Briefing Paper
December 2021
Issue 28

Dolutegravir-based ART regimens for children living with HIV

Need for better treatment options for children living with HIV

There are around 1.8 million children living with HIV worldwide. In 2019, only just over half of these children had been diagnosed and were on treatment. The majority of children living with HIV live in sub-Saharan Africa.

Children living with HIV generally do well on antiretroviral therapy. However, treatment options for children are more restricted than for adults, and the available formulations are often not ideal for children. Some of the challenges include:

- medicines tasting unpalatable
- not being available in formulations that are suitable for young children
- drug interactions between HIV drugs and TB drugs
- different drugs being used for children compared to adults, making procurement and supply chains more complicated

The potential advantages of dolutegravir-based regimens

Dolutegravir is a second-generation integrase inhibitor (INSTI) antiretroviral drug. At the time the ODYSSEY trial was developed, there were encouraging efficacy and safety data from Phase II and Phase III trials of dolutegravir in adults, both as first-line and second-line treatment, showing it was as good as, or may be better, than standard ART options in terms of viral suppression. It also seems to have a good side-effect profile in adults, although there have been concerns about excessive weight gain, particularly in women.

Key messages

- Children living with HIV do well on treatment
- However, treatment regimens for children are challenging
- Dolutegravir has a number of potential advantages as part of a treatment regimen for children, including few drug-to-drug interactions, high genetic barrier to resistance, high potency at a low milligram dose (translating into smaller tablets), good efficacy in adult trials and low cost
- ODYSSEY is the first randomised controlled trial to compare the efficacy and safety of dolutegravir-based regimens to non-dolutegravir-based standard-of-care regimens in children and adolescents
- ODYSSEY found that dolutegravir-based ART regimens were superior to standard-of-care regimens in terms of preventing treatment failure for children living with HIV
- Children on first and second-line treatment seemed to benefit similarly from dolutegravir
- Side-effect data from ODYSSEY were reassuring, particularly around lack of inappropriate weight gain and improved lipid profiles

Data from studies in adults showed it can be dosed once a day, has a good short-term safety profile, low pharmacokinetic variability, few drug-to-drug interactions, rapid and robust virological response with an optimised background treatment, a distinct resistance profile from raltegravir, a high genetic barrier to resistance and high potency at a low milligram dose. There were also data from the IMPAACT P1093 dose-finding study for children aged 6 to 18 years of age. This found that dolutegravir was well tolerated. Dolutegravir-based regimens are lower cost than other standard regimens for children living with HIV. These factors make it potentially a good drug for inclusion in paediatric antiretroviral therapy regimens, both as first-line treatment, and as second-line treatment for children who have not been exposed to first-line dolutegravir. However, there were no data comparing the efficacy of dolutegravir-based ART for children with other first-line and second-line ART regimens.

This briefing paper summarises key results from the ODYSSEY trial, which is the only randomised controlled trial to look at the efficacy and safety of dolutegravir-based first and second-line regimens for children.

The ODYSSEY trial

The ODYSSEY trial compared dolutegravir-based first-line and second-line ART regimens with standard-of-care regimens for children and young people living with HIV. The main ODYSSEY trial enrolled more than 700 children from Uganda, South Africa, Zimbabwe, Thailand, UK, Germany, Spain and Portugal. Most of these children were living in sub-Saharan Africa. Children taking part in the main trial weighed at least 14kg, and were aged from 3 to 18 years old. Nearly all children in the trial were over 6 years old. Children in the trial have been followed up for at least 96 weeks. In the standard of care arm most children on first-line ART received efavirenz-based ART (92%) and most on second-line were on lopinavir/ritonavir (72%) or atazanavir/ritonavir (25%) based ART.

ODYSSEY also randomised 85 children weighing <14kg between dolutegravir-based regimens and standard of care.

Current guidelines for treating children living with HIV

In 2018 (while the ODYSSEY trial was ongoing) the World Health Organization updated their guidelines to state "Dolutegravir in combination with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART" including children for whom there is an approved dolutegravir dosing. This is a conditional recommendation based on low-certainty evidence.

The guidelines also recommend dolutegravir combined with an optimised NRTI backbone as the preferred second-line for people for whom non-dolutegravir based regimens are failing, including children with approved dolutegravir dosing. Again, this recommendation is conditional, based on low-certainty evidence.

These recommendations were also included in the July 2021 *Consolidated Guidelines* published by the World Health Organization. In December 2020 the World Health Organization, along with other global partners, issued a statement calling for urgent country scale-up of access to dolutegravir-based ART for children living with HIV.

