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The Odyssey trial, a journey for children

The Odyssey (**O**nce **d**aily DOLUTEGRAVIR in **y**oung people v**s** **s**tandard therap**y**) trial released data in 2021 of great relevance to children. The first participants were enrolled in September 2016 and the last visits were in April 2020. Planning began in 2013 with emerging information from adult studies on efficacy, high threshold for resistance, once daily dosing, ease of manufacture and minimal drug-drug interactions of concern. Odyssey was a randomised open-label trial comparing dolutegravir (DTG) to standard of care (SOC) in children and adolescents >4 weeks and <18y of age beginning either first-or second-line therapy. The trial was conducted in 3 African countries (South Africa, Zimbabwe and Uganda), Thailand and 4 European countries (U.K. Spain, Portugal and Germany), led by Prof Di Gibb through the PENTA (Paediatric European Network for Trials in AIDS)-ID network.

The main outcome was time to virological (confirmed viral load ≥400 HIV-1 RNA copies/mL or <1 log decline by week 24 with ART switch implemented for failure) or clinical failure (any new or recurrent WHO 3 or WHO 4 event) by 96 weeks. For entry to the second-line study, participants needed to have at least one nucleoside reverse transcriptase inhibitor to be used with predicted activity to that agent. 707 children were enrolled, median age was 12.2 (2.9 to 18) years, 49% were female, 27% were WHO 3 or 4 and 22% had CD4 cell counts <200 cells/µL. In the main trial outcome, DTG was superior to SOC for first-line therapy and equivalent to SOC for second-line therapy (Table).[1] There were no major safety issues and weight gain on DTG was not excessive.

Table. Main outcomes in Odyssey trial

	DTG	SOC	NRTI	Outcome
First-line therapy				
	N = 154	N = 157 (92% EFV)	ABC+3TC 78% TDF+3TC/FTC 22%	
Virological failure (N)	15 (10%)	34 (23%)		–12.5% (95% CI: –20.6 to –4.3); p=0.003
Second-line therapy				
	N = 96	N = 200 (LPV-r 72%) (ATZ-r 25%)	ABC+3TC 55% TDF+3TC/FTC 26%	
Virological failure (N)	32 (17%)	41 (21%)		–4.6% (95% CI: –11.8 to 2.7); p=0.22

NRTI – nucleoside reverse transcriptase inhibitor, EFV – efavirenz, ABC – abacavir, 3TC – lamivudine, TDF – tenofovir disoproxil fumarate; LPV-r – lopinavir-ritonavir; ATZ-r – atazanavir-ritonavir

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Antiretroviral resistance testing was done in children with virologic failure. In children on first-line therapy resistance was detected in 90% in the SOC arm and in none in the DTG arm. In children on second-line therapy resistance to integrase inhibitors developed in 4 participants on DTG.[2] An additional 85 children weighing <14 kg were enrolled in a separate cohort: 72 were randomised to either DTG or standard of care, the latter mainly LPV-r. Median age was 1.4 (IQR: 0.6 to 2) years. At 96 weeks, 76% of children in the DTG arm had viral load <50 copies/mL compared with 50% in standard-of-care, p=0.02.[3] Two generic DTG 10 mg dispersible tablets are tentatively approved by the US FDA, with approval still pending in South Africa. In summary, DTG is an extremely useful antiretroviral for children from 4 weeks of age and is a welcome addition for treatment.

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The role of abacavir in adults

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) - it is an analogue of guanosine. Abacavir is generally well tolerated but it may cause a life-threatening systemic hypersensitivity reaction. Rechallenge after a suspected hypersensitivity reaction should never be attempted as the reaction is often more severe on rechallenge. Abacavir hypersensitivity only occurs in people with HLA-B*507, which is rare in people of African descent. The Southern African HIV Clinicians Society ART guidelines recommend excluding HLA-B*507 “if testing is affordable and available” but also says that testing is “probably not indicated” in people of African descent.[1] AfA recommends excluding HLA-B*507 before prescribing abacavir in the private sector.

Abacavir is available in fixed dose formulations with lamivudine. Abacavir is widely used in children largely because formulations of tenofovir suitable for children are not available in South Africa. In adults abacavir is recommended if the estimated glomerular filtration rate (eGFR) is <50 mL/min at baseline or if this develops on a tenofovir based regimen in guidelines from the SA HIV Clinicians Society, National Department of Health, and AfA. Abacavir is the only NRTI that does not need dose adjustment in renal failure.

