South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level Medication Review Process
Component: HIV and AIDs

TITLE: DOLUTEGRAVIR IN PREGNANT WOMEN AND WOMEN OF CHILD-BEARING POTENTIAL (WOCP)

Date: 17 June 2021

Key findings

- This review is a second update of the 2017 review. In this update, we review evidence of safety and efficacy of dolutegravir (DTG) containing ART, compared with efavirenz (EFV) containing ART in women of child-bearing potential (WOCP) and pregnant women.
- The estimate of prevalence of neural tube defects (NTDs) in infants born to women on dolutegravir (DTG) has declined since the original safety signal from the Botswana Tsepamo study as more data in that cohort has accrued. The current estimate is approximately 2 NTDs per 1000 births.
  - In the July 2020 update from this study there were 7 NTDs in 3591 births with DTG exposure (0.19%; 95%CI 0.09% to 0.40%), and 8 NTDs in 10,958 births with EFV exposure from conception (0.07%; 95%CI 0.03% to 0.17%).
  - There was no significant difference in NTD prevalence between DTG and EFV at conception (difference 0.12%; 95%CI -0.001% to 0.33%).
  - In HIV-uninfected women there were 87/119,630 with NTD (0.07%; 95%CI 0.06, 0.09%)
- The Dolphin 2 study, randomised pregnant women of 28 or more weeks to DTG (n=129) or EFV (n=128)
  - HIV viral load < 50 copies/mL at delivery: DTG 74.2% vs EFV 42.7%
- A multicentre trial, including 643 pregnant women at 14-28 weeks gestation, randomised women to DTG/FTC/TAF (n=217), DTG/FTC/TDF (n=215) or EFV/FTC/ TDF (n=211).
  - At delivery, more participants were virally suppressed at in the combined DTG containing groups than the EFV group, 98% vs 91%, difference 6·5% (95% CI 2.0% to 10.7).
  - Neonatal mortality was highest in the EFV group: DTG/FTC/TAF group 1% vs DTG/FTC/TDF 2% vs EFV 5%.
  - Composite adverse pregnancy outcome (preterm delivery/ small for gestational age/stillbirth/ spontaneous abortion) was lower in the DTG/FTC/TAF group: DTG/FTC/TAF group 24% vs DTG/3TC/TDF 33% vs EFV 33%
  - Preterm deliveries were most common in the EFV group: DTG/FTC/TAF 6% vs DTG/3TC/TDF 9% vs EFV 12%.
  - Mean weight gain was highest in the DTG/FTC/TAF group: DTG/FTC/TAF 0.378kg/week vs DTG/FTC/TDF 0.319 kg/week vs EFV/FTC/TDF 0.291kg/week. Mean weight gain in all 4 groups was lower than that recommended by the Institute of Medicine during the 2nd and 3rd trimester.
- In a RCT comparing TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV, 10% of women were obese at baseline. At 48 weeks 20% of women on TAF/FTC/DTG , 11% on TDF/FTC/DTG 9% on TDF/FTC/EFV had new onset obesity.
- In an observational cohort study in Botswana including data from 1235 HIV exposed infants whose mothers took DTG/TDF/FTC in pregnancy, and 2411 whose mothers took EFV/TDF/FTC, mother to child transmission (MTCT) was rare when either regimen started before conception: DTG 0/213 (0%, 95% CI 0.00% to 1.72%) vs EFV 1/1497 (0.07%, 95% CI 0.00% to 0.37%). MTCT rates were similar when ART was started during pregnancy DTG 8/999 vs EFV 8/883 Risk difference 0.11% (95% CI -0.79 to 1.06%).

PHC/ADULT HOSPITAL LEVEL COMMITTEE AND NEMLC RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X

Recommendation: The PHC/Adult Hospital Level Committee recommends that dolutegravir should be part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of child-bearing potential. The existing contra-indication in pregnancy should be removed from the STG.

Rationale: The risk of neural tube defects in infants exposed to dolutegravir in early pregnancy that was first identified in the Tsepamo observational study in Botswana has diminished over time, with the accumulation of further data. The risk difference between dolutegravir and efavirenz is no longer significant.
Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is unlikely to be clinically relevant.
Randomised controlled trials have shown non-inferiority in terms of maternal viral suppression rates at 48 weeks. Dolutegravir causes more rapid viral suppression than efavirenz, resulting in increased viral suppression rates by time of delivery in randomised controlled trials of ART initiation in the second and third trimester of pregnancy. This has not yet translated into a demonstrable difference in mother-to-child transmission risk, but event rates are very low with both regimens.
A standardised regimen for all adults and adolescents living with HIV is likely to be easier for nurses to provide.
Based on those findings and observations, the PHC/Adult Hospital Level Committee feel that the potential long-term benefits to pregnant women and WOCP, as well as potential short-term benefits to their infants, outweigh the risks.
Level of Evidence: Moderate certainty of evidence
Review indicator: New evidence of harms
(Refer to appendix 2 for the evidence to decision framework)

NEMLC MEETING OF 24 JUNE 2021:
NEMLC Recommendation: The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme.
It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.

Monitoring and evaluation considerations

Research priorities

BACKGROUND

The first review of dolutegravir (DTG) was conducted by the Primary Health Care (PHC) Expert Review Committee (ERC) in 2017, and was updated in 2019. In 2019 NEMLC recommended that DTG be included in South African antiretroviral therapy (ART) guidelines as a first-line agent, based on evidence of superior efficacy to efavirenz, and higher barrier to emergence of resistance. The paucity of evidence for use in pregnancy was noted, and NEMLC recommended that DTG should be avoided in early pregnancy and in women of child-bearing potential (WOCP) who are not on reliable contraception because of concerns regarding increased risk of neural tube defects (NTDs) with periconception and early first trimester exposure (Zash, Makhema, and Shapiro 2018).

A pooled sequence analysis found pretreatment HIV-1 Drug Resistance in less than 5% of antiretroviral therapy-naive adults in South Africa before 2009 (Chimukangara et al. 2019). By 2015 this had increased to 11·9% (95% confidence interval (CI) 9.2 to 15.0) in 2015. Pooled annual prevalence of non-nucleoside reverse-transcriptase inhibitor (NNRTI) resistance pre-therapy increased from below 5% in 2011 to 10.0% (95% CI 8.4 to 11.8) by 2014. In the 2017 national HIV household survey, 15 % of respondents not on ART, and 56% of ART defaulters had NNRTI resistance (Moyo et al. 2020) The increased prevalence of pre-treatment NNRTI resistance may put both antiretroviral naïve and previously ART exposed patients initiated on efavirenz at increased risk of treatment failure.

Phillips et al (2019) modelled risks and benefits of tenofovir (TDF), lamivudine (3TC), and DTG in sub-Saharan patients, including WOCP (Phillips et al. 2019). The model included drug resistance, efficacy in reducing viral load and clinical treatment outcomes, as well as potential for NTDs (based on the 12 times higher risk of NTD with DTG compared to non-DTG ART in the first Tsepamo report). In the model, benefits of averted disability adjusted life years (DALYs) of transitioning to a regimen of TDF, 3TC, and DTG for all people on ART, considerably outweighed the risks. The model projected that the reduction in risk of mother-to-child transmission was greater than the increased risk of NTD with the TDF, 3TC, and DTG for all on ART. Substantially more DALYs were averted with the TDF, 3TC, and DTG for all individuals on ART. Additionally, DTG for all on ART regimen was cost-effective in most (83% of setting scenarios) compared with the same regimen dependent on viral load suppression and intention to have more children (cost effective in <1% of setting scenarios). Dugdale *et al*., (2019) modelled three outcomes in South African women with HIV (age 15 to 49 years) starting or continuing first-line ART, and their children: (1) maternal and infant mortality, (2) sexual and pediatric HIV transmissions, and (3) NTDs (estimate of increased risk from 1st Tsepamo report) for three strategies i.e. (1) DTG for all, (2) EFV for all, or (3) EFV without contraception or DTG with contraception (WHO approach at the time)(Dugdale et al. 2019). Combined deaths among women and children were lowest with DTG (358,000) compared to the WHO approach (362,800) or EFV (367,300). DTG averted 13,700 women's deaths (0.44% decrease) compared to EFV. Over the 5-year time horizon DTG increased total pediatric deaths compared to EFV by 4,400 and WHO by 4,100 due to more NTDs. However, the combined maternal and infant mortality was more favorable for DTG compared to EFV because DTG resulted in 3.1-fold fewer deaths (13,700) among women. Clinical outcomes for woman were better in the DTG group than the EFV group (70,400 more women were virologically suppressed and 39,700 fewer severe opportunistic infections). DTG was superior to the WHO approach for all outcomes in woman. DTG resulted in fewer projected sexual transmissions to partners over five years compared with EFV or the WHO approach. Similarly, DTG averted more pediatric HIV transmissions compared to EFV and the WHO approach; 7,100 and 6,700 respectively. Compared to EFV, DTG resulted in 2,100 fewer non-NTD related deaths but 6,400 more projected NTDs. In the WHO approach most conceptions occurred among women on EFV resulting in the outcomes for WHO group being like the EFV group. Overall, in the DTG group, 3,000 more children were alive and HIV-free at five years. Both of these modelling analyses suggested considerable benefit from DTG containing ART, despite including a higher risk of NTD than more recent data suggests.

In 2019, the World Health Organisation updated its guidance to recommend DTG containing regimens as the preferred option for first line and second-line antiretroviral treatment for all populations, including pregnant women and WOCP(World Health Organization 2019).

This update focuses on use of DTG in women of childbearing potential, including pregnancy women, and reviews evidence that has emerged since the last NEMLC recommendation in 2019.[Error! Bookmark not defined.]

QUESTION: In pregnant woman and WOCP living with HIV taking first-line antiretroviral therapy, is dolutegravir more efficacious, better tolerated, and of similar safety compared to efavirenz?

METHODS

We updated the previous NEMLC DTG review (26 January 2017 (first update 11 February 2019). The original review and 2019 update included data on all adult patients. In this update, we focused on first-line treatment with DTG in pregnant woman and WOCP. We searched from June 2018, to give 6 months of overlap with the previous update. For the search strategy see Appendix 1. PubMed and the Clinical Trials.gov Register were systematically searched on 3 June 2021 (Appendix 1). Records retrieved from PubMed were extracted to Covidence while the Clinical Trials.gov results were extracted to Microsoft Excel. Screening of titles and abstracts were conducted in duplicate (ND, MR) with disagreement handled through discussion and a tie breaker (LF). Full texts were reviewed in duplicate (ND, LF) with disagreements handled by a tie breaker (KC). Records were excluded based on eligibility criteria. Data from relevant articles was extracted by 5 reviewers (KC, ND, RdW, LF, MR) into a narrative table of results.

Eligibility criteria for review

Population: Pregnant HIV positive women, WOCP

Intervention: DTG-containing ART

Comparators: EFV-containing ART

Outcomes: Viral suppression rates, mortality, development of resistance mutations, rates of perinatal transmission, adverse pregnancy outcomes (miscarriages, preterm delivery, small for gestational age, still birth, neonatal death), congenital anomalies, terminations for congenital anomalies, neural tube defects adverse events, adverse reactions.

Study designs:

- Efficacy: Systematic Reviews of Randomized Control Trials (RCTs), RCTs
- Harms: RCTs, prospective cohort studies, retrospective cohort studies, pregnancy registries, systematic reviews

RESULTS

RESULTS OF THE SEARCH

The search retrieved 134 PubMed records after removing duplicates. The Clinical Trials.gov search retrieved 13 records none of which were relevant as the studies did not meet the eligibility criteria, were ongoing or had already been retrieved in the PubMed search. After reviewing titles and abstracts in duplicate, we excluded 95 records, leaving 39 studies for full text review. After full text review, 18 reports met our inclusion criteria, of which 2 were already included in the 2019 update of this review. We also included an AIDS 2020 conference abstract and presentation which presented updated results for one of the included studies.

Table 1 reports the main characteristics and outcomes reported in the 16 study reports included in this update Table 2 summarizes the 2 papers reported initial findings from the Tsepamo study in Botswana (the previous update did not include summary tables for included studies of safety in pregnancy, so we have included these summaries to give context to the updates of this study data included in this review update). Table 3 outlines excluded studies with reasons for exclusion.

DESCRIPTION OF INCLUDED STUDIES

We included 3 RCTs comparing DTG and EFV-based ART initiated in pregnancy (Waitt et al. 2019; Kintu et al. 2020; Lockman et al. 2021).

We included 2 RCTs comparing DTG and EFV-based ART in non-pregnant adults, including WOCP (Venter et al. 2020; Venter et al. 2019; NAMSAL ANRS 12313 Study Group 2019).

We included data on pregnancy adverse outcomes from a network meta-analysis which included DTG and EFV-based ART(Kanters et al. 2020).

We included a cohort study comparing fetal biometry between DTG and EFV exposed pregnancies in Botswana(Banda et al. 2020), and a comparison of rates of gestational diabetes with DTG and EFV exposure from the same cohort(Mmasa et al. 2021)

We included two updates of the Tsepamo study analysis of prevalence neural tube defects (NTDs) with exposure to DTG and EFV at time of conception(Zash et al. 2019; Zash et al. 2020). We included a report of prospective surveillance for NTDs set up by the Botswana ministry of health in response to the initial Tsepamo signal (Raesima et al. 2019). We included an analysis of rates of NTDs within the Canadian perinatal HIV Surveillance programme (Money et al. 2019), and retrospective cohort analysis of prevalence of NTDs with DTG exposure conducted in the Brazilian antiretroviral therapy database(Pereira et al. 2021).

We included a cohort study comparing weight gain in pregnant women taking DTG and EFV(Caniglia et al. 2020).

