Metabolic implications and safety of dolutegravir use in pregnancy

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Dolutegravir is recommended for all people living with HIV because of its efficacy, high barrier to resistance, favourable safety and tolerability profile, and affordability. Dolutegravir has the highest rates of viral suppression in pregnancy, therefore preventing perinatal HIV transmission. In view of these benefits, particularly for pregnant women, an important question is if dolutegravir is safe in pregnancy. Dolutegravir has been associated with metabolic complications, including weight gain and rare events of hyperglycaemia, that could affect maternal, fetal, and postnatal health. We review the current clinically and experimentally based literature on the implications of dolutegravir use for pregnant women and for developing embryos and fetuses. Possible effects on folate status, energy metabolism, adipogenesis, and oxidative stress are considered. In many instances, insufficient data are available, pointing to the need for additional research in this important area of HIV treatment.

Introduction

Infection with HIV poses a severe disease burden, having claimed 36·3 million lives and currently affecting nearly 40 million people around the world.[1] Reducing HIV viral load in people living with HIV to undetectable and therefore untransmissible quantities remains the most effective approach at reducing the incidence of HIV infection. The UNAIDS and WHO 95-95-95 goal aims for 95% of people with HIV to be aware of their infection status, 95% of people diagnosed with HIV to receive treatment, and 95% of those on treatment to have undetectable viral loads.[2] Perinatal transmission of HIV remains a serious concern for women of childbearing age with HIV. The risk of transmission is highest at delivery and during breastfeeding, especially with detectable viraemia in pregnancy, preterm delivery, and late initiation of treatment in pregnancy.[3,4] Combination antiretroviral therapy (ART) remains the most reliable treatment option for HIV infection and effectively suppresses viral load, prevents development of AIDS, and minimises the risk of HIV transmission.[3–5] Pregnant women initiating ART before conception had a 0·03% rate of vertical HIV transmission; the rate was 0·00% in women who additionally had undetectable viral loads at conception.[4] As ART has transformed HIV infection into a manageable chronic illness, increased attention has been directed towards optimising current regimens and understanding chronic HIV-related comorbidities associated with HIV infection and ART, with the goal of improving quality of life for people with HIV over the long term.[6]

Dolutegravir-containing regimens with varied nucleoside reverse transcriptase inhibitor (NRTI) backbones have become the preferred regimens worldwide, recommended in 2019 by WHO as first-line therapy for all people with HIV.[3,5,7,8] Dolutegravir-based regimens are more affordable than other first-line ART regimens, making them favourable in low-income and middle-income countries.[5] Dolutegravir also has a high barrier to HIV resistance because mutations that confer resistance reduce HIV fitness.[9] Importantly, lower rates of viral resistance have been reported with dolutegravir use, and dolutegravir is successfully used as salvage treatment after virological failure of other regimens.[9,10] In clinical trials, dolutegravir-based regimens had the same or improved efficacy as protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and other integrase strand transfer inhibitors (INSTIs).[11–15]

In the context of pregnancy, the Safety and Pharmacokinetics of Dolutegravir in Pregnant HIV Mothers and Their Neonates (DolPHIN-1 and DolPHIN-2)[16,17] and International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network P2010 protocol (VESTED) randomised controlled trials (RCTs)[18] showed that dolutegravir was associated with more rapid and effective viral suppression compared with efavirenz, making dolutegravir especially useful in pregnancy in which rapid viral suppression is essential in preventing perinatal transmission. The Pediatric HIV/AIDS Cohort Study, Surveillance and Monitoring for ART Toxicities (SMARTT), reported better viral suppression in women receiving dolutegravir-based ART compared with non-dolutegravir ART regimens, without any differences in fetal outcomes.[19]

Dolutegravir-based treatments are associated with lower toxicity and fewer drug–drug interactions than other antiretroviral classes (eg, protease inhibitor or NNRTI-based regimens), and a good tolerability profile, all of which improve the quality of life and regimen adherence among people with HIV.[11,20] However, dolutegravir use has been associated with metabolic complications in non-pregnant adults, such as weight gain and rare events of hyperglycaemia.[21,22] In pregnancy, dolutegravir appears to be generally well tolerated; however, there are few studies available that examine metabolic parameters or postnatal outcomes.[16,17,23–26] We review available data on dolutegravir safety in pregnancy and clinically and experimentally derived data of the metabolic effects of dolutegravir. We further discuss how these metabolic effects could affect fetal and maternal health.

