SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

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Updated South African ART guidelines for use of dolutegravir (DTG) in pregnant women and women of childbearing potential (WOCP)

The Southern African HIV Clinicians' Society now recommends that all women, regardless of reproductive plans or current pregnancy gestation, be preferentially started on dolutegravir–based regimens.

Concerns about dolutegravir (DTG) and a possible association with neural tube defects (NTDs) can be traced back to the Tsepamo study in Botswana. The original report included 8 public hospital maternity wards from August 2014 to June 2018, with ten additional sites added between July 2018 and March 2019, giving coverage of approximately 70% of births in Botswana during this period. It showed a 12 times higher risk of NTDs in children born to mothers who used DTG-based regimens at time of conception compared to mothers using regimens without DTG. (1, 2) As further Tsepamo data accumulated, this association weakened and, as of 2020, the difference in NTDs in children born to mothers who conceived on DTG was no longer statistically significantly different to those who conceived on other regimens. (3, 4) The 2020 data showed 7 NTDs in 3591 births with DTG exposure (0.19%; 95%CI 0.09% to 0.40%), compared to 8 NTDs in 10,958 births with EFV exposure (0.07%; 95%CI 0.03% to 0.17%). There was no significant difference in NTD prevalence between a DTG and an EFV–based regimen at conception (difference 0.12%; 95%CI -0.03% to 0.27%). (4)

The Tsepamo data set was always an outlier – no similar safety signals were seen in data from similar, albeit smaller, cohorts elsewhere in the world.(5-8) However, this original Tsepamo safety alert linking DTG to NTDs in children born to women taking DTG had a significant global impact at the dawn of the widespread rollout of dolutegravir (DTG) in low- and middle-income countries (LMICs). Many countries barred all women of reproductive age from accessing DTG-based 1st and 2nd line therapy. (9-12)

As these safety concerns reduced with time, the World Health Organization (WHO), in 2019, initially changed its recommendation such that all women could access DTG without requiring contraception – but only if appropriately counselled about risks vs benefits.(13) For clinicians, this need to extensively counsel women prior to starting DTG became a barrier to its use, with many feeling that it was safest to prescribe efavirenz (EFV) rather than take even a small risk and give DTG instead. However, as of July 2021, the WHO has updated its guidance again in line with the most recent data. It now recommends DTG as 1st line therapy for all people initiating ART, without specific mention of any difference for women in their reproductive years.(14)

Despite later, more reassuring Tsepamo findings presented at AIDS 2020 in July of last year (15, 16) unfortunately, many countries have not yet updated their guidelines to include access to DTG for all women regardless of contraceptive uptake. This is because guideline amendment often requires peer reviewed published data to trigger evidence–based revisions of previous recommendations, and these 2020 findings remain unpublished in full. With WHO's updated 2021 recommendations, (14) it is likely that more countries will now update their national guidelines to enable equal access to DTG for women.

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Since 2018, in South Africa and across Sub–Saharan Africa, millions of women of reproductive age have encountered barriers to access of DTG, despite it being superior with respect to HIV viral suppression and drug tolerability, and it having a high resistance barrier even in the context of suboptimal adherence. (15-17) With over a fifth (23.9%) of South African women in their reproductive ages (15–49 years) living with HIV, such barriers to access of best care now need to be abolished.(18)

Many advocacy groups of women living with HIV have been vociferous that the decision to limit access to DTG was taken without them and have repeatedly appealed to the medical fraternity to give them the right to make the choice about whether to take DTG or not. The African Community Advisory Board has stated "we do think it is critical to not just see the pregnant mother, and indeed all women of childbearing potential, as vessels of babies, but as individuals in their own right, who deserve access to the very best, evidence-based treatment…" (19)

These appeals are backed up by modelling studies that have tried to weigh the impact on maternal morbidity and mortality, and new horizontal (partner-to-partner) HIV infections with potential NTDs in children born to women on DTG.(20, 21) Even though these modelling studies applied the original elevated risk of NTDs in their calculations, they still came out heavily in favour of supporting access to DTG for women in order to avert unnecessary female deaths, illness and new male partner infections. Now that the risks have been shown to be even less of a concern than originally thought, (4-6, 8), the benefits of expanding access to DTG become inarguable.

In concert with the Southern African HIV Clinicians' Society and WHO recommendations, the South African National Department of Health (NDoH) has also recently moved in the same direction. An NDoH circular (Reference: 2021/06/29/EDP/01) has now been released stating that all newly diagnosed men *and* women without contraindications should be initiated on tenofovir/lamivudine/dolutegravir (TLD) and that any client on tenofovir/emtricitabine/efavirenz (TEE) who is eligible should be switched to TLD if they are virally suppressed or have a persistent low level viraemia.

SA's transition to TLD has been slower than anticipated, creating some concerns about TEE stock levels in parts of the country. The NDoH circular is well timed and should open up access to TLD for all women. In addition, although it is not clearly stipulated in the circular, more women can now access a DTG–based 2nd line regimen in the context of confirmed 1st line treatment failure.

Importantly, for pregnant women living with HIV – of which there are over 300,000 annually in South Africa – this will enable them to access an ARV that is well known for its ability to rapidly suppress the virus. Where EFV may cause an average of 1 log drop in viral load over the course of a month, DTG can do the same in the course of just a week.(15) During pregnancy this rapid drop in viral load may reduce the risk of mother–to–child–transmission (MTCT). Women who initiate TLD during pregnancy can now also be given a better chance of attaining viral suppression prior to delivery, (15, 16) thus hopefully reducing the chances of MTCT. In addition, it is important to note that, although the caution around DTG use in pregnancy was only in place for women at < 6 weeks gestation, it has been generally observed than some clinicians preferred not to initiate or switch to TLD even in women attending antenatal care far beyond this stage in their pregnancy. Hence, removing all barriers to its use in pregnant women is critical to enabling this population to access DTG effectively.

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The medical community will need to think carefully about how to manage any similar future concerns around the safety of a medication during pregnancy and breastfeeding, and how to better ensure its safety before general rollout of the medication is already underway. Careful thought needs to be given to how much of a safety signal should warrant limiting access to a medication, as opposed to exercising caution and enabling women to make an informed decision. In addition, guideline development and revision processes need to ensure that they effectively include women from the HIV community in discussions and decisions.

This saga has also highlighted the ongoing failure of many HIV programmes and services to effectively integrate reliable contraceptive services into their offerings. Women living with HIV (WLHIV) still experience a high rate of unplanned pregnancies, undermining their and their babies' chances of attaining optimal health outcomes. All women who are attending health facilities regularly, as WLHIV are required to do, should be able to access integrated contraceptive services that meet their reproductive needs. They should also be assured of better access to long-acting reversible contraceptive options (LARCs) such as the implant and intrauterine contraceptive device (IUCD), with a reliable supply chain so that their ability to remain on contraception is not disrupted. HIV clinicians need to routinely inquire about and support the fertility options of men and women, ensuring that our clients have the tools they need to prevent unplanned pregnancies and plan healthy pregnancies when ready to do so. Better integration of contraceptive services with HIV care will be vital should any similar concerns of teratogenicity arise with other drugs in the future.

Many uncertainties remain as to how South Africa, other countries and the WHO can navigate similar conundrums in the future. We as clinicians now need to identify women who are still on TEE and ensure they are swiftly and safely switched to TLD. And we must get the message out to fellow healthcare workers, particularly to those working with pregnant women, and to the community as a whole: TLD should be the first choice for initiation and continuation of 1st line ART for everyone.

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