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

Tel: 0800 227 700 or +27 (0)21 466 1700
Fax: 0800 600 773 or +27 (0)21 466 1744

Healthcare Professional Newsletter

July 2018 – Issue 48

Potential safety issue affecting HIV+ women taking dolutegravir at the time of conception

Dolutegravir (DTG), a second generation integrase strand inhibitor, is already a first choice component of adult antiretroviral therapy (ART) in high-income countries, based on its efficacy, safety, tolerability and high resistance barrier.[1] DTG has been a first line option in Botswana since 2016 and is likely to be endorsed by WHO for resource limited settings. We reviewed DTG in pregnancy in the February 2018 newsletter, sharing preliminary evidence of safety in pregnancy but noting that vigilance for adverse events was essential.[2]

On 18th May 2018, the World Health Organization issued a statement of preliminary evidence suggesting that DTG exposure at time of conception may be associated with an increased risk for neural tube disorders (NTD) in newborn infants.[3] This was identified from a preliminary unscheduled analysis of an ongoing observational study in Botswana, which identified 4 cases (0.9%) of NTDs from 426 women becoming pregnant while taking DTG. In comparison, the risk for NTDs for women on other antiretrovirals at conception is 0.1%. Another comparison of interest is that NTDs occur in 1.3% of neonates after valproic acid exposure in the first trimester.[4]

In the Botswana study, surveillance of deliveries of women taking DTG at conception will continue until February 2019, with results to follow shortly afterwards. The Botswana study shows no evidence of NTDs in infants born to women who initiated DTG-based regimens during pregnancy. Meanwhile, other groups in diverse settings are intensifying their surveillance. An important difference between Botswana and South Africa is that in South Africa, folate fortification of bread and maize is standard so that folate deficiency, which is a risk factor for NTDs, may be less common.

NTDs may be related to folate deficiency, other medications such as valproate or family history. Recently, valproic acid has been shown to block folate receptors, a possible mechanism for NTDs.[5] Depending on the severity, management of NTDs is complex, longstanding and resource intensive. Whether DTG has a similar mechanism of action is unknown.

The South African Health Products Regulatory Authority (SAHPRA) issued the following precautionary advice:[6]

- Women trying to fall pregnant should not receive DTG
- Pregnancy should be excluded in women of childbearing age who are starting DTG-based ART
- Women of childbearing age receiving DTG should consistently use a highly effective contraception method
- Pregnant women already on DTG should not stop their ART and should speak with their health care professional for additional guidance
- ART for women of childbearing age, including pregnant women, should be based on medicines with adequate efficacy and safety data

Contributors:
Prof. Mark Cotton
Prof. Graeme Meintjes
Prof. Marc Mendelson
Prof. Gary Maartens

This newsletter has been edited by:
Liezl Dunn
Linda Doms

- As data on the safety of medicines in pregnancy is inadequate at the time of marketing approval of a medicine, post-marketing surveillance is essential. Health professionals in South Africa should report any adverse reactions including DTG-associated birth defects to the National Adverse Drug Event Monitoring Centre at (021) 4471618 or submit using a reporting form accessible at: www.mccza.com/documents/14ed44a46.04_ARF1_Jul16_v4.pdf

In addition, the following recommendations should be considered:

- For pregnant women on DTG
  - Options for NTD screening should be discussed with the patient and with the obstetrician
  - Maternal alphafetoprotein and a foetal ultrasound should be offered between 16 and 18 weeks of gestation
- Efavirenz, although initially considered a cause of NTDs, has proven safe and is a useful alternative
- Women of child bearing age and receiving DTG should be offered folate supplementation

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1. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2017. (Accessed 15 January 2018, 2018, at http://aidsinfo.nih.gov/guidelines).
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5. Fathe K, Palacios A, Finnell RH. Brief report novel mechanism for valproate-induced teratogenicity. Birth Defects Res A Clin Mol Teratol 2014;100:592-7.
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New WHO guidelines for induction therapy in cryptococcal meningitis

In March 2018, the WHO issued new guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected people. These are available online:
http://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/

In an important change from previous guidelines the recommended induction treatment for cryptococcal meningitis is a one-week course of amphotericin B deoxycholate (1.0 mg/kg/day IVI) plus flucytosine (100 mg/kg/day orally, divided into four doses per day), followed by one week of fluconazole 1200mg orally daily. This is then followed by fluconazole maintenance and consolidation. The ACTA trial that informed this recommendation was published in the New England Journal of Medicine in 2018.[1] This multi-centre trial conducted in several African countries (n=721) evaluated five different induction regimens: the oral combination of fluconazole plus flucytosine, 1 week or 2 weeks of amphotericin B plus flucytosine, or 1 or 2 weeks of amphotericin B plus fluconazole (the latter dosed at 1200mg daily). An important finding was that flucytosine was associated with reduced mortality when used as the companion drug with amphotericin B, compared with fluconazole. Of all five regimens the one associated with the lowest 10-week mortality was 1 week amphotericin B plus flucytosine (24%) and this mortality was significantly lower than 2 weeks of amphotericin B plus flucytosine (38%). This finding may be related to lower toxicity and/or lower risk of line sepsis with the shorter course.

