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Pharmacokinetics and Safety of the Integrase Inhibitors Elvitegravir and Dolutegravir in Pregnant Women With HIV

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Abstract

Objective: To synthesize data on the pharmacokinetics and safety of dolutegravir and elvitegravir in pregnant women living with HIV. **Data Sources:** A PubMed, EMBASE, Web of Science, and Google Scholar literature search (January 2010 to December 2018) was performed using the search terms *dolutegravir, elvitegravir, women, pregnant**, and *HIV*. Additional reports were identified from conference abstracts and review of reference lists. **Study Selection and Data Extraction:** English-language studies reporting pharmacokinetic and/or safety data in pregnant women receiving dolutegravir or elvitegravir/cobicistat were included. **Data Synthesis:** A total of 17 studies were selected. Studies demonstrated a modest decrease in dolutegravir concentrations in pregnancy. Preliminary data suggest an increased risk of neural tube defects when dolutegravir is used at the time of conception. Available pharmacokinetic data in pregnant women showed significantly reduced plasma concentrations of elvitegravir/cobicistat which may increase the risk of virological failure. Current guidelines recommend that dolutegravir should not be initiated in women who have the potential to become pregnant or women in their first trimester of pregnancy and elvitegravir/cobicistat should be avoided during pregnancy. **Relevance to Patient Care and Clinical Practice:** This review highlights pharmacokinetic and safety data for dolutegravir and elvitegravir/cobicistat in pregnant women. Clinicians need to be aware of these data to convey the risks and benefits of using these agents in women of child-bearing potential. **Conclusions:** Changes in guideline recommendations reflect emerging data regarding the use of dolutegravir and elvitegravir/cobicistat in pregnancy. Until further information is available, raltegravir or other first-line agents are recommended for women with HIV planning to become pregnant.

Keywords

HIV, pregnancy, elvitegravir, dolutegravir, pharmacokinetics

Introduction

In the United States and Canada, nearly a quarter of individuals living with HIV are women.[1,2] In Canada, approximately 70% of reported HIV cases in women occur in those who are of reproductive age (15-39 years).[3] Advances in HIV treatment, including the use of effective combination antiretroviral therapy (ART) in pregnant women and avoidance of breastfeeding has reduced the rate of perinatal transmission of HIV to <1%.[4] The number of pregnancies in women living with HIV is increasing; however, significant proportions (~25% to 50%) are reported as unplanned, reflecting the importance of engaging women in HIV care as well as in discussions around sexual and reproductive health.[5,6]

For people living with HIV, initiation of ART that is effective in suppressing HIV viral load while minimizing

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the risk of treatment-related toxicity is preferred. Integrase strand transfer inhibitors (INSTIs) are recommended in current guidelines to be used as part of initial therapy for most people because of favorable efficacy and adverse effect profiles when compared with other agents.[7,8] Several INSTIs are available as part of single-tablet regimens, which are associated with improved patient adherence.[7] In the case of women of childbearing potential, especially those not using an effective method of birth control, selection of ART regimens should also take into consideration available data on safety and efficacy in pregnancy.[4] It is generally recommended for women stabilized on ART and virologically suppressed prior to conception to continue the same regimen throughout pregnancy.[4] However, because women undergo major physiological changes throughout pregnancy, it is important to consider possible antiretroviral pharmacokinetic changes in the peripartum and postpartum stages. Decrease in antiretroviral exposure can result in virological breakthrough and increase the risk for perinatal transmission. Conversely, increase in antiretroviral concentrations can subject the mother, fetus, or newborn to unnecessary adverse effects.[9,10]

Accumulating pharmacokinetic and clinical evidence for the INSTI raltegravir in pregnancy has supported its role as a preferred option in both adult and pregnancy guidelines.[4,7,8] Pharmacokinetic studies of raltegravir, administered at a standard dose of 400 mg twice daily, noted lower raltegravir concentrations during pregnancy as compared with postpartum. However, raltegravir trough concentrations were comparable to historical data in nonpregnant populations and was typically more than the target concentration of 0.020 mg/L.[11] Thus, standard dosing of raltegravir is recommended during pregnancy; however, there are no data in pregnancy to guide the use of raltegravir 1200 mg (2 × 600-mg tablets) once-daily dosing. The pharmacokinetics, efficacy, and safety of raltegravir in pregnancy has been reviewed elsewhere.[12] Available evidence to date, including data from the Antiretroviral Pregnancy Registry (APR) and the French Perinatal Cohort, does not suggest an increased risk of teratogenicity associated with raltegravir use during pregnancy.[12-14] Until recently, dolutegravir was considered as an alternative INSTI in pregnancy; however, recent preliminary data suggest an increased risk in neural tube defects.[15] Elvitegravir/cobicistat is not recommended, because of pharmacokinetic changes seen in pregnancy and limited data to assess the risk of teratogenicity.[4] Bictegravir was approved in the United States and Canada in 2018; however, very limited data are available on its safety in pregnancy.[16,17] No cases of neural tube defects were seen among 25 women exposed to bictegravir during pregnancy (23 women were taking bictegravir preconception or during the first trimester).[17]

Given that INSTIs are part of recommended initial regimens in practice, the purpose of this review is to synthesize pharmacokinetic and safety data with dolutegravir and elvitegravir/cobicistat in pregnant women living with HIV.

