P.O. Box 38597, Pinelands, Cape Town, South Africa, 7430
Email: afa@afadm.co.za
Website: www.afa.co.za

Tel: 0800 227 700
Fax: 0800 600 773

Healthcare Professional Newsletter

August 2024 – Issue 56

The neuropsychiatric safety of dolutegravir in children and adolescents

The ODYSSEY study supported the use of dolutegravir as the anchor drug in initial and second line antiretroviral therapy (ART) in children and adolescents living with HIV (CALWHIV).[1]

With the data supporting the use of 50 mg immediate release tables of dolutegravir in children weighing 20 kg or more and the availability of 10 mg dispersible dolutegravir in South Africa, since 2023 clinicians in the private and public sector are initiating and switching children and adolescents to dolutegravir-based regimens.

Neurological deterioration, neuropsychiatric side effects and changing sleep patterns have long been of concern to clinicians caring for children and adolescents. These adverse effects occur in CALWHIV with and without ART. Efavirenz is well known to cause sleep disturbance and other neuropsychiatric side effects, particularly in persons with loss-of-function polymorphisms in cytochrome P450 (CYP) 2B6, which is the main metabolising enzyme of efavirenz.[2] However, dolutegravir also has neuropsychiatric toxicity.

In a review of central nervous system adverse events occurring in adults receiving dolutegravir, insomnia is reported in 6% of persons on dolutegravir vs 4.4% of those on other ART; and suicidality is reported in 0.7% of adults on dolutegravir vs 0.4% on other ART.[3] Female sex and abacavir have been identified as possible risk factors in adults.[4] Though there are good efficacy and safety data on the use of dolutegravir in CALWHIV, there were few large cohort studies specifically reporting data on neuropsychiatric effects until recently.

In the ODYSSEY study 350 CALWHIV (median age of 12.2 years and weight of 30.4 kg) were randomised to receive dolutegravir as initial or second line therapy and 357 (median age of 12.1 years and weight of 31.0 kg) were randomised to standard of care (SOC); 150 of the SOC children received efavirenz-based ART. In a secondary analysis they report both the clinician reported neuropsychiatric events as well as participant reports gathered through mood and sleep questionnaires.[5]

Sleep profiles where similar with no difference in night-time waking between dolutegravir and SOC. In 7% of participants in each group nightmares occurred frequently.[5]

The number of clinician-reported neurological and psychiatric adverse events occurred at a similar frequency in CALWHIV receiving dolutegravir versus the SOC, necessitating a medication change in 2 participants in each group. The median age of the participants at the time the neuropsychiatric events was noted was 15.9 years and time on study was a median of 72 weeks. Eleven participants had neurological events, these occurred at median age of 10.4 years (IQR 7.5–15.0) and median time from enrolment to first event was 68 weeks. Seizures occurred in 4 participants in each group. Reported psychiatric events included suicidal ideation or behaviour in 8 participants receiving dolutegravir and 7 participants on the SOC group. The rate of neuropsychiatric adverse events in the dolutegravir group was 1.91 per 1000 person years (95% CI 1.13-3.02) and in the SOC group it was 1.39 per 1000 person years (95% CI 0.74-2.38). For participants receiving efavirenz in the SOC group it was 2.01 per 1000 person years (95% CI 0.81-4.14).

Contributor:
Prof. Helena Rabie
Prof. Mark Cotton
Prof. Gary Maartens
Prof. Graeme Meintjes

This newsletter has been edited by:
Liezl Dunn

Dizziness was more common in the SOC group. There was no difference between the groups in participants reporting feeling sad or angry or reporting low mood. However, more participants on dolutegravir reported that they felt that life was not worth living or felt like self-harming.

The results reported by the ODYSSEY team further supports the general safety of dolutegravir, with few neuropsychiatric events reported. However more CALWHIV reported suicidality and self-harm on the mood questionnaire. The results highlight the importance of psychiatric manifestations in CALWHIV including those on dolutegravir and emphasised that neurological events and psychiatric events can occur after some time on stable therapy. Routine review of mental health and encouraging lifestyles and behaviours that assists with managing stress and anxiety and supporting mental wellbeing is key.

