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# Healthcare Professional Newsletter

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## Update on Dolutegravir for children

Dolutegravir (DTG), a once daily integrase inhibitor, is now widely used in adults with HIV because of its efficacy, high threshold to develop resistance, good tolerability, and high potency, which facilitates incorporation into fixed drug combinations (FDC). DTG can be used in both first- and second-line treatment.

Until recently, raltegravir was the only integrase inhibitor with paediatric formulations. However, the use of first generation integrase inhibitors like raltegravir is strongly discouraged as they have a low genetic barrier for the development of resistance, which then partially compromises DTG and can result in the further selection for high level DTG resistance.

Several paediatric formulations of DTG have been developed. DTG 10 mg and 20 mg tablets have been approved by the Food and Drug Administration (FDA) in the USA for children between 6 and 12 years of age and weighing ≥30 kg. FDA have also recently approved a film-coated dispersible tablet for use in infants from 4 weeks of age.[1] Unfortunately these paediatric formulations are not yet available in South Africa.

The ODYSSEY (Once daily dolutegravir based ART in young people vs. standard therapy) trial, conducted by PENTA-ID, is conducting a randomised multi-centre study to evaluate DTG-based versus standard antiretroviral therapy (ART) for both first- and second-line therapy. In a pharmacokinetic sub-study, children weighing between 20 and 25 kg had equivalent exposure when dosed with the film-coated 50 mg adult tablets and the dispersible 30 mg paediatric tablets.[2] In another sub-study, twice daily DTG gave adequate exposure in children on rifampicin-based treatment for tuberculosis.[3] Findings of both of these studies have been adapted in the Southern African HIV Clinicians Society guidelines, which recommend 50 mg daily for children weighing 20 kg or more, and 50 mg 12 hourly if they are on rifampicin-based treatment for tuberculosis .[4]

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## Isoniazid preventive therapy in pregnancy: update

Tuberculosis during pregnancy increases maternal mortality, causes adverse pregnancy outcomes, increases the risk of HIV transmission to the infant, and may cause congenital tuberculosis in infants. Isoniazid preventive therapy (IPT) reduces the risk of tuberculosis in people living with HIV (PLWH), but concerns about an increased risk of hepatotoxicity in pregnancy, as reported in retrospective studies,[1] has been a barrier to implementing IPT in pregnancy. Pregnancy was an exclusion criterion in trials of IPT in PLWH, so good quality evidence of efficacy and toxicity have been lacking in this important population.

The IMPAACT P1078 TB APPRISE study was a randomised placebo-controlled trial to evaluate the safety and efficacy of IPT started during pregnancy or deferred until week 12 postpartum in 956 HIV-positive women, 92% of whom were enrolled in Africa (19% in South Africa). All women were on ART, the median CD4 count was 493 cells/µL, and 63% had a suppressed viral load. Only 30% had a positive interferon gamma release assay (a test for latent tuberculosis infection). There was no significant difference in the incidence of maternal or infant tuberculosis by study arm, but the incidence of tuberculosis was very low. There was no significant difference in the primary outcome, which was safety of IPT defined as grade 3 or higher adverse events at least possibly related to IPT/placebo. There was also no difference in the incidence of hepatotoxicity between the two arms. The study thus provided the highest quality evidence to date that pregnancy does not increase the risk of toxicity of IPT. However, adverse pregnancy outcomes were worse in the immediate IPT arm: 23% versus 17% (P=0.01), with a higher risk of stillbirth and low birth weight (<2.5 kg); these findings are unexplained. The authors concluded that IPT should be deferred until after delivery. However, it is not ideal to make policy decisions based on an under-powered secondary outcome. The high CD4 counts in the study population also raised questions about generalisability.

A large South African cohort study of 43,971 pregnant HIV-positive women, 16% of whom received IPT during pregnancy, has challenged the findings of the TB APPRISE study. In contrast to the TB APPRISE study, IPT reduced the risk of adverse pregnancy outcomes by 17% (95% confidence interval (CI) 13 to 22%). IPT during pregnancy reduced the risk of tuberculosis by 29% (95% CI 19 to 37%). Women with CD4 counts ≤350 cells/µL benefitted most from IPT during pregnancy, with a 49% reduction in the risk of tuberculosis, while IPT during pregnancy did not significantly reduce the risk of tuberculosis in women with higher CD4 counts.

Based on this new evidence, the South African national guidelines recommend the use of IPT in pregnancy for pregnant women with CD4 counts ≤350 cells/µL. IPT should be deferred until after delivery in women with higher CD4 counts.

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