Methods

A literature search was performed in PubMed, EMBASE, Web of Science, and Google Scholar from January 2010 to December 31, 2018, using the following keywords: (dolutegravir OR elvitegravir) AND (pregnant* or women) AND (HIV OR HIV-1 OR human immunodeficiency virus). These search dates were chosen because dolutegravir and elvitegravir/cobicistat were not approved in the United States and Canada until 2011 or later. Titles and abstracts were screened to identify relevant studies. Studies were selected if they included pharmacokinetic and/or safety data associated with dolutegravir or elvitegravir/cobicistat in pregnant women, including preterm births, birth weight, and/or birth defects. Reference lists from identified articles were also reviewed. Abstracts were searched from the following conferences: Conference on Retroviruses and Opportunistic Infections, International Workshop on Clinical Pharmacology of Antiviral Therapy, Conference of the British HIV Association, European AIDS Conference, International AIDS Society, and HIV Glasgow. The most recent source was chosen if multiple abstracts and/or publications were available from the same study.

Results

Pharmacokinetics of Dolutegravir in Pregnancy

Three studies examined the pharmacokinetics of dolutegravir during pregnancy and postpartum, one of which was a published article and 2 were conference reports (Table 1).[18-20] Mulligan et al[18] reported on data from the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Protocol 1026s, which is an ongoing open-label study of antiretroviral pharmacokinetics in pregnant women. A total of 29 pregnant women who were taking dolutegravir 50 mg daily were enrolled, and pharmacokinetic parameters were evaluated in the second trimester (n = 15), third trimester (n = 28), and postpartum (n = 22). Prior to pharmacokinetic sampling, women had to self-report dolutegravir adherence for the past 2 weeks and dosing times that were consistent over the past 3 days. Dolutegravir was given without regard to meals, and administration was observed on sampling days. This study found that the median dolutegravir area under the curve ($AUC_{0\text{-}24}$), C_{max}, and plasma concentration at 24 hours (C_{24}) values were 25% to 51% lower in the second and third trimesters as compared with postpartum (Table 1). However, median AUC during pregnancy was similar to reported values in nonpregnant individuals, and C_{24} trough concentrations of pregnant women were more than 10 times higher than the

Table 1. Pharmacokinetics of Dolutegravir and Elvitegravir in Pregnancy and Postpartum.

Author (Year)	Second Trimester	Third Trimester	Postpartum
Dolutegravir			
Mulligan et al (2018)[18]	n = 15; Values presented as median (IQR) AUC_{0-24h}: 47.6 (33.4-63.7) mg·h/L C_{min}: 0.69 (0.56-1.28) mg/L C_{max}: 3.62 (2.57-4.63) mg/L C_{24}: 0.73 (0.63-1.34) mg/L $T_{1/2}$: 11.0 (8.9-13.1) hours	n = 28; Values presented as median (IQR) AUC_{0-24h}: 49.2 (36.4-62.0) mg·h/L C_{min}: 0.81 (0.55-1.31) mg/L C_{max}: 3.54 (2.66-4.24) mg/L C_{24}: 0.93 (0.68-1.34) mg/L $T_{1/2}$: 12.2 (10.4-15.0) hours	n = 22; Values presented as median (IQR) AUC_{0-24h}: 65.0 (47.8-88.4) mg·h/L C_{min}: 0.97 (0.70-2.06) mg/L C_{max}: 4.85 (3.83-5.97) mg/L C_{24}: 1.28 (0.80-1.95) mg/L $T_{1/2}$: 13.5 (10.6-18.6) hours
Bollen et al (2017)[19]		n = 8; Values presented as geometric mean (CV%) AUC_{0-24h}: 42.9 (39) mg·h/L C_{max}: 3.4 (33) mg/L C_{24}: 0.7 (109) mg/L $T_{1/2}$: 9.9 (50) hours	n = 5; Values presented as geometric mean (CV%) AUC_{0-24h}: 44.8 (56) mg·h/L C_{max}: 3.0 (41) mg/L C_{24}: 1.1 (71) mg/L $T_{1/2}$: 14.9 (27) hours
Waitt et al (2018)[20]		n = 7; Values presented as geometric mean (95% CI) AUC_{0-24h}: 39.4 (28.3-50.5) mg·h/L C_{max}: 2.6 (2.0-3.3) mg/L C_{24}: 0.8 (0.4-1.1) mg/L	n = 2; Values presented as geometric mean AUC_{0-24h}: 59.6, 44.3 mg·h/L C_{max}: 4.2, 4.1 mg/L C_{24}: 1.2, 0.6 mg/L
Elvitegravir			
Momper et al (2018)[34]	n = 17; Values presented as median (IQR) AUC_{0-24h}: 15.3 (11.9-19.0) mg·h/L C_{min}: 0.018 (0.012-0.188) mg/L C_{max}: 1.45 (1.13-1.58) mg/L C_{24}: 0.026 (0.018-0.067) mg/L $T_{1/2}$: 3.1 (2.6-3.9) hours	n = 26; Values presented as median (IQR) AUC_{0-24h}: 14.0 (9.1-18.8) mg·h/L C_{min}: 0.025 (0.005-0.07) mg/L C_{max}: 1.43 (0.71-1.57) mg/L C_{24}: 0.049 (0.014-0.075) mg/L $T_{1/2}$: 3.4 (2.7-4.7) hours	n = 25; Values presented as median (IQR) AUC_{0-24h}: 21.0 (13.5-32.8) mg·h/L C_{min}: 0.23 (0.086-0.85) mg/L C_{max}: 1.71 (0.96-2.28) mg/L C_{24}: 0.38 (0.23-0.57) mg/L $T_{1/2}$: 8.8 (7.0-13.2) hours

