ICAP Journal Club

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Article

Ombajo LA, Penner J, Nkuranga J, et al. **Second-Line Switch to Dolutegravir for Treatment of HIV Infection**. *N Engl J Med.* 2023;388(25):2349-2359.
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Study Summary

The Second-Line Switch to Dolutegravir trial was an open-label, randomized controlled, non-inferiority trial that evaluated the efficacy of switching adults who had achieved viral suppression on a second-line ritonavir-boosted protease inhibitor (PI) antiretroviral therapy (ART) regimen to a dolutegravir-based ART regimen without genotype information.

Study Setting

- Four HIV treatment sites in Kenya.

Methods

- Adults living with HIV were eligible to participate if they were ≥18 years of age, had been receiving second-line ART containing two nucleoside reverse-transcriptase inhibitors (NRTIs) and a ritonavir-boosted PI for at least 24 weeks, and had a viral load (VL) <50 copies/ml at least 12 weeks before enrollment and at the time of enrollment. Non-pregnant women of childbearing potential had to be using effective contraception.
- Key exclusion criteria were previous exposure to an integrase strand-transfer inhibitor (INSTI), pregnancy or breast-feeding, and baseline conditions that would result in a regimen change, such as advanced kidney or liver disease and grade 3 or 4 lipid abnormalities.
- Participants were randomly assigned (1:1) to switch to dolutegravir or to continue their ritonavir-boosted PI therapy. The baseline NRTI was maintained in both groups.
    - Dolutegravir was administered once daily in one of the following regimens: as a single 50-mg tablet, with a separate tablet of co-formulated zidovudine-lamivudine (at doses of 300 mg and 150 mg, respectively) administered twice daily; as a single co-formulated tablet of dolutegravir-lamivudine-tenofovir disoproxil fumarate (at doses of 50 mg, 300 mg, and 300 mg, respectively) administered once daily; or as a single co-formulated tablet of abacavir-dolutegravir-lamivudine (at doses of 600 mg, 50 mg, and 300 mg) administered once daily.
    - Ritonavir-boosted PI was administered in one of the following regimens: as co-formulated ritonavir-boosted lopinavir (at doses of 50 mg and 200 mg, respectively)

in two tablets administered twice daily; as co-formulated ritonavir-boosted atazanavir (at doses of 100 mg and 300 mg, respectively) in one tablet administered once daily, in combination with NRTIs as co-formulated zidovudine-lamivudine (at doses of 300 mg and 150 mg, respectively) in one tablet administered twice daily; as co-formulated tenofovir disoproxil fumarate-lamivudine (at doses of 300 mg and 300 mg, respectively) in one tablet administered once daily; or as co-formulated abacavir-lamivudine (at doses of 600 mg and 300 mg) in one tablet administered once daily.

- Visits were scheduled at weeks 4, 12, 24, 36, and 48. Adherence to therapy was assessed at each visit and adequate adherence was defined as taking at least 95% of tablets as assessed by pill counts.
- Pregnancy tests were done at each visit for women of childbearing potential. Women who became pregnant were withdrawn from the trial and followed up to document pregnancy outcomes.
- The CD4 count, fasting blood glucose and fasting lipid levels were measured at enrollment, 24 weeks and 48 weeks.
- VL was measured at weeks 4, 12, 24, and 48. Participants with a VL of ≥50 copies/ml received intensive counseling and underwent repeat testing.
- The primary end point was virologic failure at week 48, defined as two consecutive VL of ≥50 copies/ml. Genotypic resistance testing was performed in participants who had a VL >400 copies/ml.
- Secondary outcomes included treatment success, defined as a VL <50 copies/ml at 48 weeks; and safety outcomes, including clinical and laboratory adverse events, change in the fasting blood glucose level, change in fasting lipid variables, and change in body weight.
- The primary efficacy analysis was performed in the intention-to-treat exposed population, which included all the participants who underwent randomization and received at least one dose of the trial drug.
- The non-inferiority margin for the between-group difference in the percentage of participants who met the primary end point was 4%.
- A secondary efficacy analysis of treatment failure was performed using a VL threshold of ≥200 copies/ml and a noninferiority margin of −10%.
- The per-protocol population excluded participants who did not have VL values available at week 48 because of discontinuation of the trial drug for reasons other than lack of efficacy, enrollment violations, or who had any protocol violation that would be expected to affect the assessment of efficacy.
- The safety population included all the participants who received at least one dose of the trial drug.

<u>Study Population and Follow-up</u>

- From February to September 2020, 1,114 individuals were assessed for eligibility, and 795 underwent randomization, with 398 participants assigned to the dolutegravir group and 397 assigned to the ritonavir-boosted PI group.

