

## Healthcare Professional Newsletter

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### Dolutegravir in pregnancy

Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) with once daily dosage and a high genetic barrier to resistance. It is a first-line option in upper income countries, and it is anticipated that the World Health Organization (WHO) will soon follow suit. Botswana introduced dolutegravir-based first-line antiretroviral therapy (ART) for all adults, including pregnant women, regardless of CD4 count in May 2016. With the imminent arrival of affordable generic fixed dose combinations (FDC) in high burden settings, DTG is set to become widely used.

Prospective studies of DTG in pregnancy have begun. Raltegravir is also an INSTI, but has a much lower barrier to resistance and requires twice daily dosing, is already widely used in pregnancy with a good safety record. INSTIs reduce viral load more rapidly than non-nucleoside reverse transcriptase inhibitors and protease inhibitors, so they may be especially useful in late pregnancy.

#### ART and teratogenicity

Should DTG already be used in pregnancy? Data from the Antiretroviral Pregnancy Registry (APR) through January 2017 include anomalies in 2 of 77 (2.6%) 1<sup>st</sup> trimester and 2 of 56 (3.5%) 2<sup>nd</sup>/3<sup>rd</sup> trimester DTG exposures. Data presented at the International AIDS Society meeting in July 2017 report no anomalies among 116 1<sup>st</sup> trimester and 729 2<sup>nd</sup>/3<sup>rd</sup> trimester exposures in the Tsepamo Study, Botswana and in a pooled cohort analysis, 3 anomalies in 42 (7.1%) 1<sup>st</sup> trimester and 1 of 38 (2.6%) 2<sup>nd</sup>/3<sup>rd</sup> trimester exposures.<sup>1,2</sup> Combining these 3 reports, the calculated risk of congenital anomalies is 2.1% with 1<sup>st</sup> trimester and 0.4% with 2<sup>nd</sup>/3<sup>rd</sup> trimester DTG exposure. For comparison, in an updated APR report for all antenatal ART exposures, prevalence of birth defects was 2.7 per 100 live births for 1<sup>st</sup> trimester exposure (244 of 8,909 exposures; 95% confidence interval [CI], 2.4–3.1) and 2.8 per 100 live births for 2<sup>nd</sup> /3<sup>rd</sup> trimester exposure (prevalence ratio 0.99; 95% CI, 0.83–1.18).<sup>3</sup> Therefore, DTG seems to be as safe in pregnancy as other antiretrovirals, but this is based only on a small number of exposures to date.

#### DTG dosage in pregnancy

Pharmacokinetic parameters (area under the curve and troughs) are slightly lower in pregnancy than postpartum, due in part to uridine diphosphate glucuronosyl transferase (UGT1A1) induction by increased progesterone levels. UGT1A1 is responsible for both DTG and bilirubin glucuronidation and elimination.<sup>4</sup>

#### DTG elimination in newborn infants

Due to UGT1A1 immaturity in neonates, especially if premature, elimination in exposed neonates is half that of adults.<sup>4</sup> DTG passes efficiently into breast milk. In a case report of a breastfeeding mother and her infant, the infant's plasma DTG concentration was 0.10 mg/L, equivalent to the target trough plasma concentration in treatment-naïve adults.<sup>5</sup> As with raltegravir, one must be vigilant for neonatal jaundice exacerbation in DTG-exposed neonates.

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## Neuropsychiatric adverse events including depression

Postnatal depression is common, occurring in 10 to 15% of women in the first year after delivery.<sup>6</sup> Antenatal depression, regardless of HIV status, but linked to unplanned pregnancy and poverty, is common in rural South Africa.<sup>7</sup> Antenatal depression has also been linked to ART failure in pregnancy in a South African study, presumably due to poor adherence.<sup>8</sup> Screening for depression both during and after pregnancy should be a routine practice. In this context, DTG is associated with neuropsychiatric adverse events: anxiety, irritability and sleep disturbances. These events were more common in older women.<sup>9</sup>

## Conclusions

DTG is likely to be used more commonly in pregnancy. Preliminary data supports DTG safety and efficacy in pregnancy, but vigilance for adverse events is essential and should include careful monitoring of newborn infants, especially for neonatal jaundice.