	Regimen	Outcomes
Zash et al (2018);[27] surveillance study; Botswana; August, 2014–May, 2018	Dolutegravir-based ART from conception (426 newborns); dolutegravir-based ART started in pregnancy (2812 newborns); other ART (11 300 newborns); HIV-negative (66 057 newborns)	Patients receiving dolutegravir from conception had four newborns (0·94%) with NTDs (encephalocele, myelomeningocele, iniencephaly, and anencephaly); NTD rates were similar between the HIV-negative (61 NTDs, 0·09%) and other ART groups (14 NTDs, 0·12%)
Pereira et al (2021);[28] surveillance study; Brazil; January, 2015–May, 2018	Dolutegravir-based ART (382 mothers); efavirenz-based ART (1045 mothers)	No increased risk for adverse peripartum outcomes associated with dolutegravir exposure were reported; after study completion, two additional newborns with NTDs were reported, resulting in an estimated 0·18% prevalence of NTDs of 1084 pregnancies in the dolutegravir group
Raesima et al (2019);[29] surveillance study; Botswana; October, 2018–March, 2019	Dolutegravir-based ART (152 newborns); other ART (381 newborns); HIV-negative (2328 newborns)	One NTD in the group of patients receiving dolutegravir from conception (0·66%); two NTDs in HIV-negative pregnancies (0·09%)
Patel et al (2022);[19] surveillance study; the USA, Puerto Rico, and Switzerland; April, 2007–January, 2020	Dolutegravir-based ART (120 mothers); ritonavir-boosted atazanavir-based ART (464 mothers); ritonavir-boosted darunavir-based ART (185 mothers); rilpivirine-based ART (243 mothers); raltegravir-based ART (86 mothers); cobicistat-boosted elvitegravir-based ART (159 mothers)	The dolutegravir-based regimen was associated with a slightly higher risk of preterm births than non-dolutegravir-based regimens; of 95 infants exposed to dolutegravir during organogenesis (first trimester), there was one newborn with syndactyly and two newborns with polydactyly
Antiretroviral Pregnancy Registry Steering Committee (2023);[30] database analysis; Antiretroviral Pregnancy Registry; January, 1989–January, 2023	Dolutegravir-based ART (874 newborns)	29 newborns (3·3%) had congenital anomalies associated with exposure to dolutegravir in the first trimester
Zash et al (2018);[25] surveillance study; Botswana; August, 2014–August, 2016	Dolutegravir-based ART (1729 mothers); efavirenz-based ART (4593 mothers);	No increased risk of adverse birth outcomes from dolutegravir
Zash et al (2021);[31] surveillance study; Botswana; August, 2014–April, 2020	Dolutegravir-based ART (2450 mothers*); efavirenz-based ART (7459 mothers*); other ART (6492 mothers*); nevirapine-based ART (4695 mothers*); ritonavir-boosted lopinavir-based ART (841 mothers*)	The dolutegravir regimen had the same or better peripartum outcomes compared with other ART regimens in all maternal weight groups
Kintu et al (2020);[17] open-label RCT; South Africa and Uganda; January–August, 2018	Dolutegravir-based ART (135 mothers); efavirenz-based ART (133 mothers)	The dolutegravir group showed a greater proportion of adverse pregnancy events (30 [22%] of 135) than the efavirenz group (14 [11%] of 131; p=0·013)
Malaba et al (2022);[32] open-label RCT (72-week follow-up); South Africa and Uganda; January–August, 2018	Dolutegravir-based ART (135 mothers); efavirenz-based ART (133 mothers)	The dolutegravir group showed a slightly greater proportion (33 [24%]) of serious adverse events than the efavirenz (24 [18%]) group, but most adverse events were deemed not drug related
Lockman et al (2021);[18] open-label RCT; Zimbabwe, South Africa, Uganda, Brazil, Botswana, Tanzania, Thailand, the USA, and India; January, 2018–February, 2019	Tenofovir disoproxil fumarate, emtricitabine, and dolutegravir (213 mothers*, 202 newborns); tenofovir alafenamide, emtricitabine, and dolutegravir (216 mothers*, 208 newborns); tenofovir disoproxil fumarate, emtricitabine, and efavirenz (211 mothers*, 207 newborns)	The tenofovir alafenamide, emtricitabine, and dolutegravir group had fewer composite adverse pregnancy outcomes (52 [24%] of 126) than the tenofovir alafenamide, emtricitabine, and efavirenz group (69 [33%] of 211; p=0·047) and the tenofovir disoproxil fumarate, emtricitabine, and dolutegravir group (70 [33%] of 213; p=0·043); the tenofovir alafenamide, emtricitabine, and dolutegravir group had lower rates of preterm birth (12 [6%]) than the tenofovir alafenamide, emtricitabine, and efavirenz group (25 [12%]; p=0·023); the tenofovir alafenamide, emtricitabine, and dolutegravir group had higher gestational weight gain (0·38 kg/week) than the tenofovir disoproxil fumarate, emtricitabine, and dolutegravir group (0·32 kg/week; p=0·011) and the tenofovir disoproxil fumarate, emtricitabine, and efavirenz group (0·29 kg/week; p=0·0002)
Caniglia et al (2020);[33] surveillance study; Botswana; August, 2014–March, 2019	Dolutegravir (621 mothers); efavirenz (757 mothers); HIV-negative (11 280 mothers)	Over 18–36 weeks' gestation, the dolutegravir group had 0·35 kg/week weight gain, the efavirenz group had 0·31 kg/week weight gain, and the HIV-negative group had 0·44 kg/week weight gain
Jao et al (2022);[24] RCT; Botswana; August, 2016–May, 2019	Tenofovir disoproxil fumarate, lamivudine or emtricitabine, and dolutegravir (182 mothers); tenofovir disoproxil fumarate–lamivudine or emtricitabine–dolutegravir (124 mothers)	No difference in insulin sensitivity in exposed, uninfected infants born to women taking dolutegravir *vs* women taking efavirenz in pregnancy
Mmasa et al (2021);[23] prospective surveillance study;[23] Gaborone and Botswana; August, 2016–May, 2019	Dolutegravir-based ART (197 mothers); efavirenz-based ART (126 mothers); HIV-negative (163 mothers)	Lower rates of gestational diabetes were observed in dolutegravir-treated (12 [6·1%]) *vs* efavirenz-treated women (17 [13·5%]; p=0·03); both rates were similar to the HIV-negative group (12 [7·4%]; p=0·61)
Chouchana et al (2019);[34] database analysis; France; 2012–16	Dolutegravir-based ART (49 newborns); raltegravir-based ART (240 newborns); elvitegravir-based ART (70 newborns)	Higher rates of birth defects were reported in the dolutegravir group (two [4·1%]) than the raltegravir (three [1·3%]) and elvitegravir (one [1·4%]) groups
Grayhack et al (2018);[35] retrospective analysis; the USA; January, 2015–May, 2018	Dolutegravir-based ART (66 mothers, 57 newborns)	No side-effects on dolutegravir treatment were reported; two newborns (3·5%) with birth defects were reported (a congenital heart abnormality and non-immune hydrops fetalis)
Bornhede et al (2018);[36] retrospective analysis; Sweden; 2014–17	Dolutegravir-based ART (36 mothers)	The dolutegravir-based regimen showed no difference in adverse pregnancy events compared with the general population

