

Two-drug regimen as good as standard three-drug regimen for children and adolescents living with HIV

Background

There are around 2.4 million children and adolescents living with HIV worldwide. The current recommended first-line ART for most children and adolescents is a three-drug regimen including dolutegravir (DTG). This is effective at keeping the viral load suppressed. However, in recent years trials in adults have shown a two-drug regimen using DTG and lamivudine (3TC) is non-inferior to a three-drug regimen for those who are virologically suppressed on ART.

The World Health Organisation's 2025 updated recommendations on HIV clinical management recommend that DTG/3TC can be used for treatment simplification for adults and adolescents with undetectable HIV viral load who are on three-drug ART regimens and do not have active hepatitis B infection. However, this is a conditional recommendation based on moderate certainty of evidence, and does not apply to younger children.

The two-drug regimen of DTG/3TC offers a number of potential advantages to children living with HIV:

- it could reduce lifetime drug exposure
- the pills are smaller and therefore easier to swallow
- the dispersible tablet is more palatable than those used in the three-drug regimens, making it easier to give to young children
- it may reduce some long-term side-effects

However, there are concerns it might be less effective and increase the risk of drug resistance developing in children and adolescents living with HIV. The D3/Penta 21 trial was set-up to explore this.

Effectiveness of the DTG/3TC regimen

D3/Penta 21 found that, after 96 weeks of follow-up, the DTG/3TC regimen was similarly effective at preventing confirmed viral rebounds. The estimated

Key points

- Three-drug ART regimens based on dolutegravir (DTG) are effective at keeping HIV suppressed in children and adolescents living with HIV
- As the two-drug regimen of DTG and lamivudine (3TC) includes one fewer antiretroviral agent, it may offer long-term advantages by reducing exposure to additional antiretroviral-related toxicity
- The D3/Penta 21 trial looked at whether a two-drug regimen (DTG/3TC) was as good as DTG-based three-drug regimens in children and adolescents living with HIV
- D3/Penta 21 found that the two-drug DTG/3TC regimen was as good as standard three-drug DTG-based regimens at preventing confirmed viral rebound ($VL \geq 50c/mL$) by week 96
- Satisfaction with HIV treatment was high in both groups but marginally higher in the DTG/3TC group
- Based on Global Fund cost estimates, economic analysis showed that switching virologically suppressed children to DTG/3TC could save ~\$145 per child per year
- These results suggest the DTG/3TC regimen may be a good option for children and adolescents doing well on first-line ART

proportion of children with viral rebound was 5.9% in the DTG/3TC group, compared to 6.6% in the DTG-based three-drug regimen group.

The confidence interval for the difference between the groups did not cross the pre-specified non-inferiority margin. This margin was intended to

The D3/Penta 21 trial

D3/Penta 21 is a randomised controlled trial comparing:

- standard three-drug DTG-based ART
- a two-drug (DTG/3TC) ART regimen

It aimed to find out whether the two-drug regimen was similarly effective to a three-drug regimen in children and adolescents living with HIV, in terms of preventing confirmed viral rebound ($VL \geq 50$ c/mL). Visits were three-monthly; real-time viral load monitoring was carried at 6 months, 1 year and 2 years, with additional viral loads as per country guidelines. Retrospective viral loads were measured at other visits for analysis.

386 children aged 2-15 years old, weighing over 10kg, from Uganda, South Africa, Thailand, Spain and the UK took part. They were followed-up for at least 2 years (96 weeks). To join the trial, children had to be on a three-drug regimen with no history of treatment failure, and their viral load had to be suppressed.

rule out the DTG/3TC group having a viral rebound rate 9.5% higher than the group which had a DTG-based three-drug regimen. The D3/Penta 21 trial did not find the DTG/3TC regimen to be superior to the DTG-based three-drug regimen.

What happened to children whose viral load rebounded?

In the DTG/3TC group, seven out of the 11 children with confirmed viral rebound had resuppressed to <50 c/mL at 96 weeks. Three of those were still on the DTG/3TC regimen, while three were on a DTG-based three-drug regimen, and one had moved to an atazanavir-based three-drug regimen.

In the DTG-based three-drug regimen group, 9/12 children with confirmed rebound had resuppressed to <50 c/mL at week 96. One child's viral rebound was confirmed at week 96.

How did safety compare between the two regimens?

The number of children with serious adverse events, and grade 3 or higher adverse events was similar between the arms. There was no evidence that the DTG/3TC regimen reduced adverse events over the duration of the trial.

Was the two-drug regimen more acceptable to children?

At week 96 overall satisfaction with HIV treatment was high in both treatment groups, although marginally higher in the DTG/3TC group.

How do the costs of the two regimens compare?

Children receiving DTG/3TC had similar healthcare resource use. Based on Global Fund cost estimates, ARV costs were substantially lower on DTG/3TC compared with those on DTG-based three-drug regimens. Switching virologically suppressed children to DTG/3TC could save approximately \$145 per child per year.

Conclusion

The two-drug DTG/3TC regimen is an effective option for children currently suppressed on a three-drug DTG-based ART regimen. It may make treatment easier for children who struggle to swallow larger tablets, and is more acceptable to children and adolescents. Safety outcomes were similar between DTG/3TC and three-drug DTG-based regimens. This approach may also reduce costs due to the lower ARV prices.

Recommendation

Consider offering DTG/3TC as a simple treatment maintenance option for children who are suppressed on three-drug DTG-based ART regimens.

Further information

These results are being presented at the the Conference on Retroviruses and Opportunistic Infections (CROI) on 24th February 2026. We will then submit them for peer-reviewed publication. For more information about the study, visit <https://penta-id.org/hiv/d3/>

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