- The baseline characteristics were balanced between the two trial groups. Participants had a median age of 46 years (range 19-74), 66.2% were female, and 100% were Black. They had a median CD4 of 423 cells/mm^3 (interquartile range [IQR] 306 to 589) and had been on a ritonavir-boosted PI regimen for a median of 5.4 years (IQR 3.2 to 7.7).
- Combination NRTIs included tenofovir disoproxil fumarate-lamivudine in 52.8% of participants, zidovudine-lamivudine in 42.7% and abacavir-lamivudine in 4.4%.
- The baseline ritonavir-boosted PI regimen was ritonavir-boosted atazanavir in 79.4% of participants and ritonavir-boosted lopinavir in 20.6%.
- Adherence was considered adequate in 95.2% of the participants (95.5% of the participants in the dolutegravir group and 94.9% of those in the ritonavir-boosted PI group).

Efficacy Outcomes

- In the intention-to-treat exposed population, protocol-defined virologic failure at 48 weeks occurred in 5.0% of participants in the dolutegravir group and in 5.1% in the ritonavir-boosted PI group (difference, −0.04%; 95% confidence interval [CI], −3.1 to 3.0), a result that met the non-inferiority criterion for the primary end point.
- The criterion for non-inferiority was also met in the per-protocol population and in the pre-specified secondary analysis of treatment failure that used a VL threshold of ≥200 copies/ml.
- In the analysis of treatment success, 90.4% of participants in the dolutegravir group and 91.9% in the ritonavir-boosted PI group had a VL of <50 copies/ml at 48 weeks (difference, −1.5%; 95% CI, −5.4 to 2.5).
- Virologic response was similar across subgroups, including groups defined according to sex, NRTI, and baseline ritonavir-boosted PI.
- In the dolutegravir group, 19 of the 20 participants with protocol-defined virologic failure had a VL <200 copies/ml and no sample amplified for genotypic resistance testing. In the ritonavir-boosted PI group, 3 of the 20 participants with protocol-defined virologic failure had successful amplification: 1 had no mutations, and 2 had NRTI and non-nucleoside reverse-transcriptase inhibitor resistance mutations without PI resistance mutations.

Safety Outcomes

- There were 64 grade 3 or 4 adverse events, 4 events that led to treatment discontinuation (1 in the dolutegravir group and 3 in the ritonavir-boosted PI group), 16 serious adverse events, and 6 deaths; none of the deaths were considered to be drug-related.
- The distribution of adverse events was balanced between the two groups.
- The change from baseline in the total cholesterol level was −6.8% in the dolutegravir group and −1.4% in the ritonavir-boosted PI group (p<0.001).
- The change in the fasting blood glucose level was −9.1% in the dolutegravir group and −11.1% in the ritonavir-boosted PI group; the median body-weight gain was 1.5 kg (IQR, −1.0 to 4.0) in the dolutegravir group and 1.0 kg (IQR, −1.5 to 3.0) in the ritonavir-boosted PI group, with increases in body mass index of 2.1% and 1.3%, respectively (p=0.02).

- Eight participants (5 in the dolutegravir group and 3 in the ritonavir-boosted PI group) were withdrawn from the trial because of pregnancy. There were 2 pregnancy losses in the first trimester, 1 in each group. Six pregnancies ended with uncomplicated deliveries and live births at term with no congenital malformations.

Critical Analysis

This open-label, randomized controlled, non-inferiority trial found that switching to a dolutegravir-based regimen from a ritonavir-boosted PI-based regimen without genotype knowledge was non-inferior to continuation of the ritonavir-boosted PI-based regimen as second-line ART in adults with viral suppression. Regimen adherence and safety profiles were similar between the two groups.

The following points should be considered when interpreting the study findings:

- Genotype results suggest that treatment failure among trial participants was due to lack of adherence as opposed to resistance, however, the trial utilized strict VL criteria with a cutoff of 50 copies/ml. These findings may not be generalizable to country programs that utilize a VL cutoff of ≥1000 copies/ml. Provision of enhanced adherence counseling to all participants with a detectable VL is consistent with World Health Organization recommendations and allowed individuals at risk for treatment failure and possible development of resistance mutations to be identified early and supported to achieve adherence and viral suppression.
- The trial did not include children or adolescents, and only 13.9% of participants were <35 years of age, which limits the generalizability of these findings in younger age groups.
- Only INSTI-naïve participants were enrolled in the trial; however, with dolutegravir now part of first-line regimens in most countries, this population is expected to decrease in size.

Implications

This open-label, randomized controlled, non-inferiority trial demonstrated that adults who had achieved viral suppression on second-line ART with a ritonavir-boosted PI-based regimen could be safely switched to a dolutegravir-based regimen without genotype information. Dolutegravir-based regimens have many benefits, including a favorable side effect profile, lower pill burden, lower risk of drug-drug interactions and lower costs than PI-based regimens. This trial contributes to the growing body of evidence about the efficacy of dolutegravir-based regimens as second-line ART and supports switching of second-line regimens in settings without access to genotype testing.

This article synopsis was written by Dr. Cassia Wells. Share your thoughts on this article or suggest an article for Journal Club by emailing her at caw2208@columbia.edu.