(Table 1 continues on next page)

	Regimen	Outcomes
(Continued from previous page)		
Money et al (2019);[37] retrospective analysis; Canada; 2007–17	Dolutegravir-based ART (80 newborns)	Four newborns (5·0%) with exposure to dolutegravir in the first trimester had congenital anomalies, none NTDs
Zash et al (2019);[38] surveillance study; Botswana; August, 2014–March, 2019	Dolutegravir-based ART from conception (1683 newborns); non-dolutegravir-based ART (14 792 deliveries); HIV-negative (89 372 newborns)	Five newborns (0·30%) with NTDs born to women taking dolutegravir-based ART from conception; 15 NTDs (0·10%) in newborns born to women taking non-dolutegravir-based ART; 70 newborns with NTDs (0·08%) from HIV-negative pregnancies

ART=antiretroviral therapy. NTD=neural tube defect. RCT=randomised controlled trial. *Varied number for different outcomes.

Table 1: **Summary of clinical pregnancy studies that include a dolutegravir-based regimen, by study type, location, and date**

Safety in pregnancy

Pregnancy and birth outcomes

Initial clinical surveillance studies did not report an association between dolutegravir-based ART and adverse birth outcomes (table 1).[25,26] In the DolPHIN-2 open-label RCT recruiting from South Africa and Uganda, dolutegravir was associated with greater pregnancy and postpartum (also known as puerperium) adverse events compared with the efavirenz group. However, this finding was not replicated in other studies (table 1).[17,18,32] Analysis of data obtained in the Tsepamo study did not show differences in severe pregnancy outcomes, such as preterm birth, small for gestational age, or fetal demise, but an increased occurrence of maternal hypertension and increased intrapartum weight gain was reported in women receiving a dolutegravir-based versus efavirenz-based regimen.[31,33] Furthermore, dolutegravir was associated with fewer severe adverse birth outcomes in women with lower BMI.[31] In the VESTED trial, dolutegravir was associated with improved gestational weight gain and either similar or lower levels of adverse birth outcomes than efavirenz.[18]

Neural tube defects

In May, 2018, the Tsepamo surveillance study in Botswana reported four newborns with neural tube defects (NTDs) among offspring of 426 women starting dolutegravir at conception (0·94% [95% CI 0·37–2·40]), compared with a 0·12% (0·07–0·21) incidence with non-dolutegravir-based ART and 0·09% (0·07–0·12) incidence among offspring of women without HIV.[27] A 2019 follow-up to the Tsepamo study[38] reported a decrease from the initial report in NTD prevalence among dolutegravir-treated pregnant women to 5 newborns (0·30% [0·13–0·69]) of 1683 deliveries.[38] More anterior body wall defects (eg, omphalocele and gastroschisis) were also reported in those receiving a dolutegravir-based regimen from conception.[38] In a further update in March, 2022, ten newborns with NTDs were reported in 9460 women taking a dolutegravir-based regimen from conception (0·11% [0·06–0·19]) compared with 0·08% (0·04–0·14) on efavirenz and 0·07% (0·05–0·08) HIV-negative pregnancies. These findings brought the rate of newborns with NTDs in the dolutegravir group to the same proportion to that of other antiretroviral drugs and women without HIV.[39]

Additional studies have reported on dolutegravir and NTDs. Although none of these studies have the sample size of the Tsepamo study, most reported no differences in rates of congenital defects, including NTDs, between dolutegravir and other antiretroviral drugs (table 1).[28–30,37]

Despite the disappearance of the initial NTD signal, the cause of the increased rates of NTDs is unknown. The initial signal could have been a matter of chance because of a small sample size. Alternatively, there could have been other risk factors present during the 2018–19 years that had a combined effect with dolutegravir on the emergence of NTDs, such as lower population folate concentrations than present in other years or other environmental exposures. However, this proposition remains speculative. In light of the March, 2022 data from Botswana, dolutegravir remains a preferred regimen for its superior efficacy in preventing HIV-related mortality and transmission in women of childbearing potential.[40,41]

Animal and in-vitro studies

In pregnancy, dolutegravir crosses the placenta and fetal exposure can be substantial because of slow fetal metabolism of the drug.[16,26] In reproductive toxicology studies in rats and rabbits, supratherapeutic dolutegravir was not associated with fetotoxicity or higher risk for congenital defects (table 2).[44] However, in a large fetotoxicity study in C57BL/6J mice fed a folate-sufficient diet, a higher rate of NTDs (5 fetuses [0·5%] of 150 litters) was observed at the therapeutic dolutegravir dose compared with the control (0 fetuses [0·0%] in 91 litters), and surprisingly with the supratherapeutic dolutegravir dose (0 fetuses [0·0%] in 111 litters; both dolutegravir doses administered with tenofovir disoproxil fumarate and emtricitabine).[42] Mice receiving the therapeutic dolutegravir regimen also had increased rates of microphthalmia, bleeding defects, and oedema.[42] Supratherapeutic dolutegravir-only exposure from conception in C3H/HeJ mice resulted in one NTD (exencephaly) in 109 embryos from 17 litters, with evidence of neuronal damage and neuroinflammation in the pups of dolutegravir-treated dams (table 2).[43] Dolutegravir exposure in rat embryos cultured through the period of neurogenesis did not show teratogenicity, although the design of the study was brought into question, particularly the sample size, drug penetrance of the embryo, and