We included an observational cohort study in Botswana compared rates of mother to child transmission (MTCT) between women on DTG and women on EFV in pregnancy(Davey et al. 2020).

Randomised controlled trials of DTG in pregnancy

The DolPHIN-1 study randomised HIV positive ART naive women in South Africa and Uganda at 28 to 36 weeks of gestation to DTG -containing ART (n=29) or EFV-containing ART (n=31) (Waitt et al. 2019). The primary endpoint was pharmacokinetics of DTG in women and breastfed infants.

- DTG resulted in significantly faster viral suppression compared to EFV, median time to viral load (VL)<50 copies/mL 32 vs 72 days.

The DolPHIN-2 study randomised HIV positive women of 28 weeks or more weeks gestation to DTG (n=129) or EFV based regimen (n=128) (Kintu et al. 2020) . Co-primary endpoints were virological suppression at 1st post-partum visit, and drug related adverse effects. Median duration of ART was 55 days (IQR 33 to 77)

Efficacy DTG vs EFV:

- HIV viral load < 50 copies/mL at delivery: 74.2% vs 42.7%
- Median time to VL < 50copies/mL: 28 days (95% CI 28–34) vs 82 days (55–97)
- Median time to VL < 1000 copies/ml: 7 days (7–20) vs 23 days (21–27)

Adverse events DTG vs EFV:

- Drug-related serious adverse event (SAE 0 in 1 (<1%) vs 0)
- Stillbirths: 3/124 (2·2%) vs 1/120 (<1%)
- No significant difference in proportion of preterm /late-preterm births
- Congenital abnormalities did not differ between groups. No NTDS in either arm
- 4/123 (3%) infant deaths vs 2/119 (2%)

Mother to child transmission:

- 3 transmissions in DTG group, zero in EFV group

Lockman et al (IMPAACT) randomised 643 pregnant women from 9 countries at 14 to 28 weeks gestation and with less than 14 days of ART exposure to DTG/ emtricitabine(FTC)/ tenofovir alafenamide (TAF) (n=217), DTG/FTC/ tenofovir dispoproxil fumerate (TDF) (n=215) or EFV/FTC/ TDF (n=211) (Lockman et al. 2021). The primary efficacy outcome was the proportion of participants with viral suppression, (HIV-1 VL< 200 copies per mL), at or within 14 days of delivery. VL available for 605 (94%) participants. Median weight was 63 kg (56 to 73) and median BMI was 25 (95% CI 22 to 28).

Efficacy

- 98% in the combined DTG-containing groups had VL suppression at delivery compared with 91% in the EFV group, estimated difference 6.5% (95% CI 2.0 to 10.7).

Adverse events

- Composite adverse pregnancy outcome (preterm delivery/ small for gestational age/stillbirth/ spontaneous abortion): DTG/FTC/TAF group 24% vs DTG/FTC/TDF 33% vs EFV/FTC/TDF 33%
- Preterm deliveries in DTG/FTC/TAF 6% vs DTG/FTC/TDF 9% vs EFV/FTC/TDF 12%.
  - Significant difference between DTG/FTC/TAF and EFV groups, difference –6·3% (95%CI –11·8 to –0·9)
- Neonatal mortality higher in EFV group: DTG/FTC/TAF 1% vs DTG/FTC/TDF 2% vs EFV/3TC/TDF 5%.

Weight gain

- Mean weight gain was highest in the DTG/FTC/TAF group: DTG/FTC/TAF 0.378kg/week vs DTG/FTC/TDF 0.319 kg/week vs EFV/FTC/TDF 0.291kg/week. Mean weight gain in all 4 groups was lower than that recommended by the Institute of Medicine during the 2nd and 3rd trimester.

RANDOMISED TRIALS THAT INCLUDED WOMEN OF CHILDBEARING POTENTIAL

Venter et al (ADVANCE study) randomised 1053 participants, 59% of them female, median age 32 years, to DTG plus emtricitabine (FTC) plus tenofovir dispoproxil fumerate (TDF) or DTG plus emtricitabine (FTC) plus tenofovir alafenamide (TAF) or TDF plus FTC plus EFV(Venter et al. 2019). EFV-based ART was standard of care in 2017 when the trial commenced. Primary end point was virological suppression (<50 copies/mL at week 48.

Efficacy

- HIV-1 viral load< 50 copies/mL at 48 weeks: 84% in the TAF-DTG group, 85% in the TDF-DTG group, and 79% in the EFV group (meeting non-inferiority definition). Efficacy results are not presented disaggregated by sex.

Safety

- Deaths: 1 in TAF-DTG, 1 in TDF-DTG, 2 in EFV
- Weight increase (both lean and fat mass) was greatest in the TAF-DTG group and among female patients. At 48 weeks 26/133 (20% of TAF-DTG group, 13/123 (11%) of the TDF-DTG group, and 9/104 (9%) of the EFV group had new onset obesity. 10% of women in the study were obese at baseline.
- 1 discontinuation in TAF-DTG group because of asymptomatic increase in aminotransferases.
- 8 EFV-linked discontinuations because of adverse reactions: 5 with liver dysfunction of which 2 symptomatic, 2 rash, 1 with neuropsychiatric adverse effects.
- No resistance to integrase inhibitors identified in patients failing the DTG-containing regimens. Four patients on EFV and 1 on DTG were found to have new NNRTI resistance.

Pregnancy outcomes

- There were 78 pregnancies (12.5% of included women), 50 on DTG-containing ART. There were no NTDs. There was 1 neonatal death (TAF/FTC/DTG arm) and 1 stillbirth in the EFV arm.

Week 96 of the IMPAACT study(Venter et al. 2020)

Efficacy

- Viral suppression to <50 copies/mL was 79%, 78%, and 74% in the TAF-DTG, TDF-DTG, and EFV groups, respectively.
- Two patients in the TDF-DTG group and 16 patients in the EFV group had resistance mutations (none to INSTIS).

Safety

- Amongst the 623 women in the study, 28%, 18%, and 12% developed obesity in the TAF-DTG, TDF-DTG, and EFV groups, respectively.
- By 96 weeks, there were 29, 25, and 34 pregnancies, with 6, 2, and 9 miscarriages in women on TAF-DTG, TDF-DTG, and EFV, respectively.

The NAMSAL study randomised 613 participants, 65.9% of them female, to DTG or EFV 400mg-based ART(NAMSAL ANRS 12313 Study Group 2019).

- Efficacy results are not presented disaggregated by sex. Primary end point was proportion of participants with VL<50 copies/mL at week 48. This was achieved in 74.5% of the DTG group and 69% of the EFV group, difference 5.5%, (95% CI -1.6 to 12.7).
- 6.2% of female participants fell pregnant during the trial, including 13 in the DTG group, all of whom were born live and without congenital anomalies.
- There was more weight gain in the DTG group than the EFV group overall.
  - Weight gain of 10% or more was observed in 147/379 (38.8%) of women vs 44/192 (22.9 %) of men.

ADVERSE PREGNANCY OUTCOMES AND CONGENITAL ANOMALIES

The Kanters et al network meta-analysis (which included data from Tsepamo and several smaller studies) found no significant differences between DTG and EFV in terms of rates of preterm birth, low birth weight, stillbirth, small for gestational age, or congenital anomalies.

A prospective cohort study (Tshilo Dikotla) in Botswana enrolled 469 pregnant women between 16 and 36 weeks gestation, including 182 on TDF.FTC/ DTG, 127 on TDF/FTC/ EFV based regimen and 160 who were HIV negative Banda et al. 2020). There was no difference in fetal biometry between the 3 groups (Banda et al. 2020).

RISK OF NEURAL TUBE DEFECTS

Tsepamo study

The risk period for neural tube defects (NTDs) is the first 28 days post-conception. Botswana transitioned to DTG in 2016. The Tsepamo cohort study in Botswana prospectively captured birth outcomes at 8 hospitals from August 2014. In 2018, they compared outcomes in women commencing DTG or non-DTG containing-ART prior to conception- this analysis was included in the 2019 update of this review. At that stage, 89,064 births had accrued of which 88,755 (99.7%) had a surface examination at birth.

- Prevalence of neural tube defects was higher in those exposed to DTG periconception than those on non-DTG containing ART: 4/426 (0.94%) versus 14/11300 (0.12%).
- At the time of this first analysis, there were no NTDs in 2812 women who started DTG during pregnancy.
- NTDs in 61 of 66057 (0.09%) infants born to HIV negative women (Zash, Makhema, and Shapiro 2018).

Tsepamo included 8 public hospital maternity wards from August 2014 to June 2018. Ten additional sites were added between July 2018 and March 2019, giving coverage of approximately 70% of births in Botswana.

Tsepamo 2019 update (Zash et al. 2019)

As at March 31, 2019 there were 119,477 deliveries, 119,033 (99.6% had an infant surface examination. This included 1683 on DTG from conception, 14792 on non-DTG ART from conception, of which 7959 were on EFV from conception, and 3840 who started DTG pregnancy. There was data from 89272 HIV negative mothers.

- There were 98 NTDs (0.08% of deliveries)
- The prevalence of NTDS remained slightly higher in association with DTG exposure at conception than with other types of ART exposure at conception (3 per 1000 deliveries vs. 1 per 1000 deliveries).
  - 5 NTDs in 1683 deliveries in mothers taking DTG at conception, (0.30% of deliveries; 95% CI 0.13 – 0.69). (2 myelomeningocele, 1 anencephaly, 1 encephalocele, 1 iniencephaly)
  - 15 NTDs in 14792 women taking non DTG ART from conception (0.10%; 95% CI 0.06 – 0.17) infants. Prevalence difference was 0.20 (95% CI 0.01 – 0.59) vs the reference DTG from conception.
  - 3 NTDs in 7959 women taking EFV from Conception: (0.04%; 95% CI 0.01 – 0.11) infants. Prevalence Difference: 0.26 (95% CI 0.07 – 0.66) vs the reference DTG from conception
  - 1 NTD in 3840 women who commenced DTG during pregnancy (0.03%; 95% CI 0.00 – 0.15) infants. Prevalence Difference: 0.27 (95% CI 0.06 – 0.67) vs the reference DTG from conception
  - 70 NTDs in 89372 HIV negative women (0.08%; 95% CI 0.06– 0.10) infants. -Prevalence Difference: 0.22 (95% CI 0.05 – 0.62) vs the reference DTG from conception

Tsepamo 2020 update(Zash et al. 2020)

An update was presented at the AIDS conference in July 2020, including data from 39,200 additional births, which included 1908 additional DTG conception exposures.

- Since August 2014, 158,244 deliveries; 153,899 (97.2%) with infant surface exam
- 126 NTDs (0.08%, 95%CI 0.07%,0.09%)
- Prevalence of NTDs in infants born to women on DTG decline since the original safety signal. Prevalence estimate seems to be stabilizing at approximately 2 per 1000.
  - No significant difference between DTG and non-DTG- ART at conception (0.09% difference; 95%CI -0.03%, 0.30%).
  - No significant difference between DTG and EFV at conception (0.12% difference; 95%CI -0.001%, 0.33%).
  - DTG at conception, 7/3591 with NTD (0.19%; 95%CI 0.09%, 0.40%): 3 myelomeningoceles, 1 anencephaly, 2 encephaloceles, and 1 iniencephaly
  - Non DTG-ART 21/19 with NTD,361 (0.11%; 95%CI 0.07%, 0.17%)
  - EFV from conception 8/10,958 with NTD (0.07%; 95%CI 0.03%, 0.17%)
  - DTG started in pregnancy 2/4,581 with NTD (0.04%; 95%CI 0.1%, 0.16%)
  - HIV-uninfected women 87/119,630 with NTD (0.07%; 95%CI 0.06, 0.09%)

In response to the signal from the Tsepamo study, the Botswana ministry of health expanded surveillance for NTDs to 22 non-Tsepamo facilities (Raesima et al. 2019). Midwives conducted surface examination of liveborn and stillborn infants.

- From October 2018- 31 March 2019 there were 3076 deliveries, of which 2328 (76%) HIV negative, 742 (24%) HIV positive, and 6 (<1%) HIV unknown.
- There were 544 (73% with ART exposure at conception, of which 152 (28%) were DTG exposed.
- There were 3 confirmed/probable NTDs, 1 in DTG exposed, 2 in HIV negative.
  - NTD prevalence with DTG exposure was 0.66% (95%CI 0.02-3.69)
  - NTD prevalence in babies born to HIV negative mothers was 0.09% (95% CI 0.01-0.31)

- Difference between DTG based ART and non-DTG based NTD prevalence was 0.66% (95% CI -0.48-3.63)

This study lacked power for precise estimate of NTD prevalence with DTG-exposure at conception.

The Canadian perinatal HIV Surveillance programme collects data on pregnant women living with HIV (WLWH), and their babies (Money et al. 2019).

- Between 2007 and 2017, 85 of 2423 WLWH (3.5%, 95% CI 2.85–4.36%) had non-chromosomal congenital anomalies.
- Rates of congenital anomalies were similar between women who were on ART in their first trimester (3.9%, CI 1.7–7.6%) and those without 1st trimester ART exposure (3.9%, 95% CI 2.6–5.6%)
- 4/80 (5.0%, 95% CI 1.4–12.3%) neonates born to WLWH on DTG during the first trimester had congenital anomalies, none were neural tube defects (95% CI0.00–3.10%). There were very few first trimester DTG exposures and this study lacked power to detect rare events such as NTDs. The cohort included women on efavirenz, but rate of congenital anomalies not reported for EFV-containing ART.

