ICAP Journal Club

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Article

Venter WDF, Moorhouse M, Sokhela S, et al. **Dolutegravir plus two different prodrugs of tenofovir to treat HIV**. *N Engl J Med* 2019;381:803-815.
https://www.nejm.org/doi/full/10.1056/NEJMoa1902824

Study Summary

The ADVANCE trial was an open-label, non-inferiority trial that compared the efficacy and safety of three first-line antiretroviral regimens in HIV-infected people initiating antiretroviral therapy (ART).

Study Setting

- Health care settings in inner-city Johannesburg, South Africa.

Methods

- Individuals were eligible to participate in the study if they were ≥12 years of age, weighed ≥40 kilograms, had a viral load (VL) ≥500 copies/milliliter, and a creatinine clearance of >60 milliliter/minute in participants ≥19 years old or >80 milliliter/minute if <19 years old.
- Individuals were excluded from the study if they had been on any ART for >30 days, had received any ART within the past 6 months, were pregnant, or on current treatment for tuberculosis (TB).
- The trial drugs were tenofovir alafenamide fumarate (TAF) 25 mg, coformulated with emtricitabine (FTC) 200 mg; tenofovir disoproxil fumarate (TDF) 300 mg, coformulated with FTC; dolutegravir (DTG) 50 mg; and coformulated TDF–FTC plus efavirenz (EFV) 600 mg.
- Eligible participants were randomly assigned (1:1:1) to receive TAF–FTC–DTG, as two tablets daily (TAF-based group); TDF–FTC–DTG, as two tablets daily (TDF-based group); or TDF–FTC–EFV as a single tablet daily (standard-care group).
- The primary end point was the percentage of participants with VL <50 copies/milliliter at week 48.
- Secondary end points included side-effect profile and safety, including findings on physical examination, laboratory analyses, and dual-energy x-ray absorptiometry (DXA) scans.
- Data were collected from symptom screening, vital signs measurement, symptom-directed physical examination, laboratory assessments, and multiple questionnaires, including a sleep questionnaire.
- Trial visits occurred at screening, enrollment, week 4, week 12, and then every 12 weeks until week 96. This paper reports on week 48 results.
- Efficacy calculations assumed a noninferiority margin of −10 percentage points.

Study Population and Follow-up

- A total of 1053 participants underwent randomization between February 2017 and May 2018, with 351 assigned to each group.
- The mean age of participants was 32 years (range, 13 to 62); 59% were female, >99% were black, and 62% reported South Africa as their country of origin.
- The mean CD4 count at baseline was 337 cells/cubic millimeter, and 78% of participants had a baseline VL <100,000 copies/milliliter.
- By week 48, the number of participants who had discontinued treatment or who had missing data was 41 (12%) in the TAF-based group, 39 (11%) in the TDF-based group, and 55 (16%) in the standard-care group.

Primary Outcome

- In the intention-to-treat analysis, the percentage of participants with a VL <50 copies/milliliter at 48 weeks was 84% in the TAF-based group, 85% in the TDF-based group, and 79% in the standard-care group. Both DTG-containing regimens showed noninferior efficacy to the standard-care regimen.
- In the per-protocol analysis, the percentage of participants with VL <50 copies/milliliter was similar across the groups (96% in the TAF-based group, 95% in the TDF-based group, and 96% in the standard-care group).
- The time to viral suppression was longer in the standard-care group than in the other two groups, with a VL <1000 copies/milliliter at 4 weeks achieved in 90% of participants in the standard-care group, 98% in the TAF-based group and 97% in the TDF-based group. Similar viral suppression was seen across the groups by 24 weeks at a level of <50 copies per milliliter.

Secondary Outcomes

- There were eight EFV-linked discontinuations for toxicity: five with liver dysfunction, two with rash, and one with neuropsychiatric manifestations.
- The only major between-group difference in clinical and laboratory grade 3 or 4 events was a higher percentage of participants in the standard-care group having weight loss, dizziness, or an elevated level of γ-glutamyltransferase than in the other two groups.
- At week 48, absolute weight gain and the percentage of participants in whom obesity emerged during treatment were highest in the TAF-based group (6 kg, 14% new obesity), followed by the TDF-based group (3 kg, 7% new obesity), and lowest in the standard-care group (1 kg, 6% new obesity). Weight gain was significantly higher in female participants than male participants across all three groups, with no clear plateau observed in the increase.
- The TDF-containing regimens had a greater reduction in lumbar and hip bone density and a minor reduction in creatinine clearance compared to the TAF-based regimen.
- Sleep quantity and quality changed little over time, with no significant difference according to group. There were slightly more reported cases of grade 2-4 insomnia in the TAF-based group (n=6) than in the other groups (n=2 in TDF-based group, n=1 in standard-care group) but no discontinuations of the trial regimen due to insomnia.

Critical Analysis

This open-label, non-inferiority trial found that treatment with DTG combined with either TAF-FTC or TDF-FTC was noninferior to the standard-care, EFV-based ART regimen for achieving

viral suppression at 48 weeks. The standard-care group had more discontinuations and longer time to viral suppression than the other two groups, however there was significantly more weight gain with the DTG-containing regimens, especially in combination with TAF and among women.

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

- The trial was conducted in a single city, limiting generalizability to other settings. However, it did include participants from other countries in the region, most commonly Zimbabwe.
- Other limitations of the study included the open-label design and that the trial regimens had different pill quantities, which may have influenced adherence.
- The weight gain observed is unlikely to be simply a "return to health" effect, because viral suppression, CD4 recovery, and clinical events were similar across the groups.
- Participants receiving the TAF-based regimen in whom tuberculosis developed were switched to a TDF-based regimen. Therefore, interactions between TAF and rifampin were not evaluated in this study.
- Only 14 participants in the study were younger than 19 years of age, therefore further research is required to evaluate these regimens with adolescent populations.

Implications

The ADVANCE trial found that treatment with DTG, combined with FTC and either TDF or TAF, showed noninferior efficacy compared to treatment with an EFV-based regimen, with fewer treatment discontinuations and more rapid viral suppression. However there was significantly more weight gain with the DTG-containing regimens, especially when combined with TAF. These results support the current transition to regimens containing DTG and TDF as first-line therapy, but also suggest practitioners should be mindful of the potential for weight gain and associated comorbidities. Further evidence is needed on the safety of TAF in certain subpopulations, such as pregnant women and those receiving TB treatment, and its advantages related to bone density and renal function must be evaluated against the risks of weight gain.

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.