Some clinicians prescribe abacavir in second-line ART regimens after failure of first-line regimens that included tenofovir plus emtricitabine or lamivudine because they believe that changing NRTIs will be more effective against resistant virus. However, there is cross resistance between abacavir and tenofovir, both of which select for the K65R mutation. In addition, the M184V mutation that confers high level resistance to emtricitabine and lamivudine compromises abacavir but modestly enhances the efficacy of tenofovir. If both K65R and M184V resistance mutations are selected for in first-line ART tenofovir will be slightly more active than abacavir (Stanford scores of 50 and 60 for tenofovir and abacavir respectively) – this difference is probably not clinically significant.

AfA will not approve the use of abacavir in adults unless the eGFR is <50 mL/min or if tenofovir is not tolerated. Patients with established kidney disease and eGFR >50 mL/min should generally not be given tenofovir – these cases should be discussed with AfA.

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The question of TLD as second-line ART

Currently WHO and South African guidelines advise that when dolutegravir is used as a backbone in second-line ART in patients who have failed a non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing first-line regimen then at least one of the nucleoside reverse transcriptase inhibitors (NRTIs) should be changed. For example, if a patient failed tenofovir/lamivudine (or emtricitabine)/efavirenz first line then the second line should be zidovudine/lamivudine/dolutegravir (ALD).

However, the question has been asked whether it may be possible to simply switch the efavirenz to dolutegravir and maintain the same NRTI drugs in the regimen (note that emtricitabine and lamivudine have the same mechanism of action and the same mutation confers high-level resistance to both drugs; therefore, they are interchangeable). The rationale for thinking this may provide an effective second-line regimen is that dolutegravir is a potent drug with a high genetic barrier to resistance and that even when there is resistance to NRTIs they still contribute some activity in a regimen – this was learnt in protease inhibitor second-line trials such as EARNEST.[1]

This question has now been evaluated in two recently published studies: NADIA and ARTIST.

In the NADIA trial[2] patients (n=464) failing a first-line regimen of tenofovir, lamivudine (or emtricitabine) and an NNRTI were randomised to one of four second-line regimens: tenofovir/lamivudine/dolutegravir (TLD), ALD, tenofovir/lamivudine/darunavir/ritonavir, or zidovudine/lamivudine/darunavir/ritonavir. The combined dolutegravir-containing regimens were compared to the combined darunavir/ritonavir regimens and found to be non-inferior. Similarly, the combined tenofovir/lamivudine regimens were compared to the combined zidovudine/lamivudine regimens and found to be non-inferior. Virological suppression at 48 weeks was similar across all regimens: 89-93% of participants achieved a viral load < 400 copies/ml and 79-81% achieved a viral load < 50 copies/ml. Among patients who experienced viraemia on their second-line regimen and qualified for resistance testing, 3 on ALD developed dolutegravir resistance mutations, 1 on TLD developed dolutegravir resistance mutations, and no patients developed darunavir resistance mutations.

The ARTIST study[3] is a prospective study being conducted in Khayelitsha, Cape Town evaluating second-line TLD in patients who have failed a first-line regimen of tenofovir, lamivudine (or emtricitabine) and an NNRTI. Viral loads are regularly monitored. In the first 60 participants reported, at 24 weeks follow-up, 51/60 (85%) had a viral load < 50 copies/ml. A further 7 had a viral load between 50 and 1000 copies/ml. In patients who had viraemia and qualified for resistance testing no dolutegravir resistance has been detected.

Should we be using TLD as a second-line option based on this evidence? AfA does not currently recommend a change in our treatment guidelines for second-line based on this evidence. In the two trials combined, fewer than 200 patients have received TLD as second-line ART and follow-up has been relatively short (48 weeks in one study and 24 weeks in the other). There remains a concern that patients on second line TLD will be at risk for developing dolutegravir resistance. For example, cases of dolutegravir resistance have been described with TLD use in second-line in Malawi. Our view is that more patient data with longer follow-up is required before guideline changes to second-line TLD are considered. The D2EFT trial is ongoing and further participants are being enrolled in the ARTIST study.

However, given this new evidence, we will consider motivations for TLD use in second-line in individual patients where other options are poorly tolerated.

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