A retrospective cohort analysis was conducted in the Brazilian antiretroviral therapy database(Pereira et al. 2021). Women with DTG exposure within 8 weeks of estimated conception between Jan 1, 2017, and May 31, 2018 were matched 3:1 with pregnant women exposed to EFV between Jan 1, 2015, and May 31, 2018. Primary outcomes were NTD and a composite measure of NTD, stillbirth, or miscarriage.

- 382/ 1427 were exposed to DTG within 8 weeks of estimated date of conception. During pregnancy, 183 (48%) of 382 DTG-exposed and 465 (44%) of 1045 EFV-exposed women received folic acid supplementation.
- There were no NTDs in either DTG-exposed (0, 95% CI 0–0.0010) or efavirenz-exposed groups (0, 95% CI 0–0·0036).
- There were 23 (6%) stillbirths or miscarriages in 384 DTG-exposed fetuses and 28 (3%) in the 1068 EFV-exposed fetuses (p=0·0037).
- After study closure, 2 NTDs in fetuses with periconception DTG exposure were reported to public health officials. Estimate of NTD incidence incorporating these cases and the estimated number of additional DTG-exposed pregnancies between Jan 1, 2015, and Feb 28, 2019, was 1.8 (95% CI 0·5–6·7) per 1000 DTG-exposed pregnancies.

MOTHER TO CHILD TRANSMISSION

An observational cohort study in Botswana compared rates of mother to child transmission (MTCT) between women on DTG and women on EFV in pregnancy(Davey et al. 2020). The analysis included data from 1235 HIV exposed infants whose mothers took DTG/TDF/FTC in pregnancy, and 2411 whose mothers took EFV/TDF/FTC.

- Mother to child transmission (MTCT) was rare when either regimen started before conception: DTG 0/213 (0%, 95% CI 0.00% to 1.72%) vs EFV 1/1497 (0.07%, 95% CI 0.00% to 0.37%).
- MTCT rates were similar when ART was started during pregnancy DTG 8/999 (0.80%, 95% CI 0.35 to 1.57%) vs EFV 8/883 (0.91, 95% CI 0.39 to 1.78%) Risk difference 0.11% (95% CI -0.79 to 1.06%).
- Most transmissions were in women starting ART <90 days before delivery: DTG 4/8 vs EFV 6/9.

ADVERSE EVENTS FROM NON-RANDOMISED STUDIES

<u>Weight gain in mothers during pregnancy</u>

Weight gain during pregnancy was explored in pregnant women commencing DTG or EFV-based ART before 17 weeks of gestation in the Tsepamo cohort in Botswana(Caniglia et al. 2020). The analysis included 1683 women on DTG, 1464 on EFV, and 21 917 HIV uninfected women.

- Women on DTG and EFV both gained less weight during pregnancy compared to uninfected people.
- DTG was associated with decreased risk of insufficient weight gain.
- EFV was associated with less risk of excessive weight gain.

<u>Gestational diabetes</u>

The Tshilo Dikotla prospective cohort in Botswana screened 468 pregnant women for gestational diabetes using a 75g oral glucose tolerance test, of which 486 were PLWHA(Mmasa et al. 2021). Women known to be diabetic were excluded.

- 8.4% of women had gestational diabetes, this was similar between PLWHA and HIV negative women.
- PLWHA taking DTG-containing ART had lower risk of gestational diabetes than those on EFV; 6.1% vs 13.5%.
  - adjusted odds ratio 0.40, 95%CI 0.18 to 0.92), in a model including age, BMI, gravidity, CD4 count, and whether or not patient was on ART at the time of conception.

CONCLUSION

The Tsepamo study (Botswana) surveying birth outcomes in infants born to woman on DTG regimens provided the signal of harm (increased NTDs) in 2018(Zash et al. 2018). The updates in 2019 and 2020 have been reassuring - as more data has accrued the difference observed in the rate of NTDs between women taking DTG-based regimens at the time of conception compared to other antiretroviral drugs has shrunk, and is no longer significantly different(Zash et al. 2019; Zash et al. 2020). The current estimate of prevalence of NTDs in pregnancies with DTG exposure at time of conception in Botswana is 2 per 1000. The estimated prevalence in a recent retrospective cohort study in Brazil was similar (1.8 per 1000 DTG exposed pregnancies), but the study is underpowered and the estimate lacks precision(Pereira et al. 2021).

DTG causes more rapid viral load suppression in pregnancy than efavirenz. This could potentially reduce the risk of vertical HIV transmission in mothers who are initiated on DTG treatment in late pregnancy. However, rates of MTCT were similar for DTG and EFV-based ART in a cohort study in Botswana, and transmission event were rare(Davey et al. 2020).

In RCTS, both pregnant and non-pregnant women gained more weight in the DTG than the EFV arm(Venter et al. 2019; Venter et al. 2020; Lockman et al. 2021), especially in those on concomitant tenofovir alafenamide. The mechanism postulated for this difference is impaired weight gain in individuals taking EFV who have the slow metaboliser cytochrome P450 2B6 genotype, which is common in African patients(Griesel et al. 2020). Slow metabolizers have higher EFV concentrations than extensive metabolizers, which may result in increased mitochondrial toxicity from EFV. In the Tsepamo study, DTG in pregnancy was associated with decreased risk of insufficient weight gain and EFV was associated with less risk of excessive weight gain (Caniglia et al. 2020). However, women on either drug gained less weight than HIV negative women.

Based on the benefits to women in terms of viral suppression and reduced risk of drug resistance, and the fact that the risk of neural tube defects in infants exposed to dolutegravir in early pregnancy is no longer significantly different to those exposed to non-dolutegravir-based regimens, dolutegravir should form part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of childbearing potential, even if not on reliable contraception.

Reviewers: Karen Cohen, Natasha Davies, Lee Fairlie, Milli Reddy, Renee de Waal.

Declaration of interests: KC (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town), ND (Anova Health Institute), MR (Better Health Programme, South Africa), RdW (Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town) have nothing to declare in respect of dolutegravir in HIV. LF (WITS RHI) co-authored HIV publications of which some are included in this review, ND (Anova Health Institute) received a scholarship from Gilead to attend the International AIDS Society conference, in Mexico City in July 2019 and discloses involvement with Southern African HIV Clinicians' Society in development and updating of adult ART guidelines and statements pertaining to the use of dolutegravir in pregnant women and women of child-bearing potential following release of the Tsepamo data update July 2020.

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Table 1. Characteristics of included publications

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Banda FM et al. 2020.	Design: Prospective cohort study (Tshilo DIkotla cohort), Botswana, August 2016-May 2019 Funding: National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) (R01DK109881) COI: none declared	• Pregnant WLHIV and pregnant women without HIV • Between 16-36 weeks gestation • Women on TDF/FTC with DTG or EFV during pregnancy • 469 women enrolled • 182 on DTG based regimen • 127 EFV based regimen • 160 HIV negative Exclusions • Multiple gestations Fetal demise	**Exposures** TDF/FTC/DTG TDF/FTC/EFV	• Head circumference, Biparietal diameter, Abdominal circumference, Femoral length Z scores • Measurements taken during single ultrasound performed in second trimester • Association of in-utero HIV/ART exposure with each fetal biometric Z score	Median Age: EFV based: 32 years (older) DTG based 28 years p<0.01 HIV negative: 24 years Parity: EFV based: 3 DTG based 2 p<0.01 HIV negative: 1 Tertiary education: EFV based: 7.9% DTG based 14.3% p<0.01 HIV negative: 33.1% Gestational age: HIV positive: 28 weeks HIV negative: 26 weeks p<0.01 Viral load and CD4 values similar in both ART groups No significant differences in Z scores between groups, even with adjustments for maternal age, height, education level, parity, alcohol use in pregnancy	• No significant differences in fetal biometry between DTG exposed, EFV exposed and HIV unexposed fetuses Limitations: • Single study site • Small sample size • Single ultrasound (not longitudinal) • No birth follow up to confirm any congenital anomalies at birth Conclusion: • Reassuring results supporting safety of use of DTG in pregnancy.
Caniglia et al, 2020	National birth outcomes surveillance, Botswana (Tsepamo) Funding: NIH No COI declared	Inclusion: • Pregnant women • First time ART initiators • ART start before 17 weeks' gestation • DTG- or EFV-based regimens • HIV-uninfected group for comparison DTG: n=1 683 EFV: n=1 464 HIV-uninfected: n=21 917	EFV DTG HIV-uninfected	**Primary** • Weekly weight gain from 18±2 weeks' gestation to 36±2 weeks' gestation • Total weight gain over 18 weeks **Secondary** • Weight gain >0.59 kg/week • Weight gain <0.18 kg/week (above 2 categories based on Institute of Medicine recommendations) • Weight loss	**Weekly weight gain**, mean (SD) kg: EFV: 0.31 (0.23) DTG: 0.35 (0.22) HIV-uninfected: 0.44 (0.23) Adjusted mean difference versus EFV (95% CI) kg: DTG: 0.05 (0.03 to 0.07) HIV-uninfected: 0.12 (0.10 to 0.14) **Total weight gain**, mean (SD) kg: EFV: 5.3 (4.35) DTG: 6.27 (3.96) HIV-uninfected: 7.95 (4.11) Adjusted mean difference versus EFV (95% CI) kg: DTG: 1.05 (0.61 to 1.49) HIV-uninfected: 2.31 (1.85 to 2.77)	• HIV-uninfected women were more likely to be nulliparous and primigravid than HIV-infected women; women on DTG were less likely to have CD4 measured, had lower CD4 counts, and initiated ART earlier than those on EFV; other baseline characteristics were similar. • Analyses adjusted for age, CD4, employment, education, parity, gravidity, marital status, site, smoking, alcohol use, pre-pregnancy weight, baseline weight, gestational age at ART initiation, medical history (results very similar for crude analyses). • The authors state that the clinical significance of their findings is uncertain, but that lower weight gain is associated with increased risk of preterm birth and lower birth weight, and higher weight gain is associated with pregnancy and delivery complications. They also conclude that HIV and/or ART might impact weight gain.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
					Weekly weight gain >0.59 kg, adjusted risk ratio versus EFV (95% CI): EFV: 9.1% DTG: 12.9%, 1.44 (1.11 to 1.87) HIV-uninfected: 23.1%, 2.41 (1.81 to 3.21) **Weekly weight gain <0.18 kg**, adjusted risk ratio versus EFV (95% CI): EFV: 27.7% DTG: 20.2%, 0.73 (0.63 to 0.86) HIV-uninfected: 11.1%, 0.48 (0.41 to 0.57) **Weight loss**, adjusted risk ratio versus EFV (95% CI): EFV: 9.4% DTG: 4.4%, 0.43 (0.28 to 0.67) HIV-uninfected: 2.2%, 0.30 (0.19 to 0.47)	
Crowell et al, 2020.	Prospective cohort study (22 sites in United States including Puerto Rico; from 2007 to 2017) Follow-up duration: Youth followed up to 18 years Funding: Eunice Kennedy Shriver National Institute of Child Health and Human Development with co-funding from the National Institute of Dental and Craniofacial Research, the National Institute of Allergy and Infectious Diseases, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, Office of AIDS Research, the National Institute of Mental Health, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism, through Cooperative agreements	Sample size: 3747 children - HIV-exposed but uninfected (CHEU) and exposed *in utero* to ARVs Two cohorts: • Static cohort (enrolled from 2007–2009; 1–12 years; participated in prior studies with available pregnancy and birth data) • Dynamic cohort (enrolled during gestation or within 1 week after birth) Patient characteristics: 48% girls 68% black and 31% Hispanic. Maternal tobacco use: 17% Maternal alcohol use: 8% Maternal marijuana use: 8% Maternal Cocaine/opiates use: 3% Inclusion criteria: CHEU enrolled by 1 April 2017 and had a study visit for neurologic trigger assessment by 1 August 2017 (triggers for potential neurologic diagnoses defined as a febrile or afebrile	Exposures: • ARVs (3747) • EFV vs control (166 vs 3487) • DTG vs control (94 vs 688)	**Primary outcome:** Neurological adverse event associated with ARVs (febrile or afebrile seizure, microcephaly, or other neurologic or ophthalmologic disorders)	**Primary outcome:** All ARVs • ***Neurological cases:*** ○ 231/3747 (6.2%, 95% CI 5.4% to 7.0%) over a median follow-up of 4.3 years (IQR: 1.4–7.0). • ***Neurologic diagnoses*** ○ Microcephaly: 25.1% ○ Febrile seizure: 17.6% ○ Eye-related abnormalities (esotropia, exotropia,strabismus, ptosis, nystagmus, ambylopia, and optic nerve abnormalities: 16.5% ○ Nonfebrile seizure:13.5% **Sub-analyses:** EFV vs control • ***Neurological cases:*** ○ 15/166 (9%) vs 211/3487 (6.1%), adjusted RR (aRR) 1.53 (95% CI 0.94 to 2.51), p=0.090 ○ At conception: aRR = 1.92 (95% CI 1.09 to 3.36) DTG vs control • ***Neurological cases:*** ○ 15/166 (9%) vs 211/3487 (6.1%), aRR 43 (95% CI 0.75 to 7.84), p=0.14 ○ At conception: aRR = 3.47 (95% CI 0.74 to 16.36) ○ At conception: aRR = 2.95 (95% CI 0.79 to 11.1)	• An observational study to determine neurological harms associated with ARVs • As models were restricted to children born after 2007 for darunavir and raltegravir, after 2011 for rilpivirine, and after 2013 for DTG and elvitegravir – due to drug approval dates, the study cohorts for DTG (n=94) was not comparable in size to EFV (n=166) • Of 3747 children enrolled, 94 lacked detailed ARV information and was excluded from the analysis – missing information for 2.5% of study population; some concern of selection bias • Maternal substance use was through self-reporting questionnaires that may have contributed to reporting bias at baseline. • Assessors in the panel that classified neurological triggers in CHEU, were blinded to the ARVs their mothers used. • Information on the controls are not clearly reported. • Sensitivity analyses were done to account for possible bias, adjusting for confounders such as maternal factors (age, race, ethnicity, chronic health conditions, obstetrical complications, and substance use), birth cohort (<2011, 2011–2014, 2015–2017), and family/household factors (socioeconomic status, household income level, and caregiver education level). • Adjusting for confounders, resulted in persistent association of EFV exposure with a risk for neurological adverse events.