	Regimen	Treatment start	Results
Mohan et al (2021);[42] C57BL/6J female mice	150 litters given dolutegravir 2·5 mg/kg per day (therapeutic dose), emtricitabine 33·3 mg/kg per day, tenofovir disoproxil fumarate 50·0 mg/kg per day; 111 litters given dolutegravir 12·5 mg/kg per day (supratherapeutic dose), emtricitabine 33·3 mg/kg per day, tenofovir disoproxil fumarate 50·0 mg/kg per day; 91 litters in the control group (water)	Gestational day 0·5	Five cases of neural tube defects were observed in the therapeutic one-dose dolutegravir group (two had exencephaly, two had spina bifida, and one had potential anencephaly)
Bade et al (2021);[43] C3H/HeJ female mice	17 litters given dolutegravir 50·0 mg/kg per day; 9 litters in the control group (vehicle)	Gestational day 0·5	Exencephaly in one fetus in the dolutegravir group, but number insufficient for statistical power
Stanislaus et al (2020);[44] Sprague-Dawley female rats	22 litters given dolutegravir 5·0 mg/kg per day; 21 litters given dolutegravir 50·0 mg/kg per day; 27 litters given dolutegravir 100·0 mg/kg per day; 27 litters given dolutegravir 300·0 mg/kg per day; 47 litters given dolutegravir 1000·0 mg/kg per day; 49 litters in the control group	Gestational day 6	No differences in external abnormalities; one case of meningocele and absent eye bulge in the 1000 mg/kg dose group, but number insufficient for statistical power
Stanislaus et al (2020);[44] Japanese white female rabbits	19 litters given dolutegravir 40·0 mg/kg per day; 3 litters given dolutegravir 100·0 mg/kg per day; 18 litters given dolutegravir 200·0 mg/kg per day; 5 litters given dolutegravir 300·0 mg/kg per day; 24 litters given dolutegravir 1000·0 mg/kg per day; 24 litters in the control group	Gestational day 6	No differences in external abnormalities observed; one case of cranioschisis in the 40 mg/kg dose group, but N insufficient for statistical power

Table 2: **Summary of in-vivo reproductive animal-model studies with dolutegravir**

	Culture model and dosage*	Results
Kirkwood-Johnson et al (2021)[45]	46–48 aggregates of murine P19C5 pluripotent stem cells and H9 human embryonic stem cells per condition for morphogenesis (0·25 μM, 0·5 μM, 1·0 μM, 2·0 μM, 4·0 μM)	Dolutegravir was associated with impaired stem-cell morphogenesis and changes to developmental regulator genes in a dose-dependent manner in both P19C5 and H9 cells
Smith et al (2022)[46]	Five replicates of CA1S human embryonic stem cells (8·32 μM)	Dolutegravir was associated with reduced expression of pluripotency markers in CA1S cells
Smith et al (2022)[46]	Six replicates of H9 human embryonic stem cells (8·32 μM)	Dolutegravir was associated with increased rates of apoptosis in H9 cells
Posobiec et al (2021)[47]	Sprague-Dawley GD9 embryo culture (16 embryos at 12·6 μM; 16 embryos at 22·2 μM)	Dolutegravir did not affect embryo lethality, visceral yolk sac, somite number, or embryo size
Cabrera et al (2019)[48]	2–4 experimental replicates of zebrafish embryos (100 μM)	Dolutegravir was associated with developmental toxicity post-fertilisation

*Maximum concentration for dolutegravir in non-pregnant human adults is reported as 7·01–11·56 μM.[49]

Table 3: **Summary of in-vitro developmental toxicology studies with dolutegravir**

potential for metabolite teratogenicity (table 3).[47,50] In a cell culture model, dolutegravir affects morphogenesis and survival of murine pluripotent and human embryonic stem cells, and leads to transcript changes of developmental regulator genes (table 3).[43,45,46] From these studies, dolutegravir seems to be essentially safe for use in human pregnancy, although it could potentially affect some aspects of embryonic development. Although adverse developmental effects were observed in cell culture, they were rarer and milder in the in-vivo models and largely absent in clinical studies, potentially because of compensation by whole-organism homoeostatic mechanisms.

Metabolic effects and implications for safety in pregnancy

Changes to folate metabolism

Interest in investigating the association between dolutegravir and folate increased following the original 2018 Botswana report of NTDs potentially linked to use of the drug.[27] A comparison of serum folate concentrations in women participating in the ADVANCE trial found that folate concentrations increased in non-pregnant women taking dolutegravir administered with tenofovir alafenamide and emtricitabine over 12 weeks, folate concentrations remained stable in women taking tenofovir disoproxil fumarate, emtricitabine, and dolutegravir, and decreased in women taking tenofovir disoproxil fumarate, emtricitabine, and efavirenz.[51] In the 26 women who became pregnant during the study, folate concentrations increased slightly in those taking tenofovir alafenamide, emtricitabine, and dolutegravir or tenofovir disoproxil fumarate, emtricitabine, and dolutegravir and decreased slightly in those taking tenofovir disoproxil fumarate, emtricitabine, and efavirenz for 24 weeks; however, the pregnancy cohort was severely limited in sample size.[51]

Animal and in-vitro studies examining the effects on dietary folate and folate transport indicate mild effects of dolutegravir at therapeutic plasma concentrations (figure).[48,52,53] Dolutegravir is a partial antagonist of folate receptor 1 (FOLR1) in placental cell lines.[48] In the same study, folic acid supplementation was able to reverse early dolutegravir-related (100 μM) toxicity in zebrafish.[48] Data from the study by Zamek-Gliszczynski and colleagues[52] support in-vitro dolutegravir antagonism of FOLR1; however, extrapolating quantified in-vitro dolutegravir