Abbreviations: AUC, area under the curve; CV%, percentage coefficient of variation; IQR, interquartile range.

reported dolutegravir in vitro protein-adjusted 90% effective concentrations (EC_{90}) of 0.064 μg/mL. This study also demonstrated a median ratio of the dolutegravir concentration in the cord blood/maternal plasma (n = 18) of 1.25 (1.07-1.40), suggesting high placental transfer of dolutegravir, which is considered important in preventing HIV transmission to the neonate. All 28 women had a viral load <50 copies/mL in the third trimester, and 27 of 29 (93%) women had a viral load <50 copies/mL at delivery.[18] The 2 women with detectable viral loads had been receiving dolutegravir for 22 and 42 weeks. Dolutegravir exposure in the third trimester for these women was similar to the median exposure for the group. In another study, intensive pharmacokinetic data were collected in the third trimester and postpartum in pregnant women taking dolutegravir 50 mg daily.[19] Nine women were included, and data were available for 8 women in the third trimester and 5 women postpartum. All the women included had a viral load less than 50 copies/mL. The AUC_{0-24h} and C_{24} geometric mean ratios in the third trimester were decreased by 5% and 34%, respectively, when compared with postpartum. Similar to the results by Mulligan et al,[18] median cord blood/maternal plasma ratio for dolutegravir was 1.4 (0.35-1.6) in 5 mother-infant pairs. Waitt et al[20] described the pharmacokinetics of dolutegravir 50 mg daily in pregnant women in the third trimester (n = 7) and postpartum (n = 2). Women were enrolled in this study if they presented at antenatal clinics in Kampala and Cape Town with untreated HIV late in pregnancy (28-36 weeks). Samples were collected after 2 weeks on dolutegravir and at 2 weeks postpartum. By day 14, viral load was less than 50 copies/mL in 5 of 8 women; viral load was suppressed in 4 of 8 women by day 28. Two weeks postpartum, viral load was suppressed in 5 of 6 women. The investigators reported that adherence was a problem in this study. Although a modest reduction was noted in this small sample in the AUC_{0-24h}, C_{max}, and C_{24} of dolutegravir in the third trimester as compared with postpartum, the authors concluded that a dose increase was not needed.[20]

Although pharmacokinetic data are limited, taken together, these results suggest that there may be reduced dolutegravir exposures during pregnancy. However, this is unlikely to be clinically relevant because dolutegravir trough concentrations in all the pregnant women were well above the minimum effective concentration for patients who are treatment naïve.[21] In addition, the rate of viral suppression

was high in these women, and virological failure did not appear to be related to reduced exposures. Limitations of these data include lack of information on when dolutegravir was dosed in relation to prenatal vitamins and supplements that could affect the absorption of dolutegravir.

Safety of Dolutegravir in Pregnancy

A total of 10 studies reported safety data associated with dolutegravir use in pregnancy. A summary of the study design, timing of ART initiation, and birth outcomes are reported in Table 2.

A conference report described a retrospective chart review of 16 pregnant women in the United Kingdom who were prescribed dolutegravir as part of their regimen between April 2015 and January 2017.[22] The median age of these women was 29 years, and almost 90% were of black African ethnicity. Two women were on dolutegravir prior to conception, whereas the remainder started dolutegravir at a median gestational age of 16 weeks. All the women achieved viral suppression on dolutegravir treatment; 13 women who had delivered at the time of the report had viral loads <20 copies/mL at delivery.[22] One infant was born preterm at about 30 weeks' gestational age. No fetal abnormalities were observed in the infants born, and all the infants (12/12) for whom HIV DNA polymerase chain reaction (PCR) results were available were negative.

Henrard et al[23] reported findings from an observational study of 11 pregnant women taking dolutegravir-containing regimens in 2015-2016. Eight of these women were on dolutegravir prior to conception and virally suppressed. In terms of ethnicity, 91% were black African, and the median age at delivery was 33 years. All the women had viral loads <40 copies/mL at the time of delivery, and none of the infants was born preterm. HIV (DNA or RNA) PCR tests were negative at follow-up for all 12 infants. There were no cases of fetal malformations seen at birth or at follow-up.

Data on 101 women exposed to dolutegravir at various stages throughout their pregnancies were prospectively collected through the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC), NEAT-ID network, and PANNA (Pharmacokinetics of newly developed ANtiretrovirals agents in HIV-infected pregNAnt women).[24] Among them, 70% were of Black ethnicity, 10% acquired HIV through vertical transmission, and almost 40% of the women were 35 years of age or older at the time of conception. Also, 60% of women were on ART at the time of conception, although the specific regimens were not reported. Almost 60% of women had first trimester exposure to dolutegravir. Of the 101 women, 84 had outcomes reported at the time of analysis, with 1 pregnancy resulting in spontaneous abortion; 1 was an induced abortion, and 1 was a stillbirth at 10 weeks' gestation. Among data available, 11 of 80 infants (13.8%) were delivered at <37 weeks' gestational age, and 24 of 75 (18.7%) were small for gestational age.[24] Congenital abnormalities were reported in 3 live-born infants with earliest dolutegravir exposure in the first trimester and 1 with earliest exposure in the second trimester (overall 4/81 [4.9%]), which included patent foramen ovale with small left-to-right interatrial shunt, bilateral hexadactyly and hypospadias, ankyloglossia, and back hyperpigmentation. The investigators reported that the rates of preterm delivery and small for gestational age seen in this study were similar to those described in the United Kingdom.[24]