<table>
<tr><th>Citation</th><th>Study design</th><th>Population</th><th>Exposures and control</th><th>Outcomes</th><th>Effect sizes</th><th>Comments</th></tr>
<tr><td></td><td>with the Harvard T.H. Chan School of Public Health and the Tulane University School of Medicine.

Declarations: E.G.C. holds stock in Abbot and AbbVie. All other authors report no conflicts of interest.</td><td>seizure, microcephaly, or other neurologic or ophthalmologic disorders)

Exclusion criteria:
Neurologic diagnoses determined to be secondary to events occurring after birth (e.g. postnatal meningitis, trauma)</td><td></td><td></td><td></td><td>• In utero DTG exposure was associated with an increased risk of a neurologic diagnosis but imprecision was high, due to the small number of exposed cases.</td></tr>
<tr><td>Davey et al, 2020</td><td>National surveillance, Botswana.
Early Infant Treatment Study screened infants for HIV at 20% of delivery facilities in the country; those in Tsepamo registry were linked to establish ART regimen

Funding: NIH
No COI declared</td><td>Total infants screened: n=10 622

Liked to Tsepamo:
Exposed to DTG: n=1 235
Exposed to EFV: n= 2 411
Exposed to other ART: n=1 246
Exposed to multiple ART regimens: n=37
No ART exposure: n=135</td><td>DTG
EFV
Other regimens
No ART</td><td>MTCT rates</td><td>MTCT, n, % (95%CI):
Overall
DTG: 8/1 235, 0.64 (0.28 to 1.27)
EFV: 9/2 411, 0.37 (0.17 to 0.71)
Other regimens: 2/1283, 0.16 (0.02 to 0.56)
No ART: 6/135, 4.44 (1.65 to 9.24)

ART initiated before pregnancy
DTG: 0/213, 0 (0 to 1.72)
EFV: 1/1 497, 0.07 (0 to 0.37)

ART initiated during pregnancy
DTG: 8/999, 0.80 (0.35 to 1.57)
EFV: 8/883, 0.91 (0.39 to 1.78)
Risk difference: 0.11%, 95% CI -0.79 to 1.06</td><td>• Those on ‘other’ ART regimens were less likely to be diagnosed during pregnancy, less likely to start ART during pregnancy, and had a longer duration of ART exposure than those on EFV or DTG.</td></tr>
<tr><td>Kanters et al, 2020</td><td>Systematic review and network meta-analysis

Funding: WHO HIV department</td><td>For pregnancy outcomes the authors included 54 references from 35 studies. Studies included RCTs, comparative and non-comparative observational cohorts, and population-level surveillance or registries.</td><td>DTG
EFV</td><td>Preterm birth
Low birth weight
Small for gestational age
Congenital abnormalities
Still birth
Maternal death
Neonatal death
MTCT
NTDs</td><td>Pregnancies with pre- and post-conception exposures to DTG versus EFV
<table><tr><th>Outcome</th><th>Odds ratio</th><th>95% credible interval</th></tr><tr><td>Preterm</td><td>0.99</td><td>0.85 to 1.14</td></tr><tr><td>LBW</td><td>0.93</td><td>0.80 to 1.08</td></tr><tr><td>SGA</td><td>0.93</td><td>0.80 to 1.07</td></tr><tr><td>CA</td><td>1.06</td><td>0.40 to 2.86</td></tr><tr><td>Stillbirth</td><td>1.03</td><td>0.72 to 1.46</td></tr><tr><td>M. death</td><td>0.09</td><td>0.00 to 39.39</td></tr><tr><td>N. death</td><td>1.03</td><td>0.65 to 1.62</td></tr><tr><td>MTCT</td><td>6.87</td><td>0.74 to 39.10</td></tr></table>
Any adverse birth outcome
DTG: 33.2%
EFV: 35%

Neural tube defects
DTG: 6/1835
EFV: 3/8220
Risk difference 0.29% (95% CI 0.10 to 0.68)</td><td>• Most data on pregnancy outcomes is from Tsepamo (the other studies were relatively small in comparison).
• The NTD estimate is based on Tsepamo and the Raesima et al study only, because of variability in folic acid supplementation and background event rates. Tsepamo data up until March 2019 was included.
• Other outcomes (efficacy) were reported overall, and not for women separately.</td></tr>
</table>

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Kintu et al, 2020. DolPHIN-2 Study Group.	Randomised, open-label trail in Cape Town, South Africa (8 PHC facilities) and Kampala, Uganda (8 PHC antenatal facilities); from January to August 2018 Funding: Funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.	Sample size: 268 screened, 128 randomised to DTG (n=129) or EFV based regimen (n=128) Inclusion criteria: Woman≥ 18 yrs with untreated but confirmed HIV, positive pregnancy test, ± gestation of ≥28 weeks, provided consent. Exclusion Criteria: ART in the preceding year or ever received integrase inhibitors; documented virological failure of a non-nucleoside containing ART; previous EFV toxic events or clinical history precluding randomisation; estimated glomerular filtration rate <50 mL/min; haemoglobin <8.0 g/dL; decompensated liver disease or alanine aminotransferase > 5x upper limit of normal (ULN); or alanine aminotransferase >3x ULN and bilirubin >2x ULN (with >35% direct bilirubin); severe pre-eclampsia; medical, psychiatric, or obstetric condition that might affect participation; receiving any drugs significantly interacting with EFV or DTG within the preceding 2 weeks. *In June 2018, protocol amended to exclude patients with pretreatment HIV VL of < 50 copies/ml	**DTG (50 mg) or EFV** plus TDF (300 mg) plus FTC (200 mg) in South Africa or 3TC (300 mg) in Uganda) Both administered as single tablet once daily.	**Primary outcomes:** **Efficacy:** HIV viral load < 50 copies/mL at birth **Safety:** Frequency of drug-related adverse events. **Secondary Outcomes:** -viral load of <1000 copies/mL at birth, -occurrence of mother-to-child transmission -safety & tolerability of DTG in mothers and breastfed infants	**Primary outcomes:** *DTG Vs EFV :* **HIV viral load < 50 copies/mL @ birth (mothers):** 89/120 (74·2%) vs 50/117 (42·7%) **Median time to VL < 50copies/mL:** 28 days (95% CI 28–34) vs 82 days (55–97) **Median time to VL < 1000 copies/ml:** 7 days (7–20) vs 23 days (21–27) **Frequency of drug-related adverse events:** • ≥1 SAE: 30 (22%) vs 14 (11%) • ≥1 drug-related SAE 1 (<1%) vs 0 • ≥1 or immune reconstitution inflammatory syndrome (IRIS)-related SAE 1 (<1%) vs 0 **Secondary outcomes:** **Viral load of <1000 copies/mL at birth:** 112/120 (93%) vs 96/117 (82%) **Mother-to-child transmission:** 3 transmissions in DTG group **Safety & tolerability of DTG in mothers and breastfed infants:** Higher frequency of pregnancy, puerperium, and perinatal events in mothers receiving DTG vs EFV: • Stillbirths: 3/124 (2·2%) vs 1/120 (<1%). • 123 vs 119 live births • Median gestation at birth of 39 weeks (IQR 37·3–40·3) - both groups • No significant difference in proportion of preterm, late-preterm births, frequency of serious adverse events, infant birthweights • Congenital disorders (umbilical hernias, birth marks, skin dimples, acrochordon, heterochromia iridis, laryngomalacia, strabismus, talipes, cleft palate, and polydactyly) did not differ between groups • 0 neural tube defects • 4/123 (3%) infant deaths vs 2/119 (2%)	• Women on DTG regimen more likely to achieve VL< 50 copies per/ml / less likely to have a VL of ≥50 copies/mL) at time of birth (initiated in the third trimester) • Undisclosed ART unlikely - mothers with a VL < 50 copies/mL excluded at baseline • 7 & 28 day visit days used as a measure of time from randomization to viral load suppression which might have biased the true time of viral load suppression (but same in both groups) • For this population, peripartum HIV transmission strongly correlated with prevailing maternal VL therefore DTG regimens might reduce HIV transmission around birth & potentially during breastfeeding, compared with EFV regimens • 3 HIV-infected infants were likely to have had in-utero infections, but peripartum transmission cannot be excluded because infants not tested within 2 days of birth • Higher proportion of mothers who received DTG had serious adverse events Finding driven by a higher overall frequency of pregnancy, puerperium, and perinatal events in mothers receiving DTG, who had prolonged pregnancy beyond term. • 4 stillbirths - related to obstetric & severe maternal infection. • Sample size not large enough to study differences in infant transmissions, but powered to detect virological superiority before or at time of birth (best validated proxy for vertical HIV transmission) • Results were robust in sensitivity analysis. The DolPHIN-2 results strongly support global transition to DTG use in first-line ART
Kouafack et al, 2019. New Antiretroviral and Monitoring	Open-label, multicenter, randomized, phase 3 noninferiority trial (48 weeks – July 2016 – August 2017).	Sample size: N=613 Patient characteristics:	**Exposures:** • DTG regimen • EFV (400-mg) regimen	**Primary outcome:** • Proportion of participants with a VL of <50 copies/ml at week 48 **Secondary outcomes:**	**Patient Characteristics:** -Baseline values balanced between groups. Median age - 37 years. **65.9% (n=404) of the participants were women.** Median baseline VL - 5.3 $\log_{10}$ copies/ml. 66.4% -baseline VL of at least 100,000 copies/milliliter. Median CD4+ T-cell count	• Study included both men and women (no pregnant women) • Results showed noninferiority of DTG to EFV400 with regard to viral suppression at week 48.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Strategies in HIV-Infected Adults in Low-Income Countries **(NAMSAL)**	Study Setting: Cameroon Two Arms: -n=310 DTG -n=306 EFV -Randomization, 1:1 ratio, to receive DTG/EFV400 Follow-up duration: follow-up until week 96	Adults, **both males & females**, HIV – infected, HIV treatment naïve. 66.4% had a viral load (VL) of ≥100,000 copies/ml milliliter, & 30.7% had a viral load of ≥500,000 copies/ml) Inclusion criteria: ≥18 years of age, had not received ART, and had HIV-1 group M infection with a viral load of at least 1000 copies/ml. WOCP had to agree to use effective contraceptive methods. Exclusion criteria: Pregnant, breast-feeding, severe hepatic impairment, renal failure, severe psychiatric illness, & unstable tuberculosis coinfection Funding: Supported by Unitaid and the French National Agency for AIDS Research (ANRS 12313) Declarations: None		• VL with other thresholds: - VL <200 copies/ml; & virologic failure, defined by the WHO as VL>1000 copies/ml after reinforcement of adherence) at weeks 24 & 48 • Drug resistance. • Change from baseline in the CD4+ T-cell count at weeks 24 & 48 • Morbidity (WHO stage) • Adherence to treatment, -Safety, & Patient-reported outcomes (depression, anxiety, & stress; HIV treatment symptoms, including EFV related symptoms; & quality of life)	was 281/cubic mm. Adherence to treatment was similar in both groups. **Primary Outcome:** Efficacy: DTG vs EFV **(males and females)** Week 48, n=231/310 (74.5%) vs n=209/303 (69.0%) - viral load < 50copies/ml. Difference between treatment groups was 5.5 % points (95% confidence interval [CI], −1.6 to 12.7), meeting criterion for noninferiority (P<0.001) but not superiority (P = 0.13). **Results Reported for Women: DTG vs EFV Women & viral suppression:** (n=157/197 [79.7%] vs. n=147/207 [71.0%]; difference, 8.7 % points; 95% CI, 0.3 to 17.0) (favoring DTG). **Secondary Outcomes:** -25/404 (6.2%) women became pregnant - (13 DTG vs 12 EFV400) **Delivery:** 4 (30.7%) vs (66.7%) **Miscarriage:** 6 (42.2%) vs 4(33.3%) **Voluntary abortion:** 3 (23.1) vs (0 (0%) -All deliveries (n=12) born alive, without reported congenital abnormalities. Significantly > median increase in body weight in DTG group vs EFV group (5.0 kg [interquartile range, 1.0-8.0] vs. 3.0 kg [interquartile range, 0.0 - 7.0], P<0.001). Weight gain of at least 10% observed in > women vs men (147/379 [38.8%] vs. 44/192 [22.9%], P<0.001)	• Adherence to treatment was high on the basis of scores on a validated questionnaire but this measure has limitations. • The relationship between DTG and obesity as well as risks associated with childbearing potential need exploration
Lockman et al, 2021.	Design: Multicentre, phase 3, open-label, randomised controlled trial Recruitment: Jan 19, 2018, to Feb 8, 2019 Funding: National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Institute of Mental Health	Study population: Pregnant women gestation 14-28 weeks, less than 14 days of ART in sites in Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the USA, and Zimbabwe 643 pregnant women enrolled: 217 to the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate(TAF) group, 215 to the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate (TDF) group, and 211 to the	Exposures DTG/FTC/TAF DTG/3TC/TDF Control EFV/TDF/FTC 1:1:1 randomisation	Primary efficacy outcome: proportion of participants with viral suppression (< 200 copies per mL, at or within 14 days of delivery prespecified non-inferiority margin of –10% in the combined dolutegravir-containing groups versus the efavirenz-containing group Primary safety outcomes: compared pairwise among treatment	Enrolment: • Median gestational age 21·9 weeks (IQR 18·3–25·3) • median HIV-1 RNA concentration 902·5 copies/mL (152·0–5182·5 • 181 [28%] of 643 participants HIV-1 VL <200 copies/mL) • Median CD4 count was 466 cells per µL (308–624) Delivery • VL available for 605 (94%) participants. • 395 (98%) of 405 participants in the combined dolutegravir containing groups had VL	• Study pause May 18 and Oct 12, 2018 due to NTD signal in Tsepamo • Direct comparison between DTG-based and EFV SOC-based ART in pregnancy, 14-28 weeks • Superior virological efficacy in DTG-containing regimen compared to efavirenz-containing regimen • DTG/DTC/TAF has lowest composite pregnancy outcomes • Efavirenz higher neonatal death