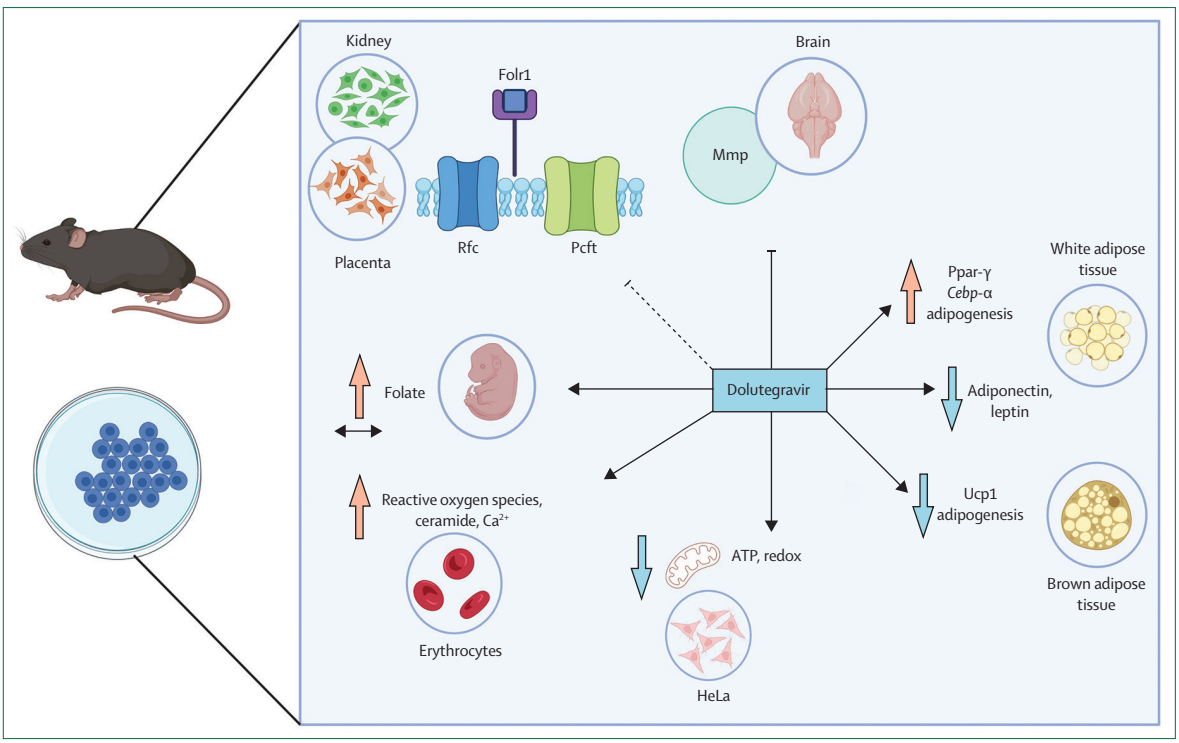

Figure: **Summary of the observed effects associated with dolutegravir from animal and in-vitro studies**
Dolutegravir effects on folate metabolism,[42,48,52,53] cellular energy homoeostasis,[54,55] adipocyte function,[54,56-58] and Mmp[43] are shown (anticlockwise from top left). Dotted line indicates variable effects reported. Red arrows indicate an increase, blue arrows indicate a decrease, and the black arrows indicate no changes. *Cebp*-α=Ccaat enhancer-binding protein α. Folr1=folate receptor 1. Mmp=matrix metalloproteinases. Pcft=proton-coupled folate transporter. Ppar-γ=peroxisome proliferator-activated receptor γ. Rfc=reduced folate carrier. Ucp1=uncoupling protein 1.

inhibition to in-vivo conditions, this effect was deemed not clinically relevant at a therapeutic dose of dolutegravir. In dolutegravir-treated placental explants and placenta cell lines, and in placentas isolated from dolutegravir-treated mice, variable changes to the gene and protein expression of the folate transport and metabolism pathway were observed. Dolutegravir treatment of placental cell lines was associated with a modest reduction in the expression of reduced folate carrier and proton-coupled folate transporter, along with a decrease in their transport function.[53] In the fetotoxicity study by Mohan and colleagues,[42] supratherapeutic dolutegravir treatment was associated with lower rates of fetal anomalies than the therapeutic dolutegravir dose, and concurrently higher concentrations of fetal folate (fetal folate concentrations in the therapeutic dose were similar to control), suggesting either potential compensation by increased folate uptake or biphasic effects of dolutegravir on a system interacting with or affecting the folate pathway.

Whether the dysregulation of folate transport or metabolism by dolutegravir has a clinical effect on human pregnancies remains unclear. Neither clinical nor animal data suggest that dolutegravir reduces folate concentrations, but there is some evidence suggesting a diminished response to folate through FOLR1 inhibition and reduced folate transport across the placenta after dolutegravir treatment. Therefore, folate insufficiency in pregnancy might exaggerate the effects of dolutegravir and proper folate supplementation should have a protective effect against adverse events. Although fetal folate concentrations and active placental folate transport cannot be quantified in human pregnancies, studies examining the interaction of maternal folate concentrations and placental nutrient transporters in women receiving dolutegravir-based ART might provide insight into the cause of adverse perinatal events.

