

ICAP Journal Club

ICAP's Journal Club is designed to inform ICAP staff and colleagues of the latest scientific literature by providing a succinct summary and critical analysis of important studies, and by discussing the implications of the research on clinical work.

Article

Turkova A, White E, Mujuru HA, et al. **Dolutegravir as first- or second-line treatment for HIV-1 infection in children.** *N Engl J Med.* 2021;385(27):2531-2543.

<https://www.nejm.org/doi/full/10.1056/NEJMoa2108793>

Study Summary

The ODYSSEY trial was an open-label, randomized, non-inferiority trial that compared the efficacy and safety of antiretroviral therapy (ART) based on dolutegravir (DTG) with standard care (non-DTG-based ART) in children and adolescents starting first-line (ODYSSEY A) or second-line (ODYSSEY B) ART.

Study Setting

- Study sites in Uganda, Zimbabwe, South Africa, Thailand, and Europe.

Methods

- Children and adolescents (age, ≥ 4 weeks to < 18 years) with HIV-1 infection who weighed ≥ 14 kg were recruited to participate. The main exclusion criteria were clinically significant liver disease, pregnancy or breastfeeding, and previous exposure to an integrase strand-transfer inhibitor (INSTI) for more than 2 weeks.
- Participants enrolled in the ODYSSEY B cohort also had to have a HIV-1 RNA viral load (VL) ≥ 500 copies/ml within the 4 weeks before or at screening.
- Participants were randomly assigned (1:1) to receive either DTG plus two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) (DTG group), or standard care using a non-nucleoside reverse-transcriptase inhibitor (NNRTI), boosted protease inhibitor (PI), or non-DTG integrase inhibitor plus two NRTIs.
- For the ODYSSEY B cohort, their second-line ART regimen included a new third agent and at least one NRTI with preserved activity on the basis of resistance tests or assumed from treatment history.
- The choice of NRTIs among abacavir, tenofovir, or zidovudine was made according to World Health Organization (WHO) or national guidelines.

- Randomization was stratified according to trial cohort (ODYSSEY A or B), routine availability of resistance tests (available or unavailable), intended standard care (boosted PI or other third agent), and intended NRTI backbone therapy.
- Participants were seen at screening, at enrollment, at weeks 4 and 12, and then every 12 weeks at visits in which height, weight, HIV disease stage, adverse events, and adherence were assessed. CD4, CD8, biochemical, and hematologic tests were performed at baseline, at weeks 4 and 24, and then every 24 weeks. Lipid levels were measured at baseline and every 48 weeks thereafter.
- Plasma samples for retrospective VL testing were obtained and stored at baseline, at weeks 4 and 12, and then every 12 weeks. Real-time VL testing was done according to local practice.
- The primary endpoint was treatment failure by 96 weeks, defined as the first occurrence of any of the following:
 - A decrease of $<1 \log_{10}$ in the VL at week 24 (or VL ≥ 50 copies/ml if the VL was <500 copies/ml at baseline) and a switch to second- or third-line ART for treatment failure;
 - Virologic failure, defined as two consecutive VL results of ≥ 400 copies/ml, the first occurring at or after week 36;
 - A new or recurrent WHO stage 4 or severe WHO stage 3 event;
 - Death from any cause.
- Participants who had a virologic endpoint event were retrospectively tested for post-treatment failure resistance.
- Secondary endpoints included change in total cholesterol level; VL <50 copies/ml or <400 copies/ml; change in the CD4 count and CD4 lymphocyte percentage; the proportion of participants in whom new resistance mutations developed; and the incidence of serious adverse events, new clinical and laboratory adverse events of grade 3 or 4, and adverse events of any grade leading to treatment modification.

Study Population and Follow-up

- Between September 2016 and June 2018, 707 eligible children and adolescents underwent randomization. A total of 350 participants were randomly assigned to receive DTG-based ART (154 in ODYSSEY A and 196 in ODYSSEY B) and 357 to receive standard care (157 in ODYSSEY A and 200 in ODYSSEY B).
- A total of 331 participants were enrolled in Uganda, 146 in Zimbabwe, 144 in South Africa, 61 in Thailand, and 25 in Europe.
- The baseline characteristics of the participants were similar in the treatment groups, with a median age of 12.2 years (range, 2.9 to 18.0) and median weight of 30.7 kg (range, 14.0 to 85.0). 49% of the participants were girls and 88% were Black African.
- In the standard-care group, 92% of the participants started efavirenz in the ODYSSEY A cohort, and 98% started a boosted PI in the ODYSSEY B cohort.

- NRTI backbone therapies were balanced across the groups; 65% of participants received abacavir and lamivudine, 23% received tenofovir disoproxil fumarate and lamivudine or tenofovir disoproxil fumarate and emtricitabine, 11% received zidovudine and lamivudine.
- The median follow-up was 142 weeks (interquartile range, 124 to 159) and 687 (97%) participants were seen at or after 96 weeks or had a primary endpoint event.

Primary Outcome

- A total of 47 participants had treatment failure by 96 weeks (estimated probability of 0.14) in the DTG group, as compared with 75 participants (estimated probability, 0.22) in the standard-care group (adjusted hazard ratio [aHR] 0.60; 95% confidence interval [CI], 0.42 to 0.86).
- Among participants who met the primary endpoint, 40 in the DTG group and 67 in the standard-care group had virologic treatment failure; 7 in the DTG group and 8 in the standard care group had new or recurrent WHO stage 4 or severe WHO stage 3 event or death.
- Treatment effects were similar in the ODYSSEY A and B cohorts ($P = 0.16$ for heterogeneity).
- In prespecified exploratory analyses, there was no evidence that the treatment effect differed according to sex, baseline age, weight, CD4 percentage, or VL.
- The difference between treatment groups was present by week 48 and sustained to week 144.

Secondary Outcomes

- At week 96, there was no significant difference between the groups in the percentage of participants with VL <400 copies/ml, VL <50 copies/ml, new or recurrent WHO stage 4 or severe WHO stage 3 events, or CD4 count.
- No participants in the DTG group of the ODYSSEY A cohort had a major drug-resistance mutation after treatment failure. Of 29 participants in the standard-care group who had virologic treatment failure and had a post-treatment failure resistance test available, 18 (62%) had NRTI-related mutations, 27 (93%) had NNRTI-related mutations, and none had PI-related mutations.
- Among participants in the ODYSSEY B cohort, 23 of 29 (79%) in the DTG group and 36 of 40 (90%) in the standard-care group had at least one major mutation after treatment failure. An INSTI-related mutation developed in 4 participants in the DTG group.
- Similar percentages of participants in each group had at least one serious adverse event (10% in the DTG group vs. 11% in the standard-care group; aHR 0.87; 95% CI, 0.55 to 1.36; $P = 0.53$). Five participants died (2 in the DTG group and 3 in the standard-care group).
- More participants had serious adverse events in the ODYSSEY A cohort (15% in the DTG group and 17% in the standard-care group) than in the ODYSSEY B cohort (6% and 7%, respectively).

- In the overall trial population, similar percentages of participants had one or more adverse events of grade 3 or higher (21% in the DTG group and 24% in the standard-care group; aHR 0.83; 95% CI, 0.61 to 1.13; P = 0.24).
- ART-modifying adverse events were less frequent in the DTG group than in the standard-care group (1% vs. 5%; aHR 0.29; 95% CI, 0.11 to 0.77; P = 0.01).
- The total cholesterol level was lower in the DTG group than in the standard-care group, with an estimated between group difference of -15 mg/dl (95% CI, -19 to -11 mg/dl; P<0.001) in the mean change from baseline at 96 weeks.
- Participants' body-mass index (BMI)-for-age z score increased more in the DTG group than in the standard-care group, with an estimated between-group difference in means of 0.13 (95% CI, 0.01 to 0.25) at 96 weeks.

Critical Analysis

The multi-national, open-label, randomized, non-inferiority ODYSSEY trial found evidence of superior efficacy by week 48 of DTG-based ART, as compared with standard care, in children and adolescents starting first-line and second-line ART for HIV-1 infection. DTG-based ART had a similar safety profile as standard care, with fewer adverse events leading to a change in ART regimen.

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

- The trial included pharmacokinetic sub-studies evaluating simplified administration of DTG and new dispersible 5-mg DTG tablets for use in children. Once these results were available, participants who were receiving DTG started receiving higher doses than what was initially approved. However, sensitivity analyses accounting for this transition found it had no impact on the primary outcome.
- Despite randomization, the average CD4 count was marginally higher and the VL marginally lower in the standard-care group than in the DTG group, both in the total trial population and in the ODYSSEY B cohort. However, analyses adjusting for baseline VL did not affect results.
- No antiviral resistance was observed in children and adolescents who started DTG-based first-line ART, which suggests a higher barrier to INSTI resistance and protection against NRTI resistance than with the first-line standard care regimens used. However, the occurrence of new INSTI resistance in 4 participants who received DTG-based second-line ART highlights the need for ongoing adherence support among children and adolescents starting second-line treatment.
- The weight gain seen in the DTG group was minimal compared to the standard-care group, but no participants received tenofovir alafenamide, which has been associated with weight gain in combination with DTG in adults¹.

Implications

The ODYSSEY trial demonstrated superior efficacy of DTG-based regimens for children and adolescents ≥ 14 kg as both first- and second-line ART. This supports the WHO recommendation of DTG-based ART as the preferred first- and second-line ART regimen in children with HIV-1 infection². A transition to DTG-based regimens for children promises to simplify treatment in children and improve HIV outcomes.

References

- 1) Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV*. 2020; 7(10): e666-e676.
- 2) World Health Organization. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland; 2019
<https://www.who.int/publications/i/item/WHO-CDS-HIV-19.15>

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.