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
		efavirenz, emtricitabine, and TDF group Inclusion criteria: • ≥18 years • 14-28 weeks gestation • HIV-1 infection Exclusion criteria • Previous ART (except 14 days for current pregnancy) • Psychiatric illness • Multiple pregnancy • Known fetal anomaly		groups, occurrence of a composite adverse pregnancy outcome (ie, either preterm delivery, the infant being born small for gestational age, stillbirth, or spontaneous abortion) in all participants with a pregnancy outcome, and the occurrence of grade 3 or higher maternal and infant adverse events in all randomised participants.	suppression at delivery compared with 182 (91%) of 200 participants in the efavirenz group (estimated difference 6·5% [95% CI 2·0 to 10·7], p=0·0052 • Slightly fewer women in DTG/FTC/TAF arm with composite adverse pregnancy outcomes (52 [24%] of 216) DTG/3TC/TDF (70 [33%] of 213; estimated difference –8·8% [95% CI –17·3 to –0·3], p=0·043) or the TEE group (69 [33%] of 211; –8·6% [–17·1 to –0·1], p=0·047) • Infants with grade 3 outcomes not different between groups • Preterm delivery lower in DTG/FTC/TAF group (12 [6%] of 208) compared to efavirenz group (25 [12%] of 207; –6·3% [–11·8 to –0·9] p=0·023) • Neonatal mortality significantly higher in efavirenz group (ten [5%] of 207 infants) DTG/FTC/TAF two [1%] of 208; p=0·019) DTG/3TC/TDF (three [2%] of 202; p=0·050)	
Money D, et al; 2019.	Canadian Perinatal (CPHSP) HIV Surveillance Programme Study Setting: 22 sites, 19 HIV referral health centres, 3 health departments from all Canadian provinces & territories). Captures ± 95% of all pregnancies in WLWH, and 100% where infant is infected with HIV Funding: No specific funding secured for the analysis. Public Health Agency of Canada (PHAC) had no role in this study's conduct and design; collection, management, analysis, or write up. Declarations: Data presented annually at the Canadian Conference on HIV/AIDS Research and other meetings.	Live-born infants born in Canada to WLWH between 2007 and 2017	ART (at conception & pregnancy)	Congenital anomalies	**From 2007 to 2017** **Patient Characteristics:** - 2591 live infants born to WLWH - 2423 had congenital anomaly data - 81.9% deliveries at term - Mean gestational age 38.2 weeks. - 2306 of the mothers had timing of HIV diagnosis known; 272 (11.8%) diagnosed with HIV during pregnancy, 40 (1.7%) at or after childbirth, 1994 (86.5%) before pregnancy. 4/80 (5.0%, 95% CI 1.4 to 12.3%) neonates born to WLWH on DTG during the first trimester had congenital anomalies vs 3/46 (6.5%, 95% CI 1.4 to 17.9%) on EFV - Anomalies for DTG included urinary tract (n = 2), circulatory system (n = 1) & musculoskeletal system (isolated polydactyly, n = 1). -NTDs on DTG (0/117; 95% CI 0.00 to 3.10%) -3 cases of NTDs since 2007, overall incidence rate of 0.12% (95% CI 0.03 to 0.36%) – none on DTG or EFV	• Small sample size due to limited use of DTG in women of reproductive age in Canada • Looked at both DTG before conception and those initiated on DTG after conception • 5% of infants of Canadian women living with HIV on DTG at conception had congenital anomalies; none had neural tube defects

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Mmasa et al, 2021	Prospective cohort, Botswana Funding: NIH No COI declared	Pregnant women ≥18 years, 16-36 weeks' gestation, without diabetes n=486 DTG: 197 EFV: 126 HIV-uninfected: 163	DTG EFV HIV-uninfected	Gestational diabetes diagnosed on oral glucose tolerance test at 24-28 weeks' gestation, or earliest prenatal visit if after 28 weeks	**Gestational diabetes** DTG: 6.1% EFV: 13.5% aOR: 0.34 (95% CI 0.12 to 0.97), adjusted for age, BMI, gravidity, CD4, ART started before pregnancy aOR: 0.40 (95% CI 0.18 to 0.92), also adjusted for duration of ART exposure HIV-uninfected: 7.4% aOR versus HIV-infected on ART: 0.83 (95% CI 0.37 to 1.85), adjusted for age, education, BMI, and gravidity	• Those on EFV, compared to those on DTG, were older, were more likely to be on ART at conception, and had a longer duration of ART exposure; other baseline characteristics were similar

Pereira GFM, et al. 2021.	Design: retrospective, observational, national, cohort study
	
	Funding:
	Brazilian Ministry of Health and the United States' National Institutes of Health
	
	COI:
	BES, FM, CCMcG, and JLC declare receiving grants from the US National Institutes of Health. All other authors declare no competing interests.
		• 1468 women included
		• 382 any DTG exposure
		• 41 any RTG exposure
		• 1045 only EFV exposure All women with possible prenatal dolutegravir exposure from 1 Jan 2017 to 31 May 2018
		• All women potentially raltegravir exposed at conception (same timeline)
		• A pool of Efavirenz exposed women, geographically matched (comparative cohort)
		
		Inclusions:
		• Aall women with reported pregnancy and an immediately previous dolutegravir-based regimen
		• All women of childbearing age receiving dolutegravir who switched to a pregnancy-recommended regimen for unclear reasons
		• All women receiving dolutegravir who received injectable or oral solution zidovudine or nevirapine (or both) as an indication of a birth event.
		• Any DTG, EFV or RTG use at any point during the periconception window (8 weeks before or after
			Exposures:
			DTG
			RTG
			EFV
			
			Cases reviewed on 3:1 ratio for EFV:DTG
				Primary outcomes
				• NTD
				• Composite measure of NTD, stillbirth >22 weeks, miscarriage < 22 weeks
					Mean age:
					EFV only: 28.5 yrs
					DTG exposure: 26.6yrs
					
					CD4 count:
					EFV only: 604 cells/ml
					DTG exposure: 530 cells/ml
					
					Undetectable VL
					EFV only: 465 (75%)
					DTG exposure: 139 (36%)
					
					Primary Outcome:
					• No NTDs among birth outcomes of women periconceptionally exposed to DTG or EFV
					• Estimated NTD prevalence = 0
					• Composite outcomes (NTD+miscarriage+stillbirth):
					  ○ DTG-exposed: 25/384 = 7%, 95% CI 0.04 to 0.094
					  ○ EFV-exposed: 43/1068 = 4%, 95% CI 0.030 to 0.054
					• Miscarriages 6% vs 3% DTG vs EFV
					• No differences with sensitivity analyses and additional of prenatal variables for the composite outcome
					• 2 additional NTDs were reported just after the end of the study (May 2019).
					• This updated the incidence of NTD in DTG exposed women to 0.0018 - Equal to 1.8/1000 DTG exposed pregnancies (95% CI 0. To 6.7).
					
					Other outcomes:
					No significant differences in preterm labour, premature rupture of membranes, pre-eclampsia, diabetes/gestational diabetes, gestational
						• Sensitivity analyses conducted to see if any difference if women exposed to more than one ART during periconception period
						
						Conclusion
						• No occurrences of NTDs in Brazilian national cohort study of women with periconceptional DTG exposure
						• After inclusion of 2 NTDs reported after study close, incidence remained well below 1%
						• Increased rate of miscarriages in women exposed to DTG but finding inconclusive as attenuated once prenatal variables added to model
						
						Limitations:
						• Likely underpowered to detect difference in NTD risk because of rarity of event
						• Uncertainty of timing of conception relative to ART exposure
						• Many women received multiple ART regimens during periconception period
						• Retrospective analysis can introduce bias
						• Missing data for some women (birth outcome, ART exposure, timing of conception)

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
		estimated date of conception) Exclusions: • Women found not pregnant, with unknown birth outcome or ART exposure and with no periconceptional exposure to DTG/RTG/EFV • Women whose estimated date of conception could not be calculated			hypertension or average weight gain per week between the groups	
Raesima MM et al. 2019.	National surveillance, Botswana	Inclusion: • All pregnancies with live-born or stillborn delivered beyond 24 weeks • 22 non-Tsepamo facilities • Delivered from October 2018- 31 March 2019 Population: • 22 sites, Botswana • 3076 deliveries • 2328 (76%) HIV negative • 742 (24%) HIV positive • 6 (<1%) HIV unknown • 544 (73%) ART exposed at conception • 152 (28%) DTG exposed	DTG-based regimen exposure Non-DTG based regimen exposure	Data collected: Surface examination (midwife) Maternal HIV status ART exposure at conception Folate exposure NOT collected Primary outcome: Estimated prevalence of NTD according to maternal HIV status and ART exposures, including DTG	• 3 confirmed/probable NTDs amongst all infants • 1 in DTG exposed, 2 in HIV negative • DTG prevalence 0.66% CI 0.02 to 3.69 • HIV negative prevalence 0.09% CI 0.01 to 0.31 • Difference between DTG based ART and non-DTG based NTD prevalence = 0.66% CI -0.48 to 3.63	• Slightly higher prevalence of NTDs among HIV positive mothers with DTG exposure at time of conception • Magnitude of NTD risk with DTG exposure at time of conception remains <1% Limitations • Short duration of study • NTD rare event, only 3 cases • Unstable prevalence estimates resulted from small sample size
Venter WDF et al. 2019.	Design: Phase 3, investigator-led, open-label, randomized trial Funding: U.S. Agency for International Development, Unitaid, and the South African Medical Research Council. Investigational drugs were donated by Gilead Sciences and ViiV Healthcare. COI: WDFV reports lecture fees and travel support from Roche, grant support,	Study population: South Africans ≥ 12 years Randomized to triple-therapy combination of emtricitabine (FTC) and DTG plus either of TAF (TAF-based group) or tenofovir disoproxil fumarate (TDF) (TDF-based group) — against the local standard-of-care regimen of TDF–FTC–efavirenz (standard-care group). Population 1053 patients randomised February 2017 through May 2018.	Exposures DTG/FTC/TAF DTG/3TC/TDF Control EFV/TDF/FTC 1:1:1 randomisation	Efficacy: The primary end point was the percentage of patients with a 48-week HIV-1 RNA level of less than 50 copies per milliliter, non-inferiority margin -10 percentage points Safety data at 48 weeks also reported	Baseline characteristics: • Mean age 32 years, mean CD4 count 337 cells/mm^3. Week 48: **Efficacy** • Percentage of patients with an HIV-1 RNA level of < 50 cps/ml 84% in the TAF-based group, 85% in the TDF-based group, and 79% in the standard-care group • DTG-containing regimens were noninferior to the standard-care/EFV regimen. • The number of patients who discontinued the trial regimen was higher in the standard-care group than in the other two groups.	• DTG-based regimens non-inferior to EFV-based SOC • TAF-based regimen less bone mineral and renal issues compared to TDF