Metabolic effects in clinical studies

Having maternal obesity, hyperglycaemia, prediabetes, type 2 diabetes, or metabolic syndrome (defined as having three or more of increased waist circumference, increased blood pressure, increased plasma triglycerides, increased fasted blood glucose, and decreased HDL cholesterol) increase the risk for adverse events in pregnancy and contribute to fetal metabolic programming towards increased risk for poor metabolic health.[59,60] Dolutegravir has been associated with weight gain and rare new-onset hyperglycaemia, and some studies report an increased risk for diabetes and metabolic syndrome.[21,22,61,62] However, few studies have addressed metabolic effects of dolutegravir in pregnancy, and

results of clinical trials generally suggest improved pregnancy outcomes for dolutegravir compared with other antiretroviral drugs, primarily efavirenz.[23,26] Larger-scale studies are needed to corroborate these results. In addition, studies comparing metabolic effects of dolutegravir in pregnancy to those of people without HIV are absent. Dolutegravir-associated transient changes to fasted blood glucose in non-pregnant female mice have been reported.[63] However, no animal studies investigating maternal glucose homoeostasis in pregnancy have been done.

Dolutegravir-based regimens are associated with greater weight gain and, in the long term, might contribute to other metabolic complications.[21,62] In patients who have received ART and patients who have not, dolutegravir-based regimens are associated with greater weight gain than are NNRTI-based, protease inhibitor-based, and some other INSTI-based regimens.[15,21,62,64–72] The degree of weight gain varies greatly in relation to the backbone formulation, demographics, and baseline characteristics of the study participants, with tenofovir alafenamide-containing NRTI backbones, female sex, older age, and Black race being independently associated with greater risk for treatment-associated weight gain.[15,21,67,73–75] In people with HIV with advanced viraemia and immune suppression (CD4$^+$ count <200 cells per μL), initiation of ART leads to weight gain as part of the process of returning to health. Weight gain among treatment-naive individuals initiating dolutegravir-based therapy is greater than in treatment-experienced people switching to dolutegravir-based regimens.[65,69,71,73,75–78] Furthermore, poor virological control, adverse events, and slower rate of viral suppression in protease inhibitor and NNRTI drugs are often cited as reasons for smaller magnitude and rate of weight gain in comparison with dolutegravir-based regimens. However, although some NNRTIs are associated with a slower rate of viral suppression in select studies, the INSTI elvitegravir exhibits a similar viral suppression rate to dolutegravir and is associated with similar weight gain to NNRTIs.[68] Furthermore, increased weight gain continues to be an issue in the long term, as shown in 5-year follow-up studies by Ando and colleagues[72] and Bourgi and colleagues.[67] In most retrospective studies, the inclusion criteria include successful viral suppression and high CD4$^+$ cell count before INSTI treatment as a way to control for the return-to-health effect. Randomised ART-switch and double-blind RCTs corroborate the weight-gain effects of dolutegravir.[21,70]

In pregnancy, women receiving dolutegravir-based ART had greater intrapartum weight gain than did those taking efavirenz-based ART; however, it was still below the recommended weekly weight gain for a healthy pregnancy.[18,31–33] Sufficient weight gain during pregnancy reduces the risk of preterm birth, small-for-gestational-age neonates, and very small-for-gestational-age neonates; therefore, dolutegravir-based regimens appear more favourable.[79]

Currently, only short-term prospective, case-report, and cross-sectional data exist on the effects of dolutegravir on metabolic health, partly due to the recent implementation of dolutegravir as a first-line treatment. There is also a substantial degree of discrepancy between various studies, with some citing dolutegravir-associated improvements to metabolic parameters[80,81] whereas others report increased risk for type 2 diabetes, metabolic syndrome, and hyperglycaemia.[22,61] In an observational prospective study interrogating changes to insulin sensitivity and circulating lipids following a switch from ritonavir-boosted protease inhibitor to a dolutegravir-containing regimen in patients with stable virological control, dolutegravir was associated with lower interleukin-6, triglycerides, LDL and total cholesterol, leptin, insulin, and homoeostasis model assessment of insulin resistance index.[80] In ART-naive patients, initiating a dolutegravir-based regimen was associated with lower rates of new-onset diabetes at 0·91%, in comparison with those starting an NNRTI-containing (1·37%) or a protease inhibitor-containing (1·50%) regimen.[81] Hsu and colleagues[82] reported no increased risk of prediabetes or diabetes in patients who have and patients who have not had ART on different INSTIs. However, being on ART was associated with higher incidence of type 2 diabetes than the general population (9–13 *vs* 6·7 per 1000 person-years).[82] A cross-sectional study examining risk factors (including ART regimen, NRTI backbone, viral load, BMI, sex, and lymphocyte count) for developing metabolic syndrome in people with HIV receiving ART for at least 6 months in Zambia reported that dolutegravir-based regimens, compared with protease inhibitor-based and NNRTI-based therapies, were independently associated with doubling of the risk for metabolic syndrome.[61] A national survey of HIV clinicians' perspectives on the tolerability and effectiveness of dolutegravir use for people with HIV in Uganda reported favourable outcomes for patients initiating or switching to dolutegravir. However, hyperglycaemia, insomnia, and decreased libido were some of the side-effects associated with dolutegravir treatment.[83]

Case reports of hyperglycaemia after the initiation of dolutegravir have appeared throughout the literature, in which hyperglycaemia occurred in patients with normal BMI, losing or gaining weight, and without previous history of insulin resistance.[84–86] Discontinuation of INSTI-based therapy normalised glycaemic control in the presented patients and they no longer needed antidiabetic medication.[84,87] A large-scale surveillance study in Uganda reported a greater incidence of new-onset hyperglycaemia in people with HIV switching to, or initiating, dolutegravir-based regimens (0·47%) than in patients receiving non-dolutegravir-based regimens (0·03%).[22] Furthermore, no association of hyperglycaemia with weight gain was observed because in most cases of hyperglycaemia the patients had lost weight.[22] A caveat to the study was that a greater proportion of individuals in

the dolutegravir group were male, older, and on ART for more than 5 years, all of which are risk factors for hyperglycaemia.[22] A study interrogating adverse drug events in treatment-experienced and treatment-naive patients observed hyperglycaemia with an incidence of 7·3% within 13–62 weeks of the initiation of a dolutegravir-based regimen.[88] Furthermore, the SPRING-1,[89] SPRING-2,[90] SAILING,[91] SINGLE,[92] and FLAMINGO[93] clinical trials, which assessed the efficacy of dolutegravir, reported hyperglycaemia among its adverse drug events; hyperglycaemia also appears as an adverse drug event leading to dolutegravir discontinuation.[88]