How does the efficacy of dolutegravir-based regimens compare to standard of care regimens for children living with HIV?

ODYSSEY found that dolutegravir-based ART regimens were superior to standard-of-care regimens in terms of preventing treatment failure (defined as viral load increase or clinical failure) for children. Children in the dolutegravir arm of the main trial, weighing at least 14kg, were 40% less likely to experience treatment failure than those in the standard of care arm by 96 weeks. 47 (14%) children in the dolutegravir arm had experienced treatment failure by 96 weeks, compared to 75 (22%) children in the standard of care arm. Most treatment failures were increases in viral load.

There was no evidence that the efficacy of dolutegravir compared to standard of care differed by whether it was being used as first-line or second-line treatment.

How do side-effects compare between dolutegravir-based regimens versus standard of care?

Overall, there was no difference in the rate of side-effects between the arms. Children in the dolutegravir arm experienced fewer events which led to treatment change than children in the standard-of-care arm, although the numbers in both arms were very small.

Based on data from adults, there were some concerns around whether children on dolutegravir-based regimens would gain excess weight. Data from ODYSSEY are reassuring: children in the dolutegravir arm of the main trial gained only 1kg extra over 96 weeks compared to those in the standard of care arm. Children randomised to dolutegravir also gained nearly 1cm extra in height. The numbers of children who became newly overweight or obese were small and similar between the arms.

Children in the dolutegravir arm had better lipid profiles than children on standard of care regimens, with lower total cholesterol, mainly due to lower low density lipoprotein levels.

The numbers of children experiencing neuropsychiatric events were small and statistically not different between dolutegravir and standard of care arms. Although more children in the dolutegravir arm reported symptoms of self-harm, "life was not worth living" or suicidal thoughts on the mood-and-sleep questionnaire, the reported symptoms were infrequent, transient and did not lead to treatment change.

What do these results mean for policy and practice?

The ODYSSEY results strengthen the evidence-base for the WHO guideline recommendations. They support the use of dolutegravir-based regimens for children on first-line and second-line ART.

The ODYSSEY results are likely to be widely generalisable, given the trial took place in both high and low and middle-income settings, including those where frequent routine viral load testing is not available. Most children in ODYSSEY came from sub-Saharan Africa, where most children living with HIV are. There is no reason to suspect that the results do not apply to children living in other settings.

Data from ODYSSEY have already contributed to licensing of dispersible paediatric formulations for children <20kg and updated dosing for children ≥20kg, providing safety and pharmacokinetic data. ODYSSEY has provided evidence for treating children ≥20kg with the adult dolutegravir tablets. This will harmonise treatment for adults and older children, simplifying supply chains and helping expand children's access to dolutegravir-based treatment.

ODYSSEY also randomised a cohort of children weighing <14kg. These younger children also had better outcomes, with fewer treatment failures in the dolutegravir arm than the standard of care arm.

A pharmacokinetic substudy in ODYSSEY has also shown that dolutegravir dosed twice daily can be given with rifampicin in children co-infected with tuberculosis. This is the first trial evidence on the use of dolutegravir-based ART for children with HIV/TB.

Conclusion

Dolutegravir-based regimens offer a number of advantages for treating children living with HIV, including:

- being better at preventing treatment failure
- can be dosed once a day
- good safety profile to ~3 years
- high potency at a low milligram dose
- few drug-to-drug interactions, and can be easily given alongside TB treatment by doubling the dose of dolutegravir
- availability as a fixed dose combination for adults and older children, making treatment simpler
- low cost

Recommendations

- Countries should start children living with HIV who are newly initiating ART on dolutegravir-based regimens
- Countries should use dolutegravir-based regimens for children who are switching to second-line treatment (where they have not previously failed on dolutegravir)
- Countries should then consider moving other children who are on first or second-line treatment to dolutegravir based regimens

Further information

Turkova A, White E, Mujuru H et al. ODYSSEY: Dolutegravir for first- and second-line HIV treatment in Children. New England Journal of Medicine. 2021

Acknowledgements

The ODYSSEY trial was sponsored by the Penta Foundation, and coordinated by the MRC Clinical Trials Unit at UCL. It was funded by ViiV Healthcare and the PENTA Foundation. It took place in Uganda, Zimbabwe, South Africa, Thailand, and participating Penta centres in Germany, UK, Portugal, Spain.

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