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
	advisory board fees, and provision of drugs from Gilead Sciences, advisory board fees from ViiV ealthcare, lecture fees from Merck and Adcock Ingram, and lecture fees and advisory board fees from Johnson & Johnson and Mylan; MM honoraria and conference attendance support from Johnson & Johnson, Cipla, and ViiV Healthcare, honoraria, advisory board fees, and conference attendance sponsorship from Gilead Sciences, advisory board fees from AbbVie, and conference attendance sponsorship from Merck; EA receiving advisory committee fees from ViiV Healthcare.	> 99% of the patients were Black, 59% female Inclusion criteria: • ≥12 years • no receipt of ART in the previous 6 months, • creatinine clearance of more than 60 ml per minute (>80 ml per minute in patients < 19 years • HIV-1 • VL ≥ 500 copies/ml Exclusion criteria: Pregnancy, current TB treatment			• In the per-protocol population, the standard-care regimen had equivalent potency to the other two regimens. **Safety** • The TAF-based regimen had less effect on bone density and renal function than the other regimens. • Weight increase (both lean and fat mass) was greatest in the TAF-based group and among female patients (mean increase, 6.4 kg in the TAF-based group, 3.2 kg in the TDF-based group, and 1.7 kg in the standard-care group). • No resistance to integrase inhibitors identified in patients receiving the DTG-containing regimens.	
Venter WDF, et al. 2020	ADVANCE study, as above. 96 week results	As above The trial included 623 women	As above	96-week outcomes reported separately for women: Viral suppression<50 copies/mL Obesity Pregnancy outcomes	**Women:** **Viral suppression <50 copies/mL** TAF/FTC/DTG: 168/214 (79%) TDF/FTC/DTG: 154/208 (74%) TDF/FTC/EFV: 147/201 (73%) **Obesity** TAF/FTC/DTG: 42/151 (28%) TDF/FTC/DTG: 23/129 (18%) TDF/FTC/EFV: 15/125 (12%) **Pregnancy outcomes** TAF/FTC/DTG: 29 pregnancies in 26 women; 6 miscarriages (21%); 1 infant death TDF/FTC/DTG: 25 pregnancies in 24 women; 2 miscarriages (8%); 0 infant deaths TDF/FTC/EFV: 34 pregnancies in 32 women; 9 miscarriages; 0 infant deaths **Overall (all trial participants, not only women):** **Viral suppression <50 copies/mL** TAF/FTC/DTG: 276/351 (79%)	• Subgroup analyses were presented for women overall, not necessarily only WOCP. The overall mean age of the study population was 32 years (range 13-62). • In the viral suppression results, patients with no viral load results were considered failures – the proportions with missing VL data weren't reported for women specifically, but were 18%, 18%, and 23% for the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV groups overall.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
					TDF/FTC/DTG: 275/351 (78%) TDF/FTC/EFV: 258/351 (74%) **Drug discontinuation due to AE** TAF/FTC/DTG: 2 TDF/FTC/DTG: 1 TDF/FTC/EFV: 10 **Resistance mutations** In those with VF and a baseline and 96-week resistance data available, 2/16 patients in the TDF/EFV/DTG group had NRTI resistance mutations (M184V); and 13/21 patients in the EFV group had various mutations. No other resistance mutations were reported.	
Waitt et al, 2019.	Open – Label Randomized Control Trial (Uganda & South Africa between 9th March 2017 & 16th January 2018). Randomized 1:1 to DTG or EFV) containing ART until 2 weeks post-partum (2wPP). Study Setting: Mulago National Referral Hospital, Kampula, Uganda Gugulethu Community Health Care Centre, Cape Town Two Arms: -(n=29) pregnant women on DTG -(n=31) pregnant women on EFV Follow-up duration: 6 months until postpartum	Sample size: N=60 mothers initiating therapy in third trimester were randomised to receive EFV based (standard of care) or DTG regimen Patient characteristics: 100% Black African, HIV – infected treatment – ART treatment naïve pregnant women (28–36 weeks of gestation, age 26 (19–42), weight 67kg (45–119). Inclusion criteria: informed consent, comply with scheduled visits, treatment plans, other required study procedures, aged atleast 18 years, untreated HIV in late pregnancy, 28–36 weeks of gestation Exclusion criteria:Pregnant mothers who received ARVs in the previous 6 months, had ever received integrase inhibitors; anaemic (hb <than	Exposures: • DTG - ART (50mg) consisting of tenofovir disoproxil fumarate with either lamivudine/emtricitabine • EFV – ART (SOC) consisting of once daily EFV; tenofovir disoproxil fumarate with either lamivudine/ emtricitabine	Primary outcome: Pharmacokinetics of DTG in HIV infected women during the third trimester of pregnancy & after two weeks postpartum as defined by the area under the concentration-time curve of DTG between 0 & 24 hours (AUC_{0-24}). Secondary outcomes: Cord to maternal plasma DTG ratio (C:M ratio), maternal breast milk to plasma DTG ratio (M:P ratio), & infant DTG concentrations at maternal steady state & at 1, 3 & 3 days following discontinuation	DTG vs EFV No differences in baseline maternal age (median 27 vs 25 years), gestation (31 vs 30 weeks), weight (65 vs 68 Kg), obstetric history, viral load (4.5log10 copies/mL both arms) & CD4 count (343 vs 466 cells/mm^3). 28 DTG vs 31 EFV live births. Median (range) gestational age at delivery DTG 39 (35–43) weeks, vs EFV 38 (34–42) weeks. No significant differences for birth weight (3kg DTG) vs 3kg EFV) **Primary Outcome:** **Pharmacokinetic Data: Predose:** n=29 -intensive PK sampling. n=1 excluded - non – adherent due to undetectable DTG concentrations. n=28 in third trimester, Cmax, C_{24} & AUC_{0-24} (geometric mean, range) were 2435 (1462–3986) ng/mL, 642 (188–3088) ng/mL and 35322 (19196–67922) ng.h/mL respectively. **Pharmacokinectic Data: Post – Dose:** n=23 - intensive post-partum PK sampling following delivery; n=6 - sampling before 7 days postpartum excluded. n=17 sampled at a median of 10 (range 7–18) days following delivery, with C_{max}, C_{24} & AUC_{0-24} of 2899 (1397–4224) ng/mL, 777 (348–1210) ng/mL and 40127 (22795–59633) ng.h/mL respectively. No significant differences in the geometric mean ratios of C_{max}, C_{24} & AUC_{0-24} in 14	• DolPHIN-1 confirms that the superior virological responses observed with DTG-based combination therapy in non-pregnant adults is also seen in pregnancy. Differences show that DTG has a role in prevention of mother to child transmissions among women who are initiated on ART in the 3rd trimester. • Standard DTG dosing potentially safe & beneficial in late pregnancy. • High infant exposures to DTG in utero, & in first week of life, may offer additional prophylaxis against HIV transmission • **Discontinuations and Resistance:** n=1 participant in the DTG-ART arm discontinued for lack of efficacy after week 4 - undetectable DTG concentrations in 3rd trimester & admitted nonadherence. Another individual in the DTG-ART arm experienced resistance & had a viral load of 2217 copies/mL at the post-partum visit. Multi-class resistance demonstrated on baseline sample (M41L, L201W, T215Y, M184V, Y188L, M46I, I84V, I54V, V32I, V82A, L33F, K43T) & attained virological suppression after transition to a regimen containing DTG & ritonavir-boosted darunavir. The n=2 that discontinued prior to the post-partum visit for other reasons (1 in each arm) both had a VL <200 copies/mL at the point of discontinuation (4 weeks).

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
	Funding: DolPHIN-1 was funded by ViiV Healthcare through an investigator-initiated study scheme https://www.viivhealthcare.com/en-gb/advancinghiv- science-and-rd/we-collaborate-to-innovate/, award number 205785 awarded to SK. CW is funded by a Wellcome Postdoctoral Training Fellowship for Clinicians WT104422MA https:// wellcome.ac.uk/funding/schemes/postdoctoralresearch-training-fellowships-clinicians. Declarations: ML declared research grants from ViiV, Janssen and personal fees from Mylan.	8 g/dL); had elevations in serum levels of alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN) or ALT >3xULN and bilirubin >2xULN (with >35% direct bilirubin); active hepatitis B; history/ clinical suspicion of unstable liver disease (presence of ascites, encephalopathy, coagulopathy, hyperbilirubinaemia, oesophageal/gastric varices/persistent jaundice); severe pre-eclampsia, or other pregnancy related events such as renal/ liver abnormalities (grade 2/ above proteinuria, elevation in serum creatinine (>2.5 x ULN), total bilirubin, ALT or AST); / clinical depression/ evidence of suicidal ideation.		of DTG. Viral load (VL) in at delivery & the change in VL over the first four weeks of therapy. Two approaches to hanndle missing VL data : 1) missing VL = failure [>50 copies/mL] (M = F) in which subjects with missing data at two weeks post-partum were assessed as experiencing failure, and 2) missing viral load equals excluded (M = X)	mothers who underwent sampling in the third trimester of pregnancy & at post-partum visit. **Cord & Maternal Blood Samples**: Paired cord & maternal blood samples available in 16 mother-infant pairs. 1 individual, both samples were < limit of quantitation (BLQ), & non-adherence was reported. n= 15 samples - median C:M ratio of 1.21 (range 0.51–2.11). **DTG levels in Breastmilk:** DTG detectable in breast milk with a BM_{max} of 84.6 (43.8–171) ng/mL and a BM_{trough} of 22.3 (3.0–64.3) ng/mL. DTG detectable in plasma of breastfed infants with an $Infant_{max}$ of 66.7 (21–654) ng/mL and an $Infant_{trough}$ of 60.9 (16.3–479) ng/mL - median of 10 (range 7–18) days of age. Infant plasma to maternal plasma (IP:MP) ratios were 0.03 (0.00–0.06) at $Infant_{max}$ and 0.08 (0.00–0.17) at $Infant_{trough}$. After discontinuation of maternal DTG, detectable in 100%, 80% and 80% breastfed infants at 48, 72 & 96 hrs after final maternal dose, respectively. **Secondary Outcomes** Safety: Both regimens tolerated, no significant differences with adverse effects. • DTG-ART - 25 (86.2%) - caesarean section & 4 (13.8%) normal delivery • EFV-ART -21 (67.7%) caesarean section & 10 (32.3%), normal delivery. **Adverse events**: n=3 **Serious adverse events**: n=1 -2 in the DTG arm: i) low HB - unrelated, & ii) hospitalisation due to maternal malaria & urinary tract infection with raised ALT, bilirubin, hypokalemia & hyponatremia. (The mother took herbal medications at onset of event). Stillbirth related to umbilical cord around neck – not DTG related. EFV arm - 1 SAE - preeclampsia - unrelated. No **congenital anomalies** in DTG arm vs 2 in EFV arm (n=1 syndactyly -unlikely to be related to EFV and n=1 with multiple skeletal, limb & cardiac malformations (possibly TARP [Talipes equinovarus, Atrial septal defect, Robin sequence,	• DTG showed superior virological suppression vs EFV among women commencing ART in late pregnancy • Two limitations: (1) related to the requirement to initiate immediate EFV-ART at HIV diagnosis, and the need to limit exposure of newborn and breastfed infants to what was not a recommended first-line regimen during the study period. Randomisation would have balanced effect in the two arms. • Some women attended postpartum visit earlier than the proposed 2 weeks, potentially minimising differences in DTG exposure as a result of late pregnancy.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
					& Persistent left superior vena cava] syndrome) - not related EFV. n=1 infant in EFV arm - neonatal sepsis-not related to EFV, recovered **Virologic Response** **Proportion undetectable:** 69.0% (20/29) and 74.1% (20/27) DTG arm vs 38.7% (12/31) & 40.0% (12/30) EFV arm, in the M= F & M= X analyses, respectively. In analyses of $\log_{10}$ HIV RNA at 2wkPP, VL was significantly lower in the DTG arm vs EFV-ART (p = 0.007). n=3 discontinued prior to the 2-week post-partum visit (2 DTG-ART & 1 EFV-ART).	
Zash R, Holmes L, Diseko M, Jacobson DL, Brummel S, Mayondi G, Isaacson A, *et al*. 2019 Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Engl J Med. 2019 Aug 29;381(9):827-840. doi: 10.1056/NEJMoa1905230. Epub 2019 Jul 22. PMID: 31329379; PMCID: PMC6995896.	Birth outcome surveillance study, Botswana (8 public hospital maternity wards from August 2014 to June 2018, 10 adiitonal sites added between July 2018 and March 2019	Sample Size: From August 15, 2014, to March 31, 2019, 119,477 deliveries, 119,033 (99.6%) had an infant surface examination Patient Characteristics: Baseline characteristics (delivery site, history of epilepsy, diabetes, and weight during pregnancy) between ART exposures groups were negligible. Folate supplementation and timing similar across the treatment groups. Funding: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Disclosures: Submitted with the publication	Exposures: • DTG from conception: (1683) • Any other non DTG ART from conception: (14792) • EFV from Conception (7959) • DTG started during pregnancy: (3840) HIV negative Mothers (89372)	**Primary Outcome:** Prevalence of neural-tube defects (NTDs) among infants	**Tsepamo Results from August 2014 to March 2019:** 98 NTDs (0.08%) **DTG from conception:** 5/1683 (0.30%; 95% CI 0.13 to 0.69) infants **Any other non DTG ART from conception:** 15/14792 (0.10%; 95% CI 0.06 to 0.17) infants. -Prevalence Difference: 0.20 (95% CI 0.01 to 0.59) vs the reference DTG from conception **EFV from Conception:** 3/7959(0.04%; 95% CI 0.01 to 0.11) infants. -Prevalence Difference: 0.26 (95% CI 0.07 to 0.66) vs the reference DTG from conception **DTG started during pregnancy**: 1/3840 (0.03%; 95% CI 0.00 to 0.15) infants. -Prevalence Difference: 0.27 (95% CI 0.06 to 0.67) vs the reference DTG from conception **HIV Negative:** 70/89372 (0.08%; 95% CI 0.06 to 0.10) infants. -Prevalence Difference: 0.22 (95% CI 0.05 to 0.62) vs the reference DTG from conception	• Prevalence of NTDs higher in association with DTG treatment at conception than with non DTG based ART at conception/ other types of ART.
Zash et al., 2020 Update on neural tube	Birth Outcomes Surveillance in government	Since August 2014 total of 158,244 deliveries; 153,899 (97.2%) had an evaluable infant surface exam, with	Exposures:	Prevalence of neural-tube defects (NTDs) among infants	**126 (0.08%, 95%CI 0.07%,0.09%) NTDs identified to date in cohort overall** **Cumulative results by group**	• After a decline since the original safety signal, the prevalence of NTD among infants born to women receiving DTG at conception seems to be stabilizing at approximately 0.2%.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
defects with antiretroviral. **This update from the Tsepamo study was presented at AIDS 2020. Abstract number OAXLB0102** ***Tsepamo Study*** https://www.natap.org/2020/IAC/IAC_112.htm	maternity sites, Botswana, since August 2014 August 2014 – July 2018 – 8 Sites (±45% of all births in Botswana) July 2018 to September 2018 – expanded to 18 surveillance sites (±72% of all births in Botswana) Since September 2019, maintained surveillance at 16 sites (±70% of all births in Botswana) Originally designed to assess NTD in infants whose mothers were exposed to exposed to EFV DTG was rolled out in Botswana in Mid 2016 Funding: National Institutes of Health &NICHD	1067 LATE BREAKER ABSTRACTS AUTHOR INDEX PUBLICATION ONLY ABSTRACTS	• DTG from conception: (1683) • Any other non DTG ART from conception: (14792) • EFV from Conception (7959) • DTG started during pregnancy: (3840) • HIV negative Mothers (89372)		**DTG at conception**, 7/3591 NTDs (0.19%; 95%CI 0.09%, 0.40%): 3 myelomeningoceles, 1 anencephaly, 2 encephaloceles, and 1 iniencephaly. **Non DTG-ART** NTD in 21/19,361 (0.11%; 95%CI 0.07%, 0.17%) EFV from conception 8/10,958 (0.07%; 95%CI 0.03%, 0.17%) DTG started in pregnancy 2/4,581 (0.04%; 95%CI 0.1%, 0.16%) HIV-uninfected women. 87/119,630 (0.07%; 95%CI 0.06, 0.09%) Difference between DTG and non-DTG- ART at conception not different (0.09% difference; 95%CI -0.03%, 0.30%). **Tsepamo Results as at March 2019:** From May 2018 to March 2019 1 NTD/1275 adiitonal exposures to DTG at conception **Tsepamo Results through to 30th April 2020: 1 April 2019 to 30 April 2020** **Number of NTDs:** Total 28/39,200 (0.07%) **DTG from conception:** 2/1908 (0.1%) **Any other non DTG ART from conception:** 6/4569 (0.1%) **EFV from Conception:** 5/2999 (0.2%) **DTG started during pregnancy**: 1/741 (0.1%) **HIV Negative:** 17/30,258 (0.1%)	• Two Women (started on DTG at conception) who delivered infants with NTDs had no medical history, did not receive other medication, and did not receive pre-conception folate supplementation