To date, only one study has reported incidence of gestational diabetes in patients receiving ART, in which dolutegravir-based ART was associated with a lower risk for gestational diabetes compared with efavirenz-based ART.[23] No change to insulin sensitivity was observed in exposed, uninfected infants born to women receiving dolutegravir-based ART versus efavirenz-based ART.[24] In the follow-up to the IMPAACT 2010 VESTED study, there were no differences in maternal or fetal glycated haemoglobin for the three regimens tested: emtricitabine, tenofovir disoproxil fumarate, and dolutegravir; emtricitabine, tenofovir alafenamide, and dolutegravir; or emtricitabine, tenofovir disoproxil fumarate, and efavirenz.[94]

Taken together, these studies show that dolutegravir is associated with metabolic changes in non-pregnant adults. There remains a gap in knowledge of whether the observed effects in non-pregnant individuals are replicated in pregnancy and relevant to perinatal outcomes.

Animal and in-vitro studies of metabolic changes

Dolutegravir-associated weight gain and hyperglycaemia observed in clinical studies might result from drug-induced changes to energy homoeostasis at the hypothalamic, tissue, or cellular levels. Animal models and in-vitro studies that used human samples have shown distinct alterations to adipose tissue function and insulin sensitivity and changes to mitochondrial function and oxidative metabolism associated with dolutegravir.[54–57,95] We summarise the studies conducted to characterise dolutegravir's effects on these pathways (figure).

Dolutegravir-associated weight gain and metabolic perturbations might be a symptom of a change to energy homoeostasis regulation by the hypothalamus. Many hormones are involved in the regulation of satiety or hunger and energy expenditure, and deviations from the physiological baseline in pregnancy could lead to fetal programming that affects fetal metabolic health.

In the tivicay (dolutegravir; GlaxoWellcome, Burgos, Spain) product monograph, dolutegravir was shown to reduce the binding of α-melanocortin stimulating hormone to MC4R by 65% at the clinical maximum concentration (C_{max}) of dolutegravir.[96] This inhibitory effect of dolutegravir might shift the anorexigenic–orexigenic balance towards increased orexigenic neural tone, thereby increasing appetite and reducing postprandial satiety, resulting in increased food intake without altering energy expenditure and leading to weight gain.[97] The potential role of MC4R in development has been sparsely documented and has not yet been thoroughly studied.[98] Analysis of MC4R binding by various INSTIs revealed a capacity for MC4R antagonism by bictegravir, cabotegravir, elvitegravir, raltegravir, and dolutegravir, with half-maximal effective concentration more than 100 times greater than the unbound plasma C_{max} for each individual drug.[97] Further studies are needed to examine the effects of dolutegravir on hormones involved in regulation of satiety, hunger, and energy expenditure, such as α-melanocortin stimulating hormone, thyroid hormones, cortisol, and leptin.

Data from in-vitro and animal studies suggest that dolutegravir is associated with adipose tissue changes that could contribute to a mechanistic understanding of the clinically observed weight gain. White adipose tissue has roles in both energy storage and endocrine signalling through adipokine secretion, whereas brown adipose tissue contributes to energy consumption through oxidising free fatty acids and generating non-shivering thermogenesis.[56] White adipocytes secrete leptin, an anorexigenic prosatiety peptide, and adiponectin, which improves insulin sensitivity. In perturbed metabolic states, such as insulin resistance, white adipose tissue tends towards hypertrophy, fibrosis, and plasma hyperlipidaemia.[95] Cold exposure, fasting, and β-adrenergic stimulation promote brown adipose tissue activation and white adipose tissue beiging, which are associated with better metabolic outcomes.[56]

Treatment with dolutegravir has been shown to cause changes to adipose tissue composition, function, and signalling.[56,57,95] In simian, non-infected, subcutaneous tissue and visceral adipose tissue, treatment with tenofovir disoproxil fumarate, emtricitabine, and dolutegravir induced fibrosis and hypertrophy of adipose tissue, with increased mRNA expression of the adipogenic peroxisome proliferator-activated receptor γ (PPAR-γ) and CCAAT enhancer-binding protein α, and decreased mRNA expression of adiponectin.[95] In people with HIV and obesity, increased adipose tissue fibrosis was seen in those treated with INSTI-based rather than non-INSTI-based treatment.[95] In cultured, proliferating human adipocyte stem cells and mature adipocytes, standalone dolutegravir treatment at C_{max} was associated with mitochondrial dysfunction, increased fibrotic markers, lipid accumulation, and lipogenesis, decreased leptin and adiponectin secretion, and decreased insulin sensitivity.[95] These findings were replicated by Pickering and colleagues,[58] who reported that dolutegravir reduced leptin and adiponectin signalling in cultured subcutaneous adipocytes while increasing proadipogenic and profibrotic PPAR-γ and collagen-6 transcripts without altering total triacylglycerol content in both subcutaneous

and visceral cultured adipocytes. In macaques infected with simian immunodeficiency virus (SIV), long-term (2-year) treatment with tenofovir disoproxil fumarate, emtricitabine, and dolutegravir was associated with a maintained profibrotic, adipogenic phenotype of subcutaneous and visceral white adipose tissue.[57] The emergent white adipose tissue phenotype of increased lipogenesis, decreased lipolysis, and insulin resistance seen in the macaques with SIV treated with dolutegravir does not co-occur under healthy conditions or under the typical progression of obesity, type 2 diabetes, and metabolic syndrome.[95] Characterisation of oxidative brown adipose tissue in cell culture and in-vivo models with short-term (ie, <2 weeks) exposure to dolutegravir shows a reduction in thermogenesis, adipogenesis, markers specific for brown adipose tissue, uncoupling protein 1 expression, and insulin sensitivity.[56,57]