Another report from the APR, an international voluntary registry that monitors antiretroviral exposures and risk for birth defects through a registered prospective cohort, identified 142 pregnancies with dolutegravir exposure (126 reported from the United States).[25] About 60% of women had earliest exposure to dolutegravir in the first trimester, with the remainder exposed during the second or third trimesters. Approximately 90% had pregnancies resulting in live births, with 7.7% spontaneous abortions and 2.1% induced abortions. Outcome data were available for 119 infants; 13 (10.9%) were preterm, and 19 (16.0%) weighed <2500 g at birth. Congenital abnormalities were reported in 4 of 133 (3%) live-born infants: 2 with earliest exposure during the first trimester (1 infant with bilateral polydactyly postaxial to both hands and 1 infant with polydactyly on the ulnar side and syndactyly on fingers) and 2 with earliest exposure in the second/third trimester (1 infant with hypoglossia-hypodactyly syndrome and 1 with Down syndrome). The researchers concluded that the APR data did not demonstrate an increased risk of congenital abnormalities with dolutegravir use beyond expected population norms.[25]

In the IMPAACT Protocol 1026s study, outcomes were reported in 29 pregnant women using dolutegravir 50 mg daily, of whom 72% were of black ethnicity, with a median age of 32 years.[18] At the third trimester visit, the median duration of dolutegravir use was 19 weeks (range = 3.6-195). Delivery data were available for 29 infants, with 4 (13.8%) born at <37 weeks' gestation and 5 (17%) small for gestational age. In all, 24 infants were confirmed HIV negative, with 5 indeterminate because of incomplete testing. Clinical abnormalities at birth were described in 7 infants; abnormalities in 5 infants were considered unrelated to dolutegravir (3 were reported as normal variants). There were 2 infants with earliest dolutegravir exposure during weeks 11 and 12 of gestation with renal abnormalities that were considered possibly related to dolutegravir; one of these infants was determined to have dysplastic right kidney and was diagnosed with cystic fibrosis.

Bornhede et al[26] published findings from a retrospective analysis of 36 pregnant women who received dolutegravir during pregnancy between 2014 and August 2017 in Sweden. About 70% of women were black African, with a

Table 2. Pregnancy Outcomes and Birth Defects in Women Who Used Dolutegravir or Elvitegravir/Cobicistat During Pregnancy.

Author (Year)	Design (Location)	n	Timing of ART Initiation	Preterm Birth: <37 Weeks	Birth Weight	Congenital Anomalies
Dolutegravir						
Simons and Kulasegaram (2017)[22]	Retrospective case review (England)	16	Preconception: 2 (12.5%) During pregnancy: median GA 16 weeks	7.7%	Median birth weight 3300 g (810-4025)	0/13 (0.0%)
Henrard et al (2017)[23]	Prospective observational (Belgium)	11	Preconception: 8 (72.7%) Second/Third trimester: 3 (27.2%)	0%	Median birth weight 3330 g (2440-3860)	0%
Thorne et al (2017)[24]	Pooled analysis of prospective observational studies: EPICC + PANNA + NEAT-ID (Europe)	101	First trimester: 58 (57.4%) Second/Third trimester: 62 (41.6%)	13.8%	Small for GA (<10% percentile): 18.7% Low birth weight (<2500 g): 16.9%	4/81 (4.9%) Overall; 3/42 (7.1%) with first trimester exposure
Vannappagari et al (2017)[25]	Prospective report: Antiretroviral Pregnancy Registry (International)	142	First trimester: 88 (62%) Second/Third trimester: 54 (38%)	10.9%	Low birth weight (<2500 g) 16.0%	4/133 (3.0%) Overall; 2/77 (2.6%) with first trimester exposure
Mulligan et al (2018)[18]	Prospective pharmacokinetic study (United States)	29	Not reported	13.8%	Small for GA (<10% percentile): 17.2% Low birth weight (<2500 g): 13.8%	2/29 (6.9%) Possibly related to dolutegravir
Bornhede et al (2018)[26]	Retrospective analysis (Sweden)	36	Preconception: 14 (38.9%) Second/Third trimester: 22 (61.1%)	3.3%	Small for GA (<10% percentile): 3.3%	0/30 (0.0%)
Zash et al (2018)[27]	Cohort (Botswana)	1729 (DTG/TDF/FTC)	Median GA 19 weeks (14-25)	18.0%	Small for GA (<10% percentile): 17.4%	0/280 (0.0%) With first trimester exposure
		4593 (EFV/TDF/FTC)	Median GA 21 weeks (16-27)	18.5%	Small for GA (<10% percentile): 18.5%	1/395 (0.3%) With first trimester exposure
Zash et al (2018)[15]	Cohort: Tsepamo study (Botswana)	426 (DTG based ART)	All on ART at the time of conception	Not reported	Not reported	4/426 (0.94%) NTD
		11 300 (non-DTG-based ART)				14/11 300 (0.12%) NTD
Grayhack et al (2018)[30]	Retrospective analysis (United States)	66	Preconception: 28 (42.4%) During pregnancy: mean GA 18 weeks	31.6%	Small for GA (<10% percentile): 15.8%	2/57 (3.5%)

