action “may favorably impact the persistent inflammatory milieu of HIV.”

Rukobia was generally safe and well tolerated. The most common adverse reactions were nausea, fatigue and diarrhea. Discontinuations due to adverse events were uncommon and typically occurred within the first six months. At 240 weeks, 8% of participants had stopped treatment because of adverse events. Eleven people did so due to an abnormal heart rhythm (QTc prolongation), but there were no reported cases of symptomatic cardiovascular disease or death. Thirteen people experienced drug-related serious adverse events, including three with immune reconstitution inflammatory syndrome (IRIS). After the second year, there were no new AIDS-defining events among people whose CD4 count rose above 200. Over the entire study period, 35 people died; most had poor immune recovery with a CD4 count remaining below 200.

Six people taking Rukobia became pregnant during the study. Three gave birth to healthy babies, there were two pregnancy complications (intrauterine growth restriction and premature birth) and one had an elective abortion; no congenital abnormalities were observed. “Although additional data are needed, these results are reassuring for highly treatment-experienced women of childbearing potential who may benefit from fostemsavir treatment,” the researchers wrote.

In summary, the study authors concluded, Rukobia plus an optimized background regimen “demonstrated durable virologic and immunologic responses with no new safety concerns between weeks 96 and 240, supporting this regimen as a key therapeutic option for highly treatment-experienced people with multidrug-resistant HIV-1.”

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