## References:

1. Thorne C, Favarato G, Peters H, et al. Pregnancy and neonatal outcomes following prenatal exposure to dolutegravir. International AIDS Society Conference. Paris, France 2017.
2. Zash R, Jacobsen DM, Mayondi G, et al. Dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) started in pregnancy is as safe as efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) in nationwide birth outcomes surveillance in Botswana. 9<sup>th</sup> International AIDS Society Conference. Paris, France 2017.
3. Antiretroviral Pregnancy Registry Steering Committee. The antiretroviral pregnancy registry interim report: Wilmington, NC: Registry Coordinating Center; 2017.
4. Mulligan N, Best BM, Capparelli EV, et al. Dolutegravir Pharmacokinetics in HIV-Infected Pregnant and Postpartum Women. CROI. Boston, USA 2016.
5. Kobbe R, Schalkwijk S, Dunay G, et al. Dolutegravir in breast milk and maternal and infant plasma during breastfeeding. AIDS 2016;30:2731-3.
6. Postpartum depression. 2018. (Accessed January 18, 2018, at [http://www.sadag.org/index.php?option=com\\_content&view=article&id=142:postpartum-depression&catid=61&Itemid=143](http://www.sadag.org/index.php?option=com_content&view=article&id=142:postpartum-depression&catid=61&Itemid=143)).
7. Rochat TJ, Richter LM, Doll HA, Buthelezi NP, Tompkins A, Stein A. Depression Among Pregnant Rural South African Women Undergoing HIV Testing. JAMA 2006;295:1376-8.
8. Hoffmann CJ, Cohn S, Mashabela F, et al. Treatment Failure, Drug Resistance, and CD4 T-Cell Count Decline Among Postpartum Women on Antiretroviral Therapy in South Africa. J Acquir Immune Defic Syndr 2016;71:31-7.
9. Menard A, Montagnac C, Solas C, et al. Neuropsychiatric adverse effects on dolutegravir: an emerging concern in Europe. AIDS 2017;31:1201-3.

## Is there still a role for nevirapine?

The non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine has been used in the AfA programme for 20 years. Nevirapine together with dual NRTIs has provided an effective antiretroviral therapy (ART) regimen, usually in patients with intolerance or contra-indication to efavirenz. In children under 3 years of age it is preferred to efavirenz, because there is uncertainty about efavirenz dose in this age group. Historically, single dose nevirapine at labour was the mainstay of therapy to prevent mother to child transmission. Finally, it is used as monotherapy in infants to prevent transmission from breastfeeding.

However, nevirapine can cause severe, life-threatening hypersensitivity reactions affecting the skin, the liver, or with multi-system involvement. These hypersensitivity reactions occur much more frequently in adults starting their first ART regimen with higher CD4 counts.

As we are moving into the era of using dolutegravir as the preferred first-line drug, it is time to re-look at nevirapine's future role. A recent network meta-analysis evaluated the efficacy and tolerability of different antiretroviral drugs (Kanters et al), which allows for the best evidence to assess the risk:benefit ratio of nevirapine. In the following table the odds ratios (with 95% confidence intervals) are given for efficacy and toxicity of nevirapine versus comparator antiretrovirals in ART regimens. In the viral suppression column an odds ratio >1 means the comparator drug has greater efficacy than nevirapine; in the toxicity column an odds ratio <1 means the comparator is less toxic than nevirapine.