(continued)

Table 2. (continued)

Author (Year)	Design (Location)	n	Timing of ART Initiation	Preterm Birth: <37 Weeks	Birth Weight	Congenital Anomalies
Money et al (2018)[31]	Retrospective analysis (active surveillance system; Canada)	75	Not reported	Not reported	Not reported	4/75 (5.3%)
Elvitegravir/cobicistat						
Squires et al (2016)[37]	Randomized controlled trial (WAVES study; International)	8 (Became pregnant in EVG-cobicistat arm) 8 (Became pregnant in PI arm)	All on ART at the time of conception	0%	Not reported	0%
Hodder et al (2018)[38]	Open label extension (WAVES study; International)	13 (Became pregnant on EVG-cobicistat) 6 (Became pregnant on PI)	All on ART at the time of conception	0%	Not reported	0%
Momper et al (2018)[34]	Open-label prospective pharmacokinetic study (United States)	30	Not reported	3.3%; Median GA 38.8 (34.6-41.3)	Median birth weight 3060 g (1885-4050)	2/26 (7.8%)
Farrow et al (2018)[17]	Retrospective analysis of Gilead global safety database (includes clinical trials, Antiretroviral Pregnancy Registry, postmarketing cases, literature; International)	630 (EVG-cobicistat)	Preconception or first trimester: 389 (61.7%) After first trimester: 94 (14.9%) Unknown: 147 (23.3%)	Not reported	Not reported	2 Cases of NTD
Rasi et al (2018)[40]	Retrospective analysis of National Study of HIV in Pregnancy and Childhood surveillance data (United Kingdom and Ireland)	33 (EVG-based regimen) 875 (RAL-based regimen)	Preconception: 26 (78.8%) Second/Third trimester: 7 (21.2%) Preconception: 222 (25.4%) First trimester: 34 (3.9%) Second/Third trimester: 600 (68.6%)	Not reported	Not reported	Overall: 0/31 (0%) Overall: 23/886 (2.59%) Exposed from conception: 5/222 (2.25%)

Abbreviations: ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; GA, gestational age; NTD, neural tube defects; RAL, raltegravir; PI, protease inhibitor; TDF, tenofovir-disoproxil fumarate.

median age of 34 years. A total of 14 women were on dolutegravir prior to pregnancy with the remainder started on dolutegravir in the second or third trimester. Four pregnancies resulted in early spontaneous abortions, 1 was terminated, and 1 was lost to follow-up, resulting in data from 30 deliveries.[26] At the time of delivery, 27 (90%) women had a viral load less than 50 copies/mL. Of the 30 infants born, 1 was delivered at 34 weeks in a mother who had preeclampsia and myelitis, and 1 infant born at term was small for gestational age. No fetal malformations were noted. All the infants had undetectable HIV RNA at 2 days of age; 29 infants with data available had undetectable HIV RNA at 6 weeks as well.

In 2016, Botswanian guidelines changed to recommend dolutegravir-containing regimens as first line in all adults living with HIV (including pregnant women). Given this, Zash et al[27] compared outcomes in pregnant women who received dolutegravir-based regimens and delivered between November 2016 and September 2017 and those women treated with efavirenz-based therapy and delivered between August 2014 and August 2016. The analysis included a total of 1729 women started on dolutegravir-based ART and 4593 women who began efavirenz-based ART postconception. The overall median maternal age was 28 years. The median gestational age at the time of ART initiation was similar: 19 weeks (14-25) for those who received dolutegravir-based ART and 21 weeks (16-27) for those on efavirenz-based ART. Socioeconomic indicators, timing of antenatal care, and delivery site were also similar in the 2 groups. There were no significant differences in stillbirths, neonatal deaths, preterm births, and small-for-gestational-age infants when comparing the dolutegravir-based therapy to efavirenz. The risk of any adverse birth outcome was comparable in the 2 groups (33.2% vs 35% among women receiving dolutegravir or efavirenz, respectively). Of 675 women exposed to ART in the first trimester (280 to dolutegravir-based ART and 395 to efavirenz-based ART), 1 major congenital abnormality (skeletal dysplasia) was noted in an infant exposed to efavirenz. When comparing women with HIV on either dolutegravir or efavirenz with HIV-negative women, it was noted that there was a significantly higher risk of an adverse birth outcome in women with HIV (adjusted RR = 1.23; 95% CI = 1.18-1.28). The authors concluded from these results that adverse birth outcomes are similar in women started on dolutegravir-based regimens during pregnancy as compared with those started on efavirenz-based regimens.