If the dolutegravir-associated changes in adipose tissue lead to clinically observable changes to circulating adipokines, such as leptin, body composition, and whole-body energy expenditure, these effects could partly explain the weight gain. Therefore, monitoring these parameters in patients receiving dolutegravir-based ART would be useful. Studying the effects of dolutegravir on leptin concentrations in the context of pregnancy would be also important because leptin is produced by the placenta and its production is altered in several pathological conditions, including pre-eclampsia and gestational diabetes.[99,100]

At a cellular level, the decreases in the oxidative capacity of brown adipose tissue and the insulin sensitivity of white adipose tissue might stem from altered cellular metabolism, initiating or resulting in oxidative stress. Oxidative stress in the context of pregnancy can negatively affect fetal development and is common in many pathways leading to congenital defects.[101] George and colleagues[55] report a reduction to mitochondrial redox reactions and ATP production, alongside increased glycolysis, in HeLa cells after 24-h dolutegravir exposure.[55] In erythrocytes, 48-h dolutegravir incubation increased reactive oxygen species production, surface ceramide and phosphatidyl serine, and cytosolic Ca^{2+}, indicating cellular oxidative stress.[54]

Dolutegravir's inhibitory action on the viral integrase is partly because of cation chelation, which is hypothesised to interfere with the host's own enzymes.[43,48,102] In the study by Bade and colleagues,[43] dolutegravir was a broad-spectrum matrix-metalloproteinase inhibitor by binding the Zn^{2+} ion bound by this class of enzymes. Matrix metalloproteinases have essential roles in neural crest migration, synapse development, axonal guidance, and angiogenesis in the embryo and contribute to uterine vascular remodelling by the cytotrophoblasts in the development of the placenta.[43,103]

The cation chelating property of dolutegravir might extend to other metal-binding enzymes, such as superoxide dismutases (SODs; eg, Mn-SOD and Cu/Zn-SOD), resulting in increased cellular reactive oxygen species, although these effects have not yet been tested. Oxidative stress at the level of the placenta might result in lower fetal weight[104] as reported in the study by Mohan and colleagues;[42] however, this effect was not observed clinically. To test if these molecular effects have a systemic effect on development, experimental studies on placental function correlated to fetal outcomes should be done. The metal-ion chelating property of dolutegravir is an interesting mechanism to consider further because it would affect a broad spectrum of pathways that could contribute to various effects observed with dolutegravir in in-vitro and model studies. Furthermore, the degree of such insult would be modified by dietary factors and could explain clinically observed outcomes. Well designed studies would be needed to assess these effects clinically.

Conclusions

The global HIV pandemic presents a severe health-care burden, which can be successfully managed by ART. Dolutegravir-based ART is a preferred treatment option in both resource-rich and resource-limited settings because of its efficacy, high barrier to resistance, favourable safety and tolerance profile, and affordability. Dolutegravir-associated changes to maternal physiology, such as weight change, hyperglycaemia, and folate metabolism, along with changes to adipose tissue, oxidative stress, and potential interference with metal-binding enzymes, might affect fetal development and influence metabolic health in the child. However, the degree to which the reported cellular changes affect physiology remains unclear, and whether targeting these pathways in treatment would improve the dolutegravir-specific side-effects observed clinically is unknown. Furthermore, despite increasing evidence of dolutegravir-associated metabolic changes in non-pregnant adults, there have not been similar reports in pregnancy, and their connection to fetal development has not yet been studied. Studies investigating maternal metabolic health, such as weight and adipose change, plasma lipid profile, adipokine concentrations, glucose homoeostasis correlating to pregnancy outcomes, and long-term fetal health, are warranted.

Specifically, addressing the following questions would provide great insight. Does dolutegravir affect maternal metabolic health? Do changes in maternal metabolic health resulting from dolutegravir treatment affect pregnancy outcomes and fetal metabolic health? How does maternal nutritional status interact with dolutegravir to influence birth outcomes? In clinical practice, increasing the focus on monitoring of maternal health and metabolic alterations occurring because of dolutegravir treatment is pertinent. Further, given the scale at which ART is being used in pregnancy, it is important that systematic monitoring of adverse events and pregnancy and birth outcomes is implemented because even small changes in

Search strategy and selection criteria

References for this Review were identified through PubMed searches, authors' general knowledge of the field, and research papers from presenting authors at HIV conferences. Only papers published in English and up to October, 2022 were included. The first search included the terms "dolutegravir.tw" AND ("pregnan*.ti" OR "conception.ti") and the second search included the terms "dolutegravir.tw" AND ("hyperglyc*.ti" OR "diabet*.ti").

risk have the potential to translate into many pregnancies and babies affected. In the absence of a mechanistic understanding, adequate nutrition and folic acid supplementation should be encouraged.

Contributors

VD and LS conceptualised the manuscript with input from all authors. VD generated the original draft with input from LS. HM, CB, JJ, NDEG, AJC, and RZ reviewed and edited the manuscript. All authors approved the final draft.

Declaration of interests

We declare no competing interests.

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