Comparator	Viral load suppressed at 96 weeks	Drug discontinuation for adverse events
Efavirenz	2.04 (1.22 to 3.33)	0.63 (0.38 to 1.04)
Rilpivirine	2.72 (1.46 to 5.11)	0.26 (0.13 to 0.50)
Dolutegravir	3.85 (2.13 to 7.14)	0.17 (0.08 to 0.35)
Raltegravir	2.94 (1.64 to 5.26)	0.29 (0.13 to 0.65)

It is clear from the evidence that the risk:benefit ratios for nevirapine versus alternative first-line comparator antiretrovirals is very unfavourable. In keeping with the Southern African HIV Clinicians Society, AfA strongly discourages the use of nevirapine in ART for adults. Patients who are virologically suppressed on a nevirapine regimen could continue until dolutegravir is recommended for first-line (anticipated later this year) – nevirapine’s toxicity is mostly limited to the first 6 weeks of therapy, but, like efavirenz, it has a low barrier to developing resistance. Rilpivirine or dolutegravir are much safer alternatives for patients who cannot tolerate efavirenz or in whom efavirenz is contraindicated. AfA continues to recommend single dose nevirapine with labour for pregnant women who have not received ART and for infants who are breastfeeding. Nevirapine is well tolerated in both these settings. Nevirapine also has a small role in ART regimens in children <3 years of age.

#### Reference:

1. Kanters S, Socias ME, Paton NI, et al. Comparative efficacy and safety of second-line antiretroviral therapy for treatment of HIV/AIDS: a systematic review and network meta-analysis. *Lancet HIV* 2017;4(10):e433-e441.

### The Xpert MTB/RIF Ultra: increased sensitivity for diagnosing HIV-associated TB with a small increase in false positive results

Laboratories across South Africa are replacing the currently used rapid PCR diagnostic test for tuberculosis, Xpert MTB/RIF, with the new Xpert Ultra test. The same laboratory instrument is used, but for Xpert Ultra the instrument requires a software update and a different cartridge is used. The PCR assay within the new cartridge has been refined to improve sensitivity.

The performance of the Xpert Ultra on sputum samples was recently evaluated in a multi-country study involving 2368 participants being investigated for pulmonary TB (Dorman, 2018). A key finding was that the sensitivity for diagnosing TB in HIV-infected participants increased from 77% using Xpert to 90% using Xpert Ultra (i.e. a 13% absolute increase in sensitivity). Three or more sputum TB cultures per patient were used as the reference standard. However, specificity with Xpert Ultra was lower than for Xpert, particularly for patients previously treated for TB and especially if this was in the preceding two years. In patients previously treated for TB specificity was 98% for Xpert and 93% for Xpert Ultra. One explanation for this is that due to its increased sensitivity Xpert Ultra may detect residual *Mycobacterium tuberculosis* DNA in the sputum of some patients previously treated for TB that does not reflect recurrent active TB disease. Xpert Ultra and Xpert performed similarly in detecting rifampicin resistance.

Xpert Ultra performed very well in a small study of TB meningitis in HIV-infected adults (Bahr, 2018). Xpert Ultra was more sensitive than culture, which is surprising as it has a similar detection threshold of about 10 bacilli per mL. This preliminary finding suggests that Xpert Ultra could be valuable in patients with suspected extrapulmonary TB, in whom false positives will probably be less common than in pulmonary TB.

Key messages for clinicians regarding Xpert Ultra are:

- Xpert Ultra has improved sensitivity compared with Xpert, yet even if the Xpert Ultra is negative it does not rule out active TB; some patients (around 10%) will be TB culture positive and Xpert Ultra negative in the sputum.
- In patients with previous TB (particularly in the last two years) a positive Xpert Ultra result should be interpreted in the clinical context, as some positive results in such patients will be false positives. Sputum for TB culture should be sent. If the patient has TB symptoms they should be treated for TB. If there is doubt regarding the diagnosis of TB and the patient is stable, the clinician should monitor clinically and await the result of the TB culture.
- Xpert Ultra appears promising in extrapulmonary specimens, but more evidence is needed.

#### References:

1. Dorman SE, Schumacher SG, Alland D, et al. Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis*. 2018 Jan; 18(1):76-84.
2. Bahr NC, Nuwagira E, Evans EE, et al. Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. *Lancet Infect Dis* 2018;18: 68–75.

