

Title: A step closer to optimal ART for all children

Authors: Intira Jeannie Collins and Anna Turkova

Affiliations: MRC Clinical Trials Unit at University College London

Corresponding author: IJ Collins, MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, University College London, London WC1V 6LJ, UK. **Email:** jeannie.collins@ucl.ac.uk

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Dolutegravir-based antiretroviral treatment (ART) is the WHO recommended first- and second-line treatments for children and adults with HIV¹. Tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD) is a once-daily, highly efficacious and safe fixed-dose combination, widely available as a low-cost generic formulation in low and-middle-income countries (LMICs) for adults and adolescents². However, there are currently no comparable fixed-dose combination for children. In The Lancet HIV, Brooks and colleagues from the IMPAACT 2019 study group report the results on the pharmacokinetics, safety and tolerability of dispersible and immediate-release abacavir/dolutegravir/lamivudine tablets for children weighing 6-40 kgs³.

The phase II study enrolled 57 children aged <12 years, across five weight bands from multiple settings, with children 6-<25kg receiving dispersible and ≥25kg immediate-release tablets. Brooks and colleagues confirmed the appropriate exposure for abacavir, dolutegravir and lamivudine in all weight bands. There were no drug-related grade 3 or 4 adverse events and no adverse events leading to treatment discontinuation by 24 weeks. All children who were virally suppressed at drug start remained suppressed <200 copies/mL through week 24. Two of the three ART-naïve children were virally suppressed by 24 weeks. The remaining child, who initiated treatment with high viral load >100,000copies/mL had a substantial reduction down to 450 copies/mL at 24 weeks. The study reported high levels of acceptability by caregivers/parents

and children, only 3 (5.3%) children discontinued treatment due to bitter taste of dispersible formulation or large size of the immediate-release tablet. The publication is timely and commendable. This will be the *only* fixed-dose combination providing a complete and WHO-recommended regimen for children in LMICs weighing ≥ 6 kg, as TLD is not recommended until children reach 30kg due to tenofovir-related renal and bone toxicity concerns, and paediatric fixed-dose combinations of tenofovir alafenamide are not yet available in many LMICs ^{2,5}.

The paper provides important supportive data on a long-awaited paediatric fixed-dose combination of abacavir/dolutegravir/lamivudine, which has been the Paediatric ARV Drug Optimization (PADO-5) priority list for LMICs⁴ and will simplify ART treatment for children across multiple weight bands. The dispersible tablet offers a user-friendly option for young children unable to swallow tablets, is easy to store and administer, which should help improve adherence and treatment outcomes. Affordable generic versions of this formulation is expected to be available this year².

However, there are important outstanding questions. The study did not assess dolutegravir exposure, safety and efficacy in children switching from efavirenz and nevirapine-based regimens, due to potential interactions with dolutegravir. With the global roll-out of dolutegravir, most children are switched from these regimens, currently with no dolutegravir dose adjustment. It would be reassuring to confirm there is no clinically-significant adverse impact. The small sample size and short duration of the study is another limitation. Data on less common and longer-term outcomes are needed, particularly in infants and young children.

The study did not attempt to explore dosing with dispersible abacavir/dolutegravir/lamivudine for children in the 3-6kg and 25-<30kg weight bands as the fixed ratio precludes achieving the currently recommended doses. Given a wide therapeutic range of abacavir/dolutegravir/lamivudine, it would be important to explore this, starting with in-silico modelling and simulation, so that young infants diagnosed early with HIV and older children who are unable to swallow large tablets may also benefit from this formulation.

Similarly, additional studies are needed to explore use of once-daily abacavir/dolutegravir/lamivudine in children receiving rifapentine or rifampicin for tuberculosis prevention/treatment, and whether dolutegravir dose

adjustments are required⁶. Another important question is the place of this regimen in second-line treatment. While there is evidence of the efficacy of ‘recycling’ tenofovir in adults, even in presence of major nucleotide reverse transcriptase inhibitors (NRTI) resistance mutations, there are no comparable data on recycling abacavir⁷. As these paediatric formulations are rolled out globally these questions need to be addressed, including the use of quality real-world data which requires strengthened health data systems and capacity in LMICs.

The findings of this study is particularly important as countries commit to ‘End AIDS in children by 2030’⁸. For over two decades children living with HIV have lagged behind adults in access to life-saving ART: only half (52%) of children received treatment in 2021 compared to 76% of adults⁹. The human cost of this persistent inequity is unbearably high - with a child dying from AIDS-related causes every 5 minutes⁸. While these child-friendly fixed-dose combinations may not be *the* panacea to this global health challenge, they do help us move one step closer to optimising ART for children.

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