Table 2: Tsepamo study reports included in the previous review update

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Zash *et al*. 2018 Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. Lancet Glob Health. 2018 Jul;6(7):e804-e810. doi: 10.1016/S2214-109X(18)30218-3. Epub 2018 Jun 4. PMID: 29880310; PMCID: PMC6071315.	Observational Study - Birth outcome surveillance study, Botswana (8 public hospital maternity wards from August 2014) Inclusion Criteria: DTG regimen started and delivery between Nov 1 2016 and Sep 3th 2017 for singleton pregnancy EFV regimen started and delivery between Aug 15th 2014 and Aug 15th 2016 for singleton pregnancy Exclusion criteria; births to mothers who switched ART regimens or stopped ART	Sample Size: Patient Characteristics: Age parity, socioeconomic indicators, timing of initiating of antenatal care and site of delivery were similar between EFV and DTG groups. HIV negative woman were younger, primiparous, higher education level compared to HIV positive woman. Similar timing of initiation and antenatal care for HIV infected and uninfected women. Funding: National Institutes of Health grants Disclosures: None declared	Exposures: • DTG based ART (1729) • EFV based ART (4593)	**Primary Outcome:** Combined endpoints of any adverse outcome **(**stillbirth, preterm birth (<37 weeks gestation), small for gestational age (SGA < 10th percentile of birthweight by gestational age) or neonatal death (withig 28 days of age) and very SGA (< 3rd percentile of birthweight by gestational age)	Aug 15th 2014 to Aug 15th 2016 n=11708 women with HIV delivered singletons -4593 (39%) on EFV based regimen after conception. Nov 1st 2016 to Sep 30th 2017, n=5418 women with HIV delivered singletons - 1729 (32%) began DTG regimen after conception. -51167 HIV negative woman had singleton pregnancies -total for both time periods Median CD4 count was similar between DTG and EFV group. Greater proportion of women in the EFV group had a CD4 count during pregnancy (2054 (44.7% vs 247 (14,2%) **Adverse outcomes**: -**Risk for any adverse outcome** among woman on DTG vs EFV was similar (n=574, 33·2% vs n=1606, 35·0%; aRR 0·95, 95% CI 0·88– 1·03), -**Risk of any severe birth outcome** was similar (n=185, 10·7% vs n=519, 11·3%; 0·94, 0·81–1·11). In 675 women (280 on DTG and 395 on EFV) with 1st trimester exposure to ART, 1 major congenital abnormality (skeletal dysplasia) in EFV exposed infant -No significant differences by regimen in individual outcomes of stillbirth, neonatal death, preterm birth, very preterm birth, SGA, or very SGA **HIV Negative Women** -134766 (28.9%) had any adverse birth outcomes -Severe adverse birth outcomes 5085 (9.9%) women	• Adverse birth outcomes were similar for DTG based ART vs FEV based ART during pregnancy • Sample size was large • Inability to fully evaluate CD4 cell count due to low number of woman in DTG group with CD4 reported (due to policy changes in testing) • Switch from EFV To DTG might put the data at historical bias (but short interval – 3 years) • Observational study – risk of confounding exists – however baseline characteristics of groups was similar, adjusted for confounding and conducted sensitivity analyses which were robust to changes • Unable to verify the data in medical records or validate gestational age dating (although any bias would be similar between the two treatment groups)
Zash R, et al, 2018. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. N Engl J Med. 2018 Sep	Letter to the Editor outlining birth outcome surveillance (n=8 government hospitals, Botswana) Funding: National Institutes of Health (R01 HD080471-01 and K23 HD088230-01A1).	May 1, 2018 Sample Size: n=89,064 births included in surveillance n=88,755 (99.7%) had an infant surface examination	Exposures: • DTG from conception: (436) • Any other non DTG ART from conception: (11,300)	Prevalence of neural-tube defects (NTDs) among infants	**n=86 NTDs identified** (0.10% of births; 95% CI, 0.08 to 0.12) **Defects included:** -42 meningocele/myelomeningocele, 30 of anencephaly, 13 encephalocele, 1 of iniencephaly **DTG from conception:** 4/426 (0.94%; 95% CI 0.37–2.4) infants had a NTD (encephalocele, myelomeningocele (with	• Previously reported (2018) the risk of adverse birth outcomes or congenital abnormalities among women who started DTG based ART after conception (including therapy initiated during the first trimester of pregnancy) was not higher than the risk among women who started EFV based therapy after conception. • NTDs in DTG from conception: The 4 mothers delivered in 3 geographically separated hospitals over a 6-month period; none had epilepsy/diabetes/received folate supplementation at conception.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
6;379(10):979-981. doi: 10.1056/NEJMc1807653. Epub 2018 Jul 24. PMID: 30037297; PMCID: PMC6550482.	Declarations: Disclosure forms provided by authors		• DTG started during pregnancy: (2812) • HIV negative Mothers (66,065)		undescended testes), & iniencephaly (with major limb defect). **Any other non DTG ART from conception:** 14/11,300 (0.12%; 95% CI 0.07 – 0.21) infants -Prevalence Difference: -0.82 (95% CI, −0.24 to −2.3) vs the reference DTG from conception **DTG started during pregnancy**: 0 /2812 (0.00%; 95% CI 0.0 – 0.13) infants. Median gestational age at initiation of ART - 19 weeks (interquartile range, 14 to 25). 75 women started ART at gestational age < 6 weeks. -Prevalence Difference: -0.94 (95% CI, −0.35 to −2.4) vs the reference DTG from conception **HIV Negative:** 61/66,057 (0.09%; 95% CI 0.07– 0.12) infants -Prevalence Difference: -0.85 (95% CI, −0.27 to −2.3) vs the reference DTG from conception **7 additional infants with NTDs** -3 born to women who started non DTG ART during pregnancy -3 to (HIV)–infected women who did not receive ART during pregnancy -1 to a woman of unknown HIV infection status not on ART.	• Potential early signal for an increased prevalence of NTDs in association with DTG based ART from the time of conception. • Small number of events • Small difference in prevalence • Study is ongoing, and more data has since been collected which has refuted this signal

Table 3. List of excluded publications

No	Citation	Reason for Exclusion
1	Alhassan Y et al. Community acceptability of dolutegravir-based HIV treatment in women: a qualitative study in South Africa and Uganda. BMC Public Health. 2020 Dec 7;20(1):1883.	Wrong study design
2	Bollen P et al. Pharmacokinetics of ANtiretroviral agents in HIV-infected pregNAnt women Network. The Effect of Pregnancy on the Pharmacokinetics of Total and Unbound Dolutegravir and Its Main Metabolite in Women Living With Human Immunodeficiency Virus. Clin Infect Dis. 2021 Jan 23;72(1):121-127.	Non-comparative pharmacokinetic study looking at outcomes not of relevance to our PICO
3	Chandiwana NC et al. Unexpected interactions between dolutegravir and folate: randomized trial evidence from South Africa. AIDS. 2021 Feb 2;35(2):205-211.	Wrong outcomes
4	Chouchana L et al. Is There a Safety Signal for Dolutegravir and Integrase Inhibitors During Pregnancy? J Acquir Immune Defic Syndr. 2019 Aug 1;81(4):481-486.	No comparison with EFV
5	Chouchana L et al. Dolutegravir and neural tube defects: a new insight. Lancet Infect Dis. 2020 Apr;20(4):405-406.	Analysis of spontaneous reports from Vigibase. This is a pharmacovigilance database of spontaneous adverse drug reaction reports, not a pregnancy registry – did not meet study design
6	Crawford M et al. Postmarketing Surveillance of Pregnancy Outcomes With Dolutegravir Use. J Acquir Immune Defic Syndr. 2020 Jan 1;83(1):e2-e5.	No comparison with EFV
7	Dickinson L et al. Infant exposure to dolutegravir through placental and breastmilk transfer: a population pharmacokinetic analysis of DolPHIN-1. Clin Infect Dis. 2020 Dec 21:ciaa1861.	Non-comparative pharmacokinetic study looking at outcomes not of relevance to our PICO
8	Grayhack C et al. Evaluating outcomes of mother-infant pairs using dolutegravir for HIV treatment during pregnancy. AIDS. 2018 Sep 10;32(14):2017-2021.	No comparison to EFV-based ART
9	Hill A, Clayden P, Thorne C, Christie R, Zash R. Safety and pharmacokinetics of dolutegravir in HIV-positive pregnant women: a systematic review. J Virus Erad. 2018 Apr 1;4(2):66-71.	Review looking at safety and pharmacokinetics of DTG. Only one of the safety studies included in the review (one of the early Tsepamo reports) met PICO, and was already included
10	Kreitchmann R et al. Two cases of neural tube defects with dolutegravir use at conception in south Brazil. Braz J Infect Dis. 2021 Mar-Apr;25(2):101572.	Wrong Study Design
11	Mulligan N et al.; IMPAACT P1026s Protocol Team. Dolutegravir pharmacokinetics in pregnant and postpartum women living with HIV. AIDS. 2018 Mar 27;32(6):729-737.	Non-comparative pharmacokinetic study looking at outcomes not of relevance to our PICO
12	Nguyen B et al.. Pharmacokinetics and Safety of the Integrase Inhibitors Elvitegravir and Dolutegravir in Pregnant Women With HIV. Ann Pharmacother. 2019 Aug;53(8):833-844.	Review looking at safety and pharmacokinetics of DTG. Relevant studies already included.
13	Podany AT et al. Comparative Clinical Pharmacokinetics and Pharmacodynamics of HIV-1 Integrase Strand Transfer Inhibitors: An Updated Review. Clin Pharmacokinet. 2020 Sep;59(9):1085-1107.	NO - pharmacokinetic comparison between InSTIs
14	Rahangdale L et al; HOPES (HIV OB Pregnancy Education Study) Group. Integrase inhibitors in late pregnancy and rapid HIV viral load reduction. Am J Obstet Gynecol. 2016 Mar;214(3):385.e1-7.	Only 4 women on DTG
15	Reefhuis J et al. Neural Tube Defects in Pregnancies Among Women With Diagnosed HIV Infection - 15 Jurisdictions, 2013-2017. MMWR Morb Mortal Wkly Rep. 2020 Jan 10;69(1):1-5.	Wrong study design
16	Schomaker M et al. Assessing the risk of dolutegravir for women of childbearing potential. Lancet Glob Health. 2018 Sep;6(9):e958-e959.	Commentary
17	Slogrove AL et al. Toward a universal antiretroviral regimen: special considerations of pregnancy and breast feeding. Curr Opin HIV AIDS. 2017 Jul;12(4):359-368.	Commentary /opinion piece
18	van De Ven NS et al. Analysis of Pharmacovigilance Databases for Dolutegravir Safety in Pregnancy. Clin Infect Dis. 2020 Jun 10;70(12):2599-2606.	No denominator to contribute to incidence of NTD with DTG vs EFV exposure
19	van der Galiën R et al. Pharmacokinetics of HIV-Integrase Inhibitors During Pregnancy: Mechanisms, Clinical Implications and Knowledge Gaps. Clin Pharmacokinet. 2019 Mar;58(3):309-323.	3 relevant studies already included / duplication
20	Vannappagari V, Thorne C; for APR and EPPICC. Pregnancy and Neonatal Outcomes Following Prenatal Exposure to Dolutegravir. J Acquir Immune Defic Syndr. 2019 Aug 1;81(4):371-378. doi: 10.1097/QAI.0000000000002035. PMID: 30939532; PMCID: PMC6905407.	No comparison with EFV
21	Zipursky J et al. Dolutegravir for pregnant women living with HIV. CMAJ. 2020 Mar 2;192(9):E217-E218.	Commentary

Appendix 1: Search strategy

Date searched for the updated review: 3 June 2021

Database: PubMed

Search Strategy

Search	Query	Results
#6	Search: (#1 AND #4) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	134
#5	Search: #1 AND #4 Sort by: Most Recent	136
#4	Search: #2 OR #3 Sort by: Most Recent	1,071,076
#3	Search: neural tube defects[mh] OR neural tube defect*[tiab] OR neurenteric cyst*[tiab] OR acrania*[tiab] OR craniorachischis*[tiab] OR diastematomyelia*[tiab] Sort by: Most Recent	31,975
#2	Search: pregnancy[mh] OR pregnant women[mh] OR pregnan*[tiab] Sort by: Most Recent	1,048,366
#1	Search: "dolutegravir" [Supplementary Concept] OR dolutegravir[tiab] Sort by: Most Recent	1,343