Flucytosine is not currently registered in South Africa or any other African country. There are ongoing international advocacy efforts to expand access to the drug and the ACTA trial findings and WHO guidelines will add impetus to this. Flucytosine can currently be accessed in South Africa only through the SAHPRA section 21 approval process.

When flucytosine is unavailable, WHO still recommends two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) plus fluconazole (1200 mg daily) for induction. It is important to note that a one week course of amphotericin B and fluconazole is not recommended, because this was the worst performing arm in the ACTA trial with 10 week mortality of 49%.

Reference:

1. Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda D, Mfinanga S, Temfack E, Lakhi S, Lesikari S, Chan AK, Stone N, Kalata N, Karunaharan N, Gaskell K, Peirse M, Ellis J, Chawinga C, Lontsi S, Ndong JG, Bright P, Lupiya D, Chen T, Bradley J, Adams J, van der Horst C, van Oosterhout JJ, Sini V, Mapoure YN, Mwaba P, Bicanic T, Lalloo DG, Wang D, Hosseinipour MC, Lortholary O, Jaffar S, Harrison TS; ACTA Trial Study Team. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa.

Treatment of cytomegalovirus retinitis

Reactivation of latent cytomegalovirus (CMV) in HIV-infected persons with advanced immunosuppression results in the commonest and most serious ocular complication of AIDS. Incidence has reduced in the ART-era, with data from the global north suggesting greater than 80% reduction.

Most cases of CMV retinitis present in persons with a CD4 count <50 cell/mm^3 and are unilateral. Commonly, patients will present with blurred vision, loss of central vision, floaters, blind spots or flashing lights may be present, depending on the extent and site of retinal damage. Patients should have dilated fundoscopy, ideally by an ophthalmologist. Characteristic findings are described as 'margherita pizza' with combination of yellow-white 'fluffy' lesions and haemorrhage.

Progression will occur without treatment. Hence, diagnosis through PCR of intravitreal fluid is necessary to exclude other causes of a similar appearance such as retinal toxoplasmosis or other herpes viruses such as varicella zoster virus, and direct appropriate treatment. Detection of CMV in blood is not enough to make the diagnosis of CMV retinitis. Retinal detachment causing acute visual loss is the commonest complication, although in patients with CMV-IRIS an 'immune recovery uveitis' may occur, characterized by an inflammatory condition leading to cystoid macular oedema and retinal neovascularisation.

AFA's clinical committee recently agreed to a change in the guidelines for induction therapy for CMV retinitis from intravenous ganciclovir, 5mg/kg 12hourly for 14 days, to oral valganciclovir 900mg 12hrly, which avoids hospitalisation and risk of venous catheter infections. Oral valganciclovir 900mg daily is recommended for maintenance therapy until CD4 count rises to above 100 cells/mm^3.

Ganciclovir or valganciclovir may cause bone marrow suppression with anaemia and leucopaenia. Ganciclovir may also cause thrombocytopaenia, so full blood count monitoring on treatment is advised.

Treatment of CMV retinitis cannot reverse visual loss but prevents progression. Systemic therapy provides some protection to the contralateral eye in unilateral disease. As CMV is most commonly associated with advanced immunosuppression, antiretroviral therapy should be started as soon as the patient is willing to start, so as to reduce the risk of developing life-threatening opportunistic infections.

Isoniazid preventive therapy (IPT) in pregnancy

Maternal tuberculosis increases maternal mortality, causes adverse pregnancy outcomes, increases the risk of HIV transmission to the infant, and may cause infant tuberculosis. The current WHO guidelines recommend IPT in pregnancy, but acknowledge that there is low quality evidence for this recommendation. Retrospective studies provide contradictory evidence on whether IPT is more hepatotoxic in pregnancy.

The evidence base on IPT in pregnancy has been strengthened by the TB APPRISE study, which was a non-inferiority randomised placebo-controlled trial to evaluate the safety of IPT started during pregnancy or deferred until week 12 postpartum in 956 HIV-infected women. Pregnant women in high burden areas (almost all in Africa, 19% from South Africa) were enrolled between 14 and 34 weeks of gestation. The primary outcome was maternal safety. Key secondary outcomes were hepatotoxicity, toxicity in utero and in infants, tuberculosis incidence, and mortality. ALT >1.25 upper limit of normal was an exclusion criterion.

All women were on ART, median CD4 count was 493 cells/µL, and 81% had a suppressed viral load. Only 30% had a positive test for latent tuberculosis infection (interferon gamma release assay). There was no significant difference in the primary endpoint of first maternal treatment-related grade 3 or higher adverse event or permanent discontinuation of study drug (15.0 vs 14.9 per 100 person years in the immediate and deferred IPT arms respectively). There was also no difference in the incidence of maternal elevated liver function tests between the two arms. An interesting finding was that ALT increased after delivery irrespective of treatment arm. There was no significant difference in the incidence of maternal or infant tuberculosis by study arm. 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).

In view of the evidence from TB APPRISE, AfA recommends against the use of IPT in pregnancy except for pregnant women with CD4 counts <100 cells/µL, who are at high risk of death from tuberculosis.

Reference:

1. Gupta A et al. Randomized trial of safety of isoniazid preventive therapy during or after pregnancy (abstract 142LB). CROI 2018.