Based on detection of a higher than expected number of neural tube defects in infants born to women who were on dolutegravir prior to conception, Zash et al[15] performed an unplanned interim analysis (deliveries to May 1, 2018) to compare neural tube defects in women on dolutegravir-based regimens prior to conception with other exposure groups. In the 426 infants born to women taking dolutegravir prior to conception, 4 infants (0.94%) had a neural tube defect (encephalocele, anencephaly, myelomeningocele, and iniencephaly). None of the women had diabetes or epilepsy or were receiving folic acid supplements at the time of conception. This was in comparison to 14 of 11 300 infants (0.12%) with neural tube defects exposed to any antiretroviral regimen not containing dolutegravir prior to conception, 0 (0%) of 2812 infants exposed to dolutegravir that was started in pregnancy, and 61 (0.09%) of 66 057 infants who were born to women who were HIV uninfected. Although these data are preliminary, this safety signal led to revised recommendations in HIV guidelines regarding the use of dolutegravir in women planning to become pregnant or not using consistent contraception methods.[28] An update to this analysis by Zash et al was presented at the AIDS 2018 conference.[29] Two additional cases of neural tube defects were reported between May 1, 2018, and July 15, 2018: one in an infant whose mother was started on dolutegravir during pregnancy and one in an HIV-uninfected woman. The updated prevalence of neural tube defects in women started on dolutegravir prior to conception was 4/596 (0.67%; 95% CI = 0.26-1.7). This prevalence rate is lower than that in the previously reported interim analysis; however, it still does not overlap with other exposure groups.

Following release of the data on increased risk of neural tube defects in the Tsepamo study in Botswana, a retrospective analysis of 66 pregnant women with HIV in the United States who received dolutegravir in pregnancy between January 2015 and May 2018 was published.[30] The mean age was 28.5 years, and 85% of women were of black ethnicity; 12 women (18%) acquired HIV perinatally. A little more than 40% of women were on dolutegravir prior to pregnancy, and the median gestational age at the time of starting dolutegravir during pregnancy was 18 weeks. During the study period, 57 pregnancies resulted in a live delivery, and 44 of these women (77%) had a viral load <20 copies/mL. Preterm birth was noted in 18 (31.6%), and 9 infants were small for gestational age. Two infants were noted to have a birth defect: one developed nonimmune hydrops fetalis, and the second had a congenital heart abnormality. There were no cases of neural tube defects, and all the infants were confirmed to be HIV negative.

Researchers in Canada analyzed data from the Canadian Perinatal HIV Surveillance Program, an active surveillance system, to determine rates of congenital anomalies in pregnancies where women were exposed to dolutegravir.[31] Between 2007 and 2017, there were 2539 infants born, of whom 2322 had congenital anomaly data. In this analysis, the investigators found no signal of neural tube defects with dolutegravir. There were 3 infants with neural tube defects reported (overall rate of 0.13%), of whom none were exposed to dolutegravir. Of the 75 infants exposed to dolutegravir, there were 4 cases of

nonchromosomal congenital anomalies (5.3%), including 2 urinary, 1 circulatory, and 1 musculoskeletal. These investigators also found no statistically significant difference in the rates of congenital anomalies based on first trimester exposure to nonnucleoside reverse transcriptase inhibitor–based, protease inhibitor–based, or INSTI-based regimens as compared with no antiretroviral exposure in the first trimester.[31]

To date, the available data from observational studies suggest that there is no increased risk of preterm deliveries, infants born small for gestational age, or congenital anomalies in infants born to women started on dolutegravir during pregnancy. Although small studies in the United States and Canada did not detect any cases of neural tube defects in women receiving dolutegravir,[30,31] an interim analysis in women from Botswana found a much higher than expected risk of neural tube defects in women receiving dolutegravir prior to conception.[15] Until additional information is available, current guidelines recommend that for individuals who are starting dolutegravir and are not known to be pregnant, a pregnancy test should be ordered to document a negative test.[28] Individuals of child-bearing potential should be counselled about the risk of neural tube defects associated with dolutegravir when it is taken around the time of conception. For those individuals taking dolutegravir who are pregnant and present for care in the first trimester, the benefits and risks of continuing treatment with dolutegravir-based regimens should be discussed.[4] The guidelines suggest that dolutegravir is a preferred INSTI to use in individuals who are pregnant and are in the second or third trimester.[4] To maximize dolutegravir absorption, the guidelines recommend that dolutegravir should be administered separately (at least 2 hours) from prenatal vitamins or other products containing calcium or iron.[4] At this time, it is not clear whether additional supplementation with folic acid, a common practice during pregnancy in countries such as the United States and Canada, may prevent the risk of neural tube defects possibly associated with dolutegravir.

Pharmacokinetics of Elvitegravir/Cobicistat in Pregnancy

Elvitegravir is coadministered with a pharmacokinetic booster, cobicistat, which is a potent inhibitor of cytochrome-P450 3A4.[7] Although there have been case reports describing elvitegravir/cobicistat pharmacokinetics during pregnancy,[32,33] only 1 intensive pharmacokinetic study of elvitegravir/cobicistat in pregnant women has been reported to date.[34] As part of the IMPAACT P1026s, an ongoing open-label prospective study, 30 pregnant women taking elvitegravir/cobicistat/emtricitabine with either tenofovir disoproxil fumarate or tenofovir alafenamide were enrolled. The investigators found that when compared with paired postpartum data, elvitegravir $AUC_{0\text{-}24h}$ was 24% lower in the second trimester (n = 14; $P = 0.058$), and 44% lower in the third trimester (n = 24; $P = 0.0001$). When compared with paired postpartum data (values similar to those previously reported in nonpregnant adults), the elvitegravir C_{24} trough was 81% lower in the second trimester ($P = 0.009$) and 89% lower in the third trimester ($P = 0.0001$). Cobicistat $AUC_{0\text{-}24h}$ and C_{24} values were also found to be statistically significantly lower in the second and third trimesters, respectively (44% and 59%; and 60% and 76%). The median ratio of cord blood to maternal plasma concentration (n = 15) of elvitegravir was 0.91 (0.65-1.03), suggesting high placental transfer of elvitegravir. Overall, this study found significantly reduced exposures to elvitegravir/cobicistat during pregnancy, with C_{24} trough values in the second and third trimesters (Table 1) lower than the reported elvitegravir protein-binding–adjusted concentration required to inhibit viral replication by 95% (EC_{95}) of 0.045 mg/L,[35] which may increase the risk of virological failure. Viral suppression (<50 copies/mL) was reported in 76.5% of women in the second trimester, 92.3% in the third trimester, and 76% at delivery and postpartum. The authors did not provide any further data on the viral loads in nonsuppressed women; however, they did note that there was no relationship between elvitegravir exposure and viral suppression. Limitations of the study include the fact that meals at the time of dose administration were not standardized in terms of calorie and fat content, and some participants may not have taken their dose with food. Previous pharmacokinetic studies have shown that elvitegravir exposures are 87% higher with heavy meals (~800 kcal) and 34% higher with light meals (~370 kcal) relative to fasting conditions.[36] In addition, data were not available regarding when elvitegravir/cobicistat was administered in relation to prenatal vitamins with minerals, which could possibly impair the absorption of elvitegravir/cobicistat.