## Treatment of multi-drug resistant gonorrhoea – what's in the pipeline?

Bacterial sexually transmitted infections (STI) are a major global public health concern, affecting 357 million people per year, with 78 million *Neisseria gonorrhoeae* (*N. gonorrhoeae*) infections in 2012.<sup>1</sup> Africa has amongst the highest incidence (567 per 100,000 population per annum) of male urethral discharge, which is primarily due to *N. gonorrhoeae* and *Chlamydia trachomatis*. Gonorrhoea is associated with significant morbidity and, if not treated appropriately, it can have serious complications: pelvic inflammatory disease, ectopic pregnancies, abortions, neonatal conjunctivitis and blindness. Gonorrhoea co-infection enhances the transmission of HIV by 3-5 fold.<sup>2</sup>

Over the past few years, we have seen an alarming increase of *N. gonorrhoeae* resistant to antibiotics. In the U.S, *N. gonorrhoeae* has been included as one of three organisms presenting an urgent threat by the Center for Disease Prevention & Control. Sequentially, penicillin, fluoroquinolones, and macrolides have been lost as first-line treatment options, and now increasing cephalosporin resistance means that we face the stark reality of untreatable *N. gonorrhoeae*. If gonorrhoea does become untreatable, what effect might it have on our HIV programme?

Despite this alarming increase in antibiotic resistance, the drug development pipeline for *N. gonorrhoeae* has remained dry. The development of a gonococcal vaccine faces challenges that are difficult to overcome.<sup>3</sup> The WHO Global Action Plan to control the spread and impact of antibiotic resistance in *N. gonorrhoeae* has identified new treatment options as a priority area.<sup>4</sup>

Three candidate antibiotics have been identified as potential new gonorrhoea treatments. Solithromycin (Cempra®) is a novel oral fluoroketolide, which has activity against Gram-positive and fastidious Gram-negative bacteria including *N. gonorrhoeae*. Although it binds to bacterial 23S ribosomal RNA to disrupt protein synthesis like macrolides, its novelty lies in an ability to bind to an extra site on the ribosomal RNA, which overcomes macrolide resistance. However, concerns around increased incidence of drug-induced liver injury (similar to the related macrolide, telithromycin) has caused concern.

Gepotidacin (GSK) is a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor, which selectively inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism not utilised by any currently approved therapeutic agent.<sup>5</sup> It is being evaluated for oral and intravenous treatment for a number of different infections, including multi-drug resistant bacteria. Most trials are still at phase II.

Zoliflodacin (Entasis Therapeutics) is the most promising of the three candidates and is being accelerated through a partnership between the company and the Global Antibiotic Research and Development Partnership (GARDP) with a target product profile solely aimed at gonorrhoea. It is a first-in-class spiropyrimidinetrione, which inhibits bacterial topoisomerase II and has shown potent *in vitro* activity against fluoroquinolone- and extended spectrum cephalosporin-resistant *N. gonorrhoeae* isolates. GARDP is supporting core activities to accelerate regulatory, public health and sustainable access programmes relating to Zoliflodacin. The partnership is supporting a global phase III clinical trial, including sites in South Africa.

A potential new drug to address untreatable gonorrhoea is a welcome development, not only for individual patients, but for the HIV programme in South Africa, which can ill afford increased HIV transmission due to prolonged, difficult to treat, STIs.

### References:

1. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. PLoS One. 2015;10(12):e0143304.
2. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect. 1999;75(1):3–17.
3. Gottlieb SL, Johnston C. Future prospects for new vaccines against sexually transmitted infections. Curr Opin Infect Dis [Internet]. 2016;0. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27922851>.
4. WHO. Global action plan to control the spread and impact of AMR in *Neisseria gonorrhoeae*. Geneva; 2012.
5. Bax BD, Chan PF, Eggleston DS, Fosberry A, Gentry DR, Gorrec F, et al. Type IIA topoisomerase inhibition by a new class of antibacterial agents. Nature [Internet]. 2010;466(7309):935–40. Available from: <http://dx.doi.org/10.1038/nature09197>.