References:

1. Turkova A, White E, Mujuru HA,et al. Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children. N Engl J Med. 2021 Dec 30;385(27):2531-2543. doi: 10.1056/NEJMoa2108793. PMID: 34965338; PMCID: PMC7614690.
2. Lisa Van de Wijer, Grace D Kinabo, Deborah N Mchaile, Quirijn de Mast, Arnt F A Schellekens, André J A M van der Ven, Safety Evaluation of Efavirenz in Children: Don't Forget the Central Nervous System, Clinical Infectious Diseases, Volume 66, Issue 7, 1 April 2018, Page 1150, https://doi.org/10.1093/cid/cix926
3. Hill A, Mitchell H, Hughes S, et al. Risks of cardiovascular or central nervous system adverse events and immune reconstitution inflammatory syndrome, for dolutegravir versus other antiretrovirals: meta-analysis of randomized trials. Current Opinion in HIV and AIDS 13(2):p 102-111, March 2018. | DOI: 10.1097/COH.0000000000000445.
4. Hoffmann C, Llibre JM. Neuropsychiatric Adverse Events with Dolutegravir and Other Integrase Strand Transfer Inhibitors. AIDS Rev. 2019;21(1):4-10. doi: 10.24875/AIDSRev.19000023. PMID: 30899113.
5. Turkova A, White E, Kekitiinwa AR, et al. ODYSSEY trial team. Neuropsychiatric manifestations and sleep disturbances with dolutegravir-based antiretroviral therapy versus standard of care in children and adolescents: a secondary analysis of the ODYSSEY trial. Lancet Child Adolesc Health. 2023 Oct;7(10):718-727. doi: 10.1016/S2352-4642(23)00164-5. Epub 2023 Aug 8. PMID: 37562418.

New evidence to prevent cardiovascular disease in people with HIV

HIV increases the risk of cardiovascular disease independently of other risk factors. Chronic inflammation due to HIV, which improves but does not resolve on ART, is thought to be the reason for the increased risk. Until recently, the only effective preventive strategies for cardiovascular disease in people with HIV (PWH) were lifestyle interventions, and close monitoring for and treatment of modifiable risk factors. Statins reduce LDL-cholesterol but also have anti-inflammatory properties – therefore, they might reduce the risk of cardiovascular disease.

REPRIEVE was a large phase 3 trial, which studied the efficacy of pitavastatin versus matching placebo in PWH at low-moderate risk of cardiovascular disease who did not qualify for statin therapy in current guidelines.[1] Inclusion criteria included age 40-75 years and no prior statin therapy within 90 days. 7769 participants were enrolled: median age was 50 years, 68.9% were men, 41.3% were black, 14.9% were enrolled in sub-Saharan Africa, median CD4 count was 621 cells/µL, and 87.1% had an undetectable viral load.

REPRIEVE only evaluated pitavastatin, which isn't available in South Africa. The effect of statins on cardiovascular risk reduction is a class effect, so there is no reason to believe that pitavastatin will be the only member of the class to be effective. Doses of statins that are available in South Africa which achieve a similar reduction in LDL-cholesterol to pitavastatin 4mg used in REPRIEVE are rosuvastatin 5 mg, atorvastatin 20 mg, and simvastatin 40 mg – the registered doses of pravastatin, fluvastatin, and lovastatin do not achieve similar reductions in LDL-cholesterol. The trial was stopped early due to a reduction of major cardiovascular events of 35% (P=0.002) in the pitavastatin arm. Pitavastatin was generally well tolerated but the incidence of grade 3 or higher myopathy or myalgia (incidence rate ratio, 1.74; 95% CI, 1.24 to 2.45) and of new onset diabetes mellitus (incidence rate ratio, 1.35; 95% CI, 1.09 to 1.66) were higher in the pitavastatin arm, both of which are well known adverse effects of statins.