Safety of Elvitegravir/Cobicistat in Pregnancy

Limited data have been published or presented regarding the safety of elvitegravir/cobicistat in pregnancy. The Women AntiretroViral Efficacy and Safety study (WAVES) was a randomized controlled, double-blind phase 3 study comparing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate with a ritonavir-boosted protease inhibitor regimen in women with HIV.[37] During the study period, 24 women became pregnant, and 16 of these women continued study drugs (8 in the elvitegravir-cobicistat arm and 8 in the protease inhibitor arm). Four of the 16 women had a spontaneous abortion in the first trimester (2 in each arm), and 12 women delivered at term with no congenital malformations reported.[37] At week 48, 12 of these women had viral suppression, although 1 woman in the elvitegravir-cobicistat arm had rebound viremia at week 48 (viral load 14 500 copies/mL) but achieved viral suppression at the time of delivery. Additional information regarding the mothers and their infants was not reported.

In an open-label extension of the WAVES study, an additional 19 women had 20 pregnancies.[38] Five pregnancies ended in elective abortions, and 6 ended in spontaneous abortions (4 on elvitegravir-cobicistat). Of the remaining pregnancies, 7 resulted in uncomplicated delivery at term (4 on elvitegravir-cobicistat). Virological suppression was reported in all these women, and no congenital anomalies were noted. The outcome for 2 pregnancies was unknown.

As part of the IMPAACT P1206s study, Momper et al[34] reported outcome data for 30 women receiving elvitegravir/cobicistat (and either tenofovir disoproxil fumarate or tenofovir alafenamide) during pregnancy.[34] One woman (3.3%) had preterm labor, and 2 congenital abnormalities considered to be possibly treatment related were noted: 1 infant that had amniotic band syndrome, microcephaly, and intrauterine growth restriction, and 1 had ulnar postaxial polydactyly. Infant HIV status was reported for these 30 infants in the US prescribing information for elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (Genvoya) as follows: 25 were uninfected, 2 had indeterminate status, and no information was available for 3 infants.[39]

Data from the Gilead global safety database identified 630 pregnancies in women on elvitegravir-containing regimens to May 31, 2018.[17] The global safety database includes pregnancy exposures reported from clinical trials, the APR, postmarketing reports, and the literature. One retrospective case of a fetal neural defect (anencephaly) was reported during pregnancy in a woman who took elvitegravir/ cobicistat/ tenofovir alafenamide/emtricitabine prior to conception, then switched to raltegravir/tenofovir disoproxil fumarate/ emtricitabine 48 days after the last menstrual period. After this analysis window, 1 additional case of myelomeningocele was reported at 14 weeks' gestation in a patient who started elvitegravir/cobicistat/tenofovir disoproxil fumarate/ emtricitabine 2 weeks after the last menstrual period. In both these cases, other risk factors, including folate use, were not reported. It should be noted that a prevalence rate of neural tube defects could not be calculated because the data were retrospective and drawn from a pooled group with an unknown number of exposed pregnancies.

Rasi et al[40] evaluated data collected prospectively for pregnant women receiving elvitegravir/cobicistat or raltegravir. Data were extracted from the National Study of HIV in Pregnancy and Childhood in the UK and Ireland. A total of 875 women were exposed to raltegravir in pregnancy and 33 to elvitegravir/cobicistat. Nearly 70% of women were black African with a median age of approximately 33 years; 27% overall were on an INSTI at the time of conception. In the elvitegravir/cobicistat group, viral load at delivery was reported for 6 women, of whom 5 were undetectable ($<$50 copies/mL). There were no cases of congenital anomalies in the elvitegravir/cobicistat arm and an overall prevalence of anomalies in the raltegravir-exposed infants of 2.59%, which is within population norms.

Based on the limited outcome data available and significantly reduced plasma concentrations that may lead to virological failure, regimens containing elvitegravir/cobicistat are not recommended in pregnancy.[4] These guidelines also suggest that for women who become pregnant while taking elvitegravir/cobicistat, consideration should be given to switching to a more effective, recommended regimen in pregnancy. If elvitegravir/cobicistat is continued in pregnancy, it should be taken with food for best absorption and not administered within 2 hours of products containing calcium or iron, including prenatal vitamins.[4] Viral load should be monitored closely and therapeutic drug monitoring, where available, should be considered.

