

ICAP Journal Club

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Article

Paton NI, Musaazi J, Kityo C, et al. **Dolutegravir or Darunavir in Combination with Zidovudine or Tenofovir to Treat HIV.** *N Engl J Med.* 2021;385(4):330-341.

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Study Summary

The Nucleosides and Darunavir/Dolutegravir in Africa (NADIA) Trial is a multicenter, two-by-two factorial, randomized, open-label, noninferiority trial comparing dolutegravir with darunavir, and comparing tenofovir with zidovudine as second-line antiretroviral therapy (ART) in people living with HIV in whom a first-line nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based regimen has failed.

Study Setting

- Seven sites in Uganda, Kenya, and Zimbabwe.

Methods

- Eligible participants were ≥ 12 years of age; received tenofovir, lamivudine (or emtricitabine), and an NNRTI for at least 6 months continuously before screening; had missed ≤ 3 days of treatment in the prior month; and had a viral load (VL) ≥ 1000 copies/ml within the prior 6 months or met that VL threshold on two tests performed during screening.
- Participants were excluded if they had previously been on protease or integrase inhibitors, were pregnant, had severe hepatic impairment, or had an estimated glomerular filtration rate (eGFR) of < 50 ml/min.
- Participants were randomly assigned (1:1:1:1 ratio, following the two-by-two factorial design) to a regimen containing either dolutegravir (50 mg) once daily or ritonavir-boosted darunavir (800 mg of darunavir plus 100 mg of ritonavir) once daily, given in combination with either tenofovir (300 mg) plus lamivudine (300 mg) once daily or zidovudine (300 mg) plus lamivudine (150 mg) twice daily.
- Randomization was stratified according to site and VL at screening ($< 100,000$ copies/ml or $\geq 100,000$ copies/ml).
- The randomly assigned nucleoside reverse-transcriptase inhibitors (NRTIs) were given as a fixed-dose combination pill; other drugs were given as separate pills.

- Participants with tuberculosis took dolutegravir twice daily or rifabutin-based tuberculosis treatment with darunavir–ritonavir, and participants in the zidovudine group who had hepatitis B coinfection had tenofovir added to their regimen.
- Visits were scheduled at weeks 4, 8, 12, 24, 36, and 48 and were mostly nurse-led. Adherence and adverse events were assessed at each visit.
- A complete blood count was obtained and alanine aminotransferase and creatinine levels were measured at weeks 12 and 48, and a CD4 cell count was obtained at weeks 24 and 48.
- VL was measured in samples obtained at week 12 (stored for later batched testing) and at weeks 24 and 48 (results returned to the clinician).
- Participants with a VL of ≥ 1000 copies/ml received intensive adherence counseling, and VL was repeated after 12 weeks; if the VL was confirmed to be ≥ 1000 copies/ml, the participant underwent evaluation for a switch to third-line ART.
- Genotypic resistance testing was performed on a plasma sample stored at baseline and at the time of a confirmed VL rebound of ≥ 1000 copies/ml.
- The primary outcome for both factorial comparisons was a VL of < 400 copies/ml at week 48.
- Secondary outcomes included VL < 1000 copies/ml at week 48, confirmed VL rebound (≥ 1000 copies/ml) by week 48, and confirmed VL rebound with at least one major mutation conferring resistance to dolutegravir or darunavir.
- Analysis of the primary outcome was performed in the intention-to-treat population and the non-inferiority margin was set at -12 percentage points.

Study Population and Follow-up

- Between July and December 2019, 783 people were screened, and 464 were enrolled into the study, with 235 assigned to receive dolutegravir, 229 assigned to receive boosted darunavir, 233 assigned to receive tenofovir plus lamivudine, and 231 assigned to receive zidovudine plus lamivudine.
- Five participants died and one was lost to follow-up before week 48.
- Participants received their assigned regimen for 96% of follow-up time, attended more than 99% of scheduled visits, and reported complete adherence at 80% of visits.
- Overall, 58.5% of the participants had viral mutations that were associated with intermediate- or high-level resistance to tenofovir at baseline; 57.8% of those who were randomly assigned to the tenofovir group had no NRTIs that were predicted to have activity in their prescribed regimen.
- Participant characteristics were balanced across the groups and overall 60.8% of participants were female, 75.6% were born in Uganda, and the median age was 34 years (interquartile range [IQR] 28-41).
- At baseline, participants had received first-line ART for a median of 3.7 years (IQR 1.6-6.2), median CD4 cell count was 194 cells/mm³ (IQR 68-367) and median VL was 4.4 log₁₀ copies/ml (IQR 3.9-5.1).