The findings of REPRIEVE are compelling and recommends the use of statins at the doses above for all PWH above the age of 40 years. It is important to remember that there are important drug-drug interactions between most statins and the protease inhibitors, so the doses recommended above will need to be adjusted. Regular screening for diabetes mellitus needs to be done.

Reference:

1. Greenspoon S, et al. Pitavastatin to Prevent Cardiovascular Disease in HIV Infection. N Engl J Med 2023;389:687-99.

Switching from an integrase inhibitor to an alternative antiretroviral class because of weight gain

Patients who start an ART regimen that includes dolutegravir compared with efavirenz gain more weight during follow-up[1], and some patients who switch from an efavirenz-based regimen to a dolutegravir-based regimen can experience substantial weight gain after the switch. Initially, this phenomenon was thought to be caused by dolutegravir driving weight gain through an off-target effect on appetite or metabolism. However, strong evidence now points to this phenomenon being related to efavirenz having suppressive effects on weight gain rather than dolutegravir being the cause. The suppressive effect is seen to the greatest extent in patients who are slow metabolisers of efavirenz and therefore have the highest exposures to efavirenz.[2]

In terms of clinical management, one question that has been asked is whether switching to an alternative antiretroviral class can reverse the weight gain experienced on integrase inhibitors such as dolutegravir and bictegravir (a drug closely related to dolutegravir and associated with the same weight gain phenomenon).

Studies presented at the 12th International AIDS Society Conference on HIV Science (IAS 2023) in Brisbane, Australia, in July 2023 addressed this. In the DEFINE study conducted in the US, participants (n=103) who had gained more than 10% body weight on an integrase inhibitor (81% of whom were on bictegravir) were randomised to stay on the same regimen or switch to a darunavir-based regimen. There was no significant difference in weight gain between the study arms at week 24.[3]

Two other studies were presented (P017 and P018) that involved switching to a doravirine and islatravir regimen. Doravirine is a next generation non-nucleoside reverse transcriptase inhibitor and islatravir is a novel nucleoside reverse transcriptase translocation inhibitor. In study P018, participants switched from a bictegravir, tenofovir alafenamide and emtricitabine regimen to a doravirine and islatravir regimen or remained on the same regimen. There was no difference in weight gain between the regimens at 48 weeks. Similarly in study P017, there was no difference in weight gain between those who switched to doravirine and islatravir versus the group that remained on an integrase inhibitor regimen.[4]

In summary, these studies showed that switching from an integrase inhibitor (in these studies mainly bictegravir) to a darunavir- or a doravirine-based regimen did not reverse weight gain during 24-48 weeks follow-up. Rather participants who switched continued to gain weight at a similar rate to participants remaining on an integrase inhibitor.

An important aspect of management of patients who experience weight gain on dolutegravir is to discuss with them that the weight gain is not directly caused by dolutegravir, but results from the treatment of HIV with suppression of viral replication combined with lifestyle factors. Diet and exercise counselling are key aspects of managing this phenomenon.

References:

1. Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): Week 96 results from a randomised, phase 3, non-inferiority trial. Lancet HIV. 2020;7: e666-e676.
2. Maartens G, Sinxadi P, Venter WDF. Weight gain on dolutegravir: Association is not the same as causation. S Afr J HIV Med 2023;24(1):a1500.
3. Short WR et al. A prospective, randomized trial to assess a protease inhibitor-based regimen switch strategy to manage integrase inhibitor-related weight gain. 12th International AIDS Society Conference on HIV Science (IAS 2023), Brisbane, Australia, abstract OALBB0502, 2023.
4. McComsey GA et al. Weight and body composition after switch to doravirine/islatravir (DOR/ISL) 100/0.75 mg once daily: week 48 results from two randomized active-controlled phase 3 trials, MK8591A-017 (P017) and MK8591A-018 (P018). 12th International AIDS Society Conference on HIV Science (IAS 2023), Brisbane, Australia, abstract OAB0203, 2023.