Relevance to Patient Care and Clinical Practice

Treatment of HIV in pregnancy is critical for maternal health and reducing transmission to the infant.[4] In nonpregnant individuals living with HIV, INSTI-based regimens are increasingly used, particularly those that are available as single-tablet regimens.[7] With the growing use of these agents first line, it is likely that more women with HIV taking dolutegravir or elvitegravir/cobicistat will become pregnant. Thus, it is important for clinicians to be aware of emerging data on the safety and pharmacokinetics of dolutegravir and elvitegravir/cobicistat in this population.

Available data from pharmacokinetic studies suggest that dolutegravir concentrations are moderately decreased during pregnancy as compared with postpartum, most likely because of physiological changes that occur such as changes in blood volume or decreases in serum albumin.[41] Dolutegravir is primarily metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A1, with some metabolism by CYP3A4.[42] The activity of UGT 1A1 and CYP3A4 increases during pregnancy, which may also contribute to decreased concentrations.[41] However, trough concentrations of dolutegravir in pregnant women appeared to be well above the target protein-adjusted EC_{90}, leading to recommendations that dose adjustments in pregnant women are not required. This is further supported by clinical data that suggest that women receiving dolutegravir during pregnancy achieved or maintained viral suppression. On the other hand, available pharmacokinetic data suggest that both elvitegravir and cobicistat concentrations are significantly reduced during pregnancy, with elvitegravir concentrations less than the target protein-adjusted EC_{95} in the majority of women.[34] Elvitegravir is predominantly metabolized by CYP3A4 as well as through glucuronidation via UGT1A1/3; cobicistat is a CYP3A4 substrate as well.[43] CYP3A4 and UGT1A1/3 are both affected by hormonal fluctuations throughout pregnancy, which may cause enzyme induction.[41] As a result, both elvitegravir and cobicistat are cleared more rapidly from the body in pregnant

women, which contributes to pharmacokinetic changes and increases the risk of virological failure and the possibility of transmission to the neonate. Data are limited in terms of viral suppression in pregnant women; in 1 pharmacokinetic study, more than 20% of pregnant women were not suppressed at the time of delivery, although this was reported to be not drug concentration dependent.[34]

In terms of safety, there are data on more than 2500 women who have received dolutegravir during pregnancy. Dolutegravir appears to be as safe as efavirenz in women started on this agent during pregnancy.[27] However, based on a recent preliminary analysis, there is a safety signal suggesting an increased risk of neural tube defects when dolutegravir is used in women at the time of conception.[15] Further data from the Tsepamo study is expected in 2019. At the current time, it is unclear whether there is a similar risk with other INSTIs. Given that neural tube defects are quite uncommon, a high number of periconception exposures (2000 or more) are needed with individual drugs to rule out an increased risk of neural tube defects.[44] Of note, there have been no reports of neural tube defects with dolutegravir used around the time of conception in the US APR or in Canadian active surveillance data, although the numbers are relatively small.[28,31] Two cases of neural tube defects have been reported, retrospectively associated with elvitegravir/cobicistat exposure preconception or periconception in the Gilead global safety database. It is important to keep in mind that most of the data thus far were collected retrospectively, and relevant information in the case of neural tube defects, such as diet, periconception folic acid intake, medical and social history, and concomitant medication use, is missing or incomplete. The overall background rate of birth defects in the US general population is approximately 3%.[45] In terms of the prevalence of neural tube defects, estimates vary significantly by country and study ranging from <6 per 10 000 births in Canada and the United States to >22 per 10 000 births in some countries.[46] The background rate of neural tube defects may be higher in developing countries, especially those without mandatory food folate supplementation. Based on available data to date, there does not appear to be a signal for increased risk of other congenital anomalies associated with dolutegravir or elvitegravir use during pregnancy. Data thus far do not suggest a signal for birth defects with raltegravir use during pregnancy either.[13,14,40]

The Department of Health and Human Services Antiretroviral Guidelines Panels suggest to not initiate dolutegravir in women who are planning to become pregnant or those who are sexually active and not using effective contraception.[7,28] Dolutegravir may be considered in women who are not planning pregnancy; however, pregnancy testing is recommended prior to starting dolutegravir, and women should be using effective contraception. For those who become pregnant while taking a dolutegravir-based regimen and are in the first trimester, women should be counselled about the possible risk of neural tube defects and the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen.[4] Dolutegravir is a preferred INSTI after the first trimester in pregnant women.[4] Elvitegravir is not recommended in pregnancy, and changing this medication to one that has stronger evidence of efficacy and safety is suggested.[4]

Clinicians are encouraged to report antiretroviral use in pregnancy to the APR in the United States in order to learn more about the safety of all ART in pregnancy.

Conclusion

Balancing efficacy in terms of viral suppression, tolerability, and ease of administration of newer INSTIs with available safety data in pregnancy can be challenging when making treatment decisions for women of child-bearing potential. It is important for clinicians to be aware of emerging safety and pharmacokinetic data for dolutegravir and elvitegravir/cobicistat in order to discuss the risks and benefits of these agents with patients. Until further data are available, for women with HIV planning to become pregnant, raltegravir or other first-line agents in pregnancy (ritonavir-boosted atazanavir or darunavir) may be preferable. This is a rapidly evolving field and clinicians are advised to consult the most recent guidelines, which reflect the newest data.

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