Primary Outcome

- A VL of <400 copies/ml was found in 212 participants (90.2%) in the dolutegravir group and in 210 (91.7%) in the darunavir group (difference, -1.5 %; 95% confidence interval [CI], -6.7 to 3.7), which met the pre-specified noninferiority criterion.
- No interaction was detected between the zidovudine-tenofovir and darunavir-dolutegravir randomization factors for the primary outcome (P = 0.99).
- A VL of <400 copies/ml was found in 215 participants (92.3%) in the tenofovir group and in 207 participants (89.6%) in the zidovudine group (difference, 2.7%; 95% CI, -2.6 to 7.9), which met the pre-specified noninferiority criterion.
- More than 90% of the participants who were taking either dolutegravir or darunavir and had no NRTIs that were predicted to have activity had a VL of <400 copies/ml at 48 weeks.

Secondary Outcomes

- Results were consistent with VL thresholds of 1000 copies/ml (dolutegravir 92.3% vs. darunavir 93.0%; tenofovir 94% vs. zidovudine 91.3%) and 50 copies/ml (dolutegravir 80.9% vs. darunavir 79.5%; tenofovir 80.7% vs. zidovudine 79.7%).
- Confirmed virologic rebound occurred in 14 (6.0%) participants in the dolutegravir group and 13 (5.7%) participants in the darunavir group. Dolutegravir resistance-associated viral mutations were detected in four participants in the dolutegravir group (conferring high-level resistance in three and intermediate-level resistance in one); no darunavir resistance-associated mutations were detected in the darunavir group.
- Confirmed virologic rebound occurred in 11 (4.7%) participants in the tenofovir group and in 16 (6.9%) participants in the zidovudine group.

Safety Outcomes

- In total, 30 grade 3 or 4 adverse events, 2 events that led to drug cessation (both events were anemia, leading to discontinuation of zidovudine), 22 serious adverse events, 5 deaths and 4 new WHO stage 4 events (all cryptococcal meningitis) occurred, with a balanced distribution between the groups in each factorial comparison.
- Two participants (both taking tenofovir and darunavir) had an eGFR of <60 ml/min and six participants (four of whom were taking zidovudine) had a hemoglobin level <9 g/dL.
- Changes in body-mass index and the incidence of obesity (25 cases, all in female participants) were similar in the two groups in each factorial comparison.

Critical Analysis

This multicenter, two-by-two factorial, randomized, open-label, noninferiority trial found that dolutegravir with two NRTIs was effective and non-inferior to ritonavir-boosted darunavir with two NRTIs for second-line therapy, even in those with extensive NRTI resistance mutations. The study also showed that tenofovir with lamivudine was non-inferior to zidovudine with lamivudine in second-line therapy.

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

- Treatment was delivered using a public health approach, with nurse-led care, an emphasis on adherence counseling, infrequent VL and safety monitoring, and without baseline genotypic resistance testing to guide the selection of NRTIs. This design makes the findings more generalizable in real-world, resource-limited settings.
- Four cases of intermediate- or high-level dolutegravir resistance within 48 weeks were found, with no similar cases in the darunavir group. However, integrase resistance testing is not widely available in real-world settings, suggesting that surveillance for emerging dolutegravir resistance after large-scale programmatic treatment switches may be warranted.
- This was an open-label trial, therefore participants and clinicians were not blind to the assigned regimens. However, the use of laboratory-based outcomes helped to reduce the likelihood of substantial bias.
- The findings suggest a limited relationship between predicted NRTI activity and outcomes, whether NRTIs are combined with dolutegravir or boosted darunavir. The mechanism for this is unclear, but does highlight the limitations of predictive algorithms.

Implications

The multicenter, two-by-two factorial, randomized, open-label, noninferiority NADIA Trial found that a second-line ART regimen containing dolutegravir with two NRTIs was effective and non-inferior to ritonavir-boosted darunavir with two NRTIs, even in those with extensive NRTI resistance mutations. This supports the World Health Organization's (WHO) public health approach of recommending broad use of dolutegravir-based regimens, even in settings where NRTI resistance mutations are common and resistance data are not available at the time of switching.¹ The study also found that tenofovir with lamivudine was non-inferior to zidovudine with lamivudine as second-line therapy. The WHO recommends that those taking tenofovir-based first-line therapy switch to zidovudine for second-line therapy. These findings suggest that the WHO guidelines could be simplified to recommend maintaining tenofovir and lamivudine at the time of a switch to second-line treatment, which may also be preferable for clients as zidovudine is a twice-daily medication.

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

References

1. World Health Organization. Update of Recommendations on First- and Second-line Antiretroviral Regimens. Geneva: July 2019. Available at: <https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf>