The treatment optimisation ODYSSEY for children with HIV

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The ODYSSEY trial provided valuable evidence that dolutegravir-based antiretroviral therapy (ART) was more efficacious than standard of care (SOC) in children aged 4 weeks or older with HIV who started first-line or second-line ART.[1] Those findings reinforced WHO guidance to use dolutegravir as a preferred agent in initial and second-line paediatric HIV treatment and gave confidence to providers rolling out dolutegravir treatment for children with HIV globally. In *The Lancet HIV*, Ellen White and colleagues[2] report additional analyses of ODYSSEY data about virological outcomes, regimen composition, and drug resistance that offer reassuring insights into areas of remaining uncertainty around paediatric ART optimisation.

The traditional approach to selecting the nucleoside reverse transcriptase inhibitor (NRTI) backbone for second-line ART regimens has been to select NRTIs with the greatest expected antiviral activity based on testing for individual HIV drug resistance mutations or NRTI treatment history (or both). Since most adults received tenofovir disoproxil fumarate and either lamivudine or emtricitabine as initial therapy, this approach commonly resulted in second-line NRTI backbones composed of zidovudine (with lamivudine or emtricitabine), combined with a boosted protease inhibitor or integrase strand transfer inhibitor (INSTI). The need to use this so-called optimised NRTI backbone in adults—that included replacing tenofovir disoproxil fumarate with zidovudine, a drug with twice per day dosing, poor tolerability, greater long-term adverse effects, and absence of coformulation as a single pill, whole regimen with a boosted protease inhibitor or INSTI—was refuted by the results of NADIA and other trials.[3,4,5] In the NADIA trial, after unsuccessful treatment with a first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, second-line dolutegravir-based or darunavir-based regimens performed significantly better until 96 weeks when tenofovir disoproxil fumarate (with lamivudine or emtricitabine) was continued rather than switched to zidovudine—even when tenofovir disoproxil fumarate (and usually lamivudine or emtricitabine) drug resistance mutations were present.[3,4]

Although the results from NADIA were compelling for the management of adults with HIV, major questions remained about the applicability of these findings to children, most of whom receive abacavir rather than tenofovir disoproxil fumarate (unless weighing at least 30 kg, especially in low-income countries) in their initial treatment regimens. Would children requiring second-line ART who could not receive tenofovir disoproxil fumarate have better outcomes if they continued abacavir in their second-line regimen or if they switched to zidovudine? At enrolment to ODYSSEY B, most participants had been receiving NNRTI-based first-line ART (391 [96%] of 407), and only 18 (4%) participants had resistance data available to guide NRTI choice in second-line regimens. Participants were offered at least one NRTI with preserved activity (if available) based on treatment history or resistance tests (in the few for whom such results were available). This approach resulted in 376 (92%) starting a new NRTI in their second-line regimen, including 217 (53%) who received abacavir plus lamivudine, 103 (25%) received tenofovir disoproxil fumarate plus lamivudine or emtricitabine, and 83 (20%) received zidovudine plus lamivudine. In one of the most important findings among second-line participants starting dolutegravir, children starting tenofovir disoproxil fumarate had similar rates of virological failure compared with those starting abacavir (HR 1·19 [95% CI 0·50–2·83]; p=0·70), whereas those starting zidovudine had higher rates of virological failure compared with those starting abacavir (2·22 [1·01–4·88]; p=0·048). Furthermore, the time to virological failure in children receiving second-line dolutegravir and abacavir was similar in those with high-level baseline abacavir resistance and those with low-level or absent resistance (0·90 [0·23–3·61]; p=0·88), suggesting no effect of abacavir drug resistance mutations on virological outcome. Even when comparing those starting zidovudine without high-level zidovudine resistance to those starting abacavir with high-level abacavir resistance, the rate of virological failure was numerically—although not significantly—lower with abacavir (2·56 [0·70–9·31]; p=0·15). Taken together, these results suggest that children in need of second-line ART have better treatment outcomes continuing or starting abacavir rather than changing to zidovudine—even when resistance to abacavir is present and resistance to zidovudine is absent.

The current ODYSSEY report offers other valuable insights into the use of dolutegravir-based regimens in children. Virological suppression occurred earlier and virological failure rates were lower with dolutegravir regimens than with SOC regimens. In all four treatment groups, virological failure occurred at a viral load of at least 1000 copies per mL in at least 94% of participants, so definitions and laboratory platforms limited to that threshold will identify almost all virological failure in children. Most children (30 [59%] of 51) with virological failure starting dolutegravir resuppressed without changing their treatment regimen. Emergent drug resistance with first-line ART failure occurred less often with dolutegravir (estimated 1% [95% CI 0 to 2]) than with SOC (estimated 20% [14 to 26]), and there was no emergent dolutegravir resistance. These observations strengthen confidence in robust performance of dolutegravir as initial therapy, with adherence support in cases of virological failure. Virological failure rates were higher in second-line regimens than in initial regimens but dolutegravir based regimens still outperformed SOC regimens (197 [96%] participants received boosted protease inhibitor; virological failure by 96 weeks occurred in 33 [16%] of 202 in the dolutegravir group *vs* 43 [21%] of 205 in the SOC group). INSTI resistance was estimated to emerge in 17% (95% CI 3 to 31) of participants with virological failure, and in 3% (0 to 5) of all participants receiving second-line dolutegravir regimens. These findings are an important reminder that although uncommon, resistance to dolutegravir can occur. Four (80%) of the five participants with INSTI resistance were also taking zidovudine, a higher proportion than the 42 (20%) of second-line dolutegravir participants overall who were taking zidovudine, and similar to the observation in NADIA that most (four of five) high-level INSTI resistance occurred in adults taking zidovudine as part of their unsuccessful second-line dolutegravir regimen,[4] which is another sign that providers should avoid zidovudine in second-line dolutegravir regimens.

There are important limitations to these results from the ODYSSEY trial. This is a secondary analysis that makes non-randomised comparisons and often deals with small numbers in subgroups, and resistance testing was not available for all participants, which warrants caution before drawing overly confident conclusions.

Important questions remain in paediatric HIV treatment: although virological failure is usually not linked to dolutegravir resistance and dolutegravir emerges infrequently, it does occur. What is the duration of persistent viraemia or other criteria that merit consideration of dolutegravir drug resistance mutation testing? When dolutegravir resistance is detected in children with virological failure, what is the right approach to their management? When choosing dolutegravir-based or boosted protease inhibitor-based second-line regimens, regimen choice guided by individual drug resistance testing—compared with no resistance testing—made no difference in virological outcomes in a randomised trial in Tanzania.[6] Will dolutegravir drug resistance mutation testing be useful for determining which children should switch to a boosted protease inhibitor regimen? Perhaps other characteristics of antiretroviral drugs (eg, tolerabilty or intracellular pharmacokinetics) are more important than resistance mutations in predicting virological outcomes. These crucial questions remain unanswered. But in the meantime, ODYSSEY adds to our confidence in relying on dolutegravir for first-line and second-line ART in children and suggests that NRTI drug resistance mutation testing and zidovudine have no use in second-line dolutegravir regimens in children.

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