Number of studies: 134

Database: Clinical Trials.Gov

Search terms: dolutegravir AND (pregnancy OR pregnant women)

Records retrieved: 13

Appendix 2: Evidence to decision framework

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>EVIDENCE OF BENEFIT</td><td>What is the size of the effect for beneficial outcomes?
Large [ ] Moderate [X] Small [ ] None [ ] Uncertain [ ]</td><td>Compared with EFV,
- viral suppression rates are non-inferior by 48 weeks;
- viral suppression rates are superior by the time of delivery;
- rates of vertical transmission are not significantly different, but event rates are very low with both regimens;
- risk of insufficient weight gain in pregnancy is lower; and
- risk of development of resistance mutations in those who fail first line regimens is lower.</td></tr>
<tr><td>EVIDENCE OF HARMS</td><td>What is the size of the effect for harmful outcomes?
Large [ ] Moderate [ ] Small [X] Uncertain [ ]</td><td>Compared with EFV:
- - Risk of NTD is not significantly different;
-risk of other adverse pregnancy outcomes are not significantly different;
- weight gain is higher, but the clinical significance of this is unknown (WLHIV on both regimens had less weight gain in pregnancy than HIV-uninfected women</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do desirable effects outweigh undesirable harms?
Favours intervention [x] Favours control [ ] Intervention = Control or Uncertain [ ]</td><td></td></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the certainty/quality of evidence?
High [ ] Moderate [x] Low [ ] Very low [ ]
High quality: confident in the evidence
Moderate quality: mostly confident, but further research may change the effect
Low quality: some confidence, further research likely to change the effect
Very low quality: findings indicate uncertain effect</td><td>RCT data for efficacy, resistance, and some adverse events (eg weight). Observational data for NTDs is consistent.</td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [X] Uncertain [ ]</td><td>Price of medicines/ 28 days:
<table><tr><th>Medicine</th><th>Price</th></tr><tr><td>TDF+FTC+EFV (TEE)</td><td>R104.56</td></tr><tr><td>TDF+3TC+DTG (TLD)</td><td>R 98.18</td></tr></table>Contract circular RT71-2019ARV</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [X] Major [ ] Uncertain [ ]
Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td><td>Standardised first line regimens for all adults and adolescents living with HIV is likely to be valued by prescribers. Access to DTG for WOCP has been advocated for by patient advocacy groups.</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [x] No [ ] Uncertain [ ]</td><td>There is likely to be a positive effect in terms of reducing health inequity.</td></tr>
</table>

REFERENCES

- Banda, F. M., K. M. Powis, S. Sun, J. Makhema, G. Masasa, L. M. Yee, and J. Jao. 2020. 'Fetal biometry following in-utero exposure to dolutegravir-based or efavirenz-based antiretroviral therapy', *AIDS*, 34: 2336-37.
- Caniglia, Ellen C., Roger Shapiro, Modiegi Diseko, Blair J. Wylie, Chloe Zera, Sonya Davey, Arielle Isaacson, Gloria Mayondi, Judith Mabuta, Rebecca Luckett, Joseph Makhema, Mompati Mmalane, Shahin Lockman, and Rebecca Zash. 2020. 'Weight gain during pregnancy among women initiating dolutegravir in Botswana', *EClinicalMedicine*, 29.
- Chimukangara, B., R. J. Lessells, S. Y. Rhee, J. Giandhari, A. B. M. Kharsany, K. Naidoo, L. Lewis, C. Cawood, D. Khanyile, K. A. Ayalew, K. Diallo, R. Samuel, G. Hunt, A. Vandormael, B. Stray-Pedersen, M. Gordon, T. Makadzange, P. Kiepiela, G. Ramjee, J. Ledwaba, M. Kalimashe, L. Morris, U. M. Parikh, J. W. Mellors, R. W. Shafer, D. Katzenstein, P. Moodley, R. K. Gupta, D. Pillay, S. S. Abdool Karim, and T. de Oliveira. 2019. 'Trends in Pretreatment HIV-1 Drug Resistance in Antiretroviral Therapy-naive Adults in South Africa, 2000-2016: A Pooled Sequence Analysis', *EClinicalMedicine*, 9: 26-34.
- Davey, S., G. Ajibola, K. Maswabi, M. Sakoi, K. Bennett, M. D. Hughes, A. Isaacson, M. Diseko, R. Zash, O. Batlang, S. Moyo, S. Lockman, M. Lichterfeld, D. R. Kuritzkes, J. Makhema, and R. Shapiro. 2020. 'Mother-to-Child HIV Transmission With In Utero Dolutegravir vs. Efavirenz in Botswana', *J Acquir Immune Defic Syndr*, 84: 235-41.
- Dugdale, C. M., A. L. Ciaranello, L. G. Bekker, M. E. Stern, L. Myer, R. Wood, P. E. Sax, E. J. Abrams, K. A. Freedberg, and R. P. Walensky. 2019. 'Risks and Benefits of Dolutegravir- and Efavirenz-Based Strategies for South African Women With HIV of Child-Bearing Potential: A Modeling Study', *Ann Intern Med*, 170: 614-25.
- Griesel, Rulan, Gary Maartens, Maxwell Chirehwa, Simiso Sokhela, Godspower Akpomiemie, Michelle Moorhouse, Francois Venter, and Phumla Sinxadi. 2020. 'CYP2B6 Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz', *Clinical Infectious Diseases*.
- Kanters, Steve, Marco Vitoria, Michael Zoratti, Meg Doherty, Martina Penazzato, Ajay Rangaraj, Nathan Ford, Kristian Thorlund, Prof Aslam H. Anis, Mohammad Ehsanul Karim, Lynne Mofenson, Rebecca Zash, Alexandra Calmy, Tamara Kredo, and Nick Bansback. 2020. 'Comparative efficacy, tolerability and safety of dolutegravir and efavirenz 400mg among antiretroviral therapies for first-line HIV treatment: A systematic literature review and network meta-analysis', *EClinicalMedicine*, 28.
- Kintu, Kenneth, Thokozile R. Malaba, Jesca Nakibuka, Christiana Papamichael, Angela Colbers, Kelly Byrne, Kay Seden, Eva Maria Hodel, Tao Chen, Adelline Twimukye, Josaphat Byamugisha, Helen Reynolds, Victoria Watson, David Burger, Duolao Wang, Catriona Waitt, Miriam Taegtmeyer, Catherine Orrell, Mohammed Lamorde, Landon Myer, and Saye Khoo. 2020. 'Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial', *The Lancet HIV*, 7: e332-e39.
- Lockman, S., S. S. Brummel, L. Ziemba, L. Stranix-Chibanda, K. McCarthy, A. Coletti, P. Jean-Philippe, B. Johnston, C. Krotje, L. Fairlie, R. M. Hoffman, P. E. Sax, S. Moyo, N. Chakhtoura, J. S. Stringer, G. Masheto, V. Korutaro, H. Cassim, B. T. Mmbaga, E. João, S. Hanley, L. Purdue, L. B. Holmes, J. D. Momper, R. L. Shapiro, N. K. Thoofer, J. F. Rooney, L. M. Frenkel, K. R. Amico, L. Chinula, and J. Currier. 2021. 'Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial', *Lancet*, 397: 1276-92.
- Mmasa, K. N., K. Powis, S. Sun, J. Makhema, M. Mmalane, S. Kgole, G. Masasa, S. Moyo, M. Gerschenson, T. Mohammed, J. Legbedze, E. J. Abrams, I. J. Kurland, M. E. Geffner, and J. Jao. 2021. 'Gestational diabetes in women living with HIV in Botswana: lower rates with dolutegravir- than with efavirenz-based antiretroviral therapy', *HIV Med*.
- Money, D., T. Lee, C. O'Brien, J. Brophy, A. Bitnun, F. Kakkar, I. Boucoiran, A. Alimenti, W. Vaudry, J. Singer, and L. J. Sauve. 2019. 'Congenital anomalies following antenatal exposure to dolutegravir: a Canadian surveillance study', *Bjog*.
- Moyo, S., G. Hunt, K. Zuma, M. Zungu, E. Marinda, M. Mabaso, V. Kana, M. Kalimashe, J. Ledwaba, I. Naidoo, S. Takatshana, T. Matjokotja, C. Dietrich, E. Raizes, K. Diallo, G. Kindra, L. Mugore, and T. Rehle. 2020. 'HIV drug resistance profile in South Africa: Findings and implications from the 2017 national HIV household survey', *PLoS One*, 15: e0241071.
- NAMSAL ANRS 12313 Study Group. 2019. 'Dolutegravir-Based or Low-Dose Efavirenz–Based Regimen for the Treatment of HIV-1', *New England Journal of Medicine*, 381: 816-26.
- Pereira, Gerson Fernando Mendes, Ahra Kim, Emilia M. Jalil, Fernanda Fernandes Fonseca, Bryan E. Shepherd, Valdilea G. Veloso, Fernanda Rick, Rachel Ribeiro, Maria Cristina Pimenta, Andrea Beber, Renato Girade Corrêa, Renato Lima, Fernanda Maruri, Catherine C. McGowan, Adele Schwartz Benzaken, Beatriz Grinsztejn, and Jessica L. Castilho. 2021. 'Dolutegravir and pregnancy outcomes in women on antiretroviral therapy in Brazil: a retrospective national cohort study', *The Lancet HIV*, 8: e33-e41.
- Phillips, T. K., P. Sinxadi, E. J. Abrams, A. Zerbe, C. Orrell, N. C. Hu, K. Brittain, Y. Gomba, J. Norman, L. Wiesner, L. Myer, and G. Maartens. 2019. 'A Comparison of Plasma Efavirenz and Tenofovir, Dried Blood Spot Tenofovir-Diphosphate, and Self-Reported Adherence to Predict Virologic Suppression Among South African Women', *J Acquir Immune Defic Syndr*, 81: 311-18.
- Raesima, Mmakgomo M., Chibuike M. Ogbuabo, Vasavi Thomas, Sara E. Forhan, Gadzikanani Gokatweng, Eldah Dintwa, Chipo Petlo, Catherine Motswere-Chirwa, Elizabeth M. Rabold, Sarah C. Tinker, Shifawu Odunsi, Sifelani Malima, Omphemetse Mmunyane, Thusoetsile Modise, Kelame Kefitlhile, Kunle Dare, Mpho Letebele, Michelle E. Roland, Cynthia A. Moore, Surbhi Modi, and Dhelia M. Williamson. 2019. 'Dolutegravir Use at Conception — Additional Surveillance Data from Botswana', *New England Journal of Medicine*, 381: 885-87.
- Venter, W. D. F., M. Moorhouse, S. Sokhela, L. Fairlie, N. Mashabane, M. Masenya, C. Serenata, G. Akpomiemie, A. Qavi, N. Chandiwana, S. Norris, M. Chersich, P. Clayden, E. Abrams, N. Arulappan, A. Vos, K. McCann, B. Simmons, and A. Hill. 2019. 'Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV', *N Engl J Med*.
- Venter, W. D. F., S. Sokhela, B. Simmons, M. Moorhouse, L. Fairlie, N. Mashabane, C. Serenata, G. Akpomiemie, M. Masenya, A. Qavi, N. Chandiwana, K. McCann, S. Norris, M. Chersich, G. Maartens, S. Lalla-Edward, A. Vos, P. Clayden, E. Abrams, N. Arulappan, and A. Hill. 2020. '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*, 7: e666-e76.
- Waitt, C., C. Orrell, S. Walimbwa, Y. Singh, K. Kintu, B. Simmons, J. Kaboggoza, M. Sihlangu, J. A. Coombs, T. Malaba, J. Byamugisha, A. Amara, J. Gini, L. Else, C. Heiburg, E. M. Hodel, H. Reynolds, U. Mehta, P. Byakika-Kibwika, A. Hill, L. Myer, M. Lamorde, and S. Khoo. 2019. 'Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: A randomised trial (DolPHIN-1 study)', *PLoS Med*, 16: e1002895.

- World Health Organization. 2019. *WHO recommends dolutegravir as preferred HIV treatment option in all populations. https://www.who.int/news/item/22-07-2019-who-recommends-dolutegravir-as-preferred-hiv-treatment-option-in-all populations. Accessed 3 June 2021*.
- Zash, R., L. Holmes, M. Diseko, D. Jacobson, G. Mayondi, Isaacson A., S. Davey, J. Mabuta, Mmalane M., Gaolathe T., Lockman S., Makhema J., and Shapiro R. 2020. "Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. Late Breaker abstract number OAXB0102." In *23rd international AIDS Conference*. Virtual Conference.
- Zash, R., D. L. Jacobson, M. Diseko, G. Mayondi, M. Mmalane, M. Essex, T. Gaolethe, C. Petlo, S. Lockman, L. B. Holmes, J. Makhema, and R. L. Shapiro. 2018. 'Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study', *Lancet Glob Health*, 6: e804-e10.
- Zash, R., J. Makhema, and R. L. Shapiro. 2018. 'Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception', *N Engl J Med*, 379: 979-81.
- Zash, Rebecca, Lewis Holmes, Modiegi Diseko, Denise L. Jacobson, Sean Brummel, Gloria Mayondi, Arielle Isaacson, Sonya Davey, Judith Mabuta, Mompati Mmalane, Tendani Gaolathe, M. Essex, Shahin Lockman, Joseph Makhema, and Roger L. Shapiro. 2019. 'Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana', *New England Journal of Medicine*.