

Evaluating outcomes of mother–infant pairs using dolutegravir for HIV treatment during pregnancy

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Objectives: Dolutegravir (DTG), a second-generation integrase inhibitor, is an effective treatment for HIV but its safety and efficacy are not well established in pregnancy. Here, we assess maternal and infant outcomes of mother–infant pairs using DTG-containing regimens during pregnancy.

Methods: We performed a retrospective cohort analysis of pregnant women with HIV on DTG from two urban clinics in the United States, 2015–2018. Maternal outcomes included viral suppression (viral load of <20 copies/ml prior to delivery), development of resistance, and tolerability to DTG. Infant outcomes included preterm delivery (birth at <37 weeks), small for gestational age (SGA, weight <10th percentile), infant HIV status at birth, birth defect(s), and Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scores. We performed a trend analysis to assess DTG use over time.

Results: A total of 66 women used DTG during pregnancy and the proportion on DTG increased each year: in 2015, 8% (5/60) of women were on DTG, versus 22% (15/67) in 2016, 42% (30/71) in 2017, and 59% (16/27) in 2018 ($P < 0.05$). Among women who delivered ($n = 57$), 77.2% were undetectable at delivery. There were no drug resistance and no reported side effects during pregnancy. Infants had a mean APGAR score of 8 (SD 1.5) at 1 min and 9 (SD 0.8) at 5 min; 31.6% were born prematurely and 15.8% were SGA, and 2 infants had a birth defect. No cases of HIV transmission occurred.

Conclusion: Our findings suggest that DTG can be an effective treatment during pregnancy. Infant outcomes (preterm deliveries and birth defects) need to be investigated in larger studies.

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Introduction

Dolutegravir (DTG), a second-generation HIV-1 integrase strand transfer inhibitor (INSTI), is a preferred regimen for adults living with HIV [1] and, until recently, was a second-line regimen for pregnant women living with HIV (WLWH) [2]. Emerging data from an ongoing NIH-funded study in Botswana consisting of 5438 mother–infant pairs [3], revealed an increased risk of neural tube defects among infants of women who were on DTG at the time of conception. The study found a risk of neural tube defects of 0.9% (4/426) among infants exposed to DTG compared with 0.1% for infants exposed to other antiretrovirals (ART). On the basis of these results, the World Health Organization [4] and HIV treatment guidelines in Europe and the United States [5–7] now recommend against the use of DTG among women of childbearing age who intend to be pregnant or among pregnant women in their first trimester. Treatment guideline committees acknowledge that the neural tube defect findings are preliminary and advice may change as more data emerge.

Currently, studies of DTG use during pregnancy from resource-rich countries consist mostly of case studies showing DTG to be effective at achieving viral suppression and preventing perinatal HIV transmission, even in the setting of late presentation in prenatal care or resistant virus [8,9]. Pharmacokinetic studies show a reduced trough concentration in pregnancy but good placental and breastmilk penetration, which can be beneficial for protecting infants from perinatal HIV [10,11]. However, there remains a knowledge gap regarding viral suppression, development of resistance and neonatal outcomes from infants with in-utero exposure to DTG. Here, we describe the trends of DTG use of pregnant WLWH from two urban clinics, as well as maternal and neonatal outcomes (including any neural tube defects) at delivery.

Methods

Patient population

Two university-affiliated Ryan White-funded clinics with large prenatal populations participated in a multicenter retrospective cohort study: Drexel University College of Medicine, Philadelphia, Pennsylvania, USA and the Grady Infectious Diseases Program, Atlanta, Georgia, USA. This study was approved by the institutional review boards at Drexel and Emory Universities, and the Grady Research Oversight

Committee. A database search identified all female pregnant patients who received DTG during pregnancy, between 1 January 2015 and 28 May 2018. Treatment-naïve patients who initiated DTG in pregnancy, and treatment-experienced patients who were either already on DTG before pregnancy or were switched to DTG during pregnancy, were eligible for this study. We also queried the database to obtain the number of pregnant women who were on non-DTG-based regimen to obtain the percentage of DTG use over time. DTG could be given as a single tablet regimen with abacavir/lamivudine or in combination with other ART. Women with elective or spontaneous abortion, or with deliveries outside our institutions, were noted but not excluded. Demographic and clinical data were obtained on mother–infant pairs by chart review during pregnancy and up to delivery.

Infant outcomes

Infant outcomes included the detection of birth defects using a neonatal ultrasound or physician documentation at birth, preterm birth (gestational age of <37 weeks at delivery), small for gestational age (SGA, weight less than the 10th percentile for the gestational age), infant HIV status at birth by clinical documentation, and Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scores at 1 and 5 min.

Maternal outcomes

Maternal outcome variables were having an undetectable viral load of less than 20 copies/ml prior to delivery; documented resistance to either DTG or other ART; and tolerability to DTG, collected via physician documentation. For women who had already delivered, third trimester viral load closest to delivery was used. When delivery had not yet occurred, the last available viral load and the gestational age associated with date of collection were recorded. Demographic variables included maternal age at delivery, race/ethnicity, and maternal country of birth (US versus non-US born). Clinical variables included years living with HIV and HIV diagnosed before or during pregnancy. We reported the number of women on DTG prior to pregnancy who were also on DTG at the time of conception. For women previously on a non-DTG-based regimen who were started on a DTG-based regimen, we included the gestational age at the time of the switch. We reported the number of women, not previously on ART, who initiated a DTG-based regimen and the gestational age at DTG initiation.

Analysis

We described the proportion and characteristics of mother–infant pairs using DTG during the study period. For women who had not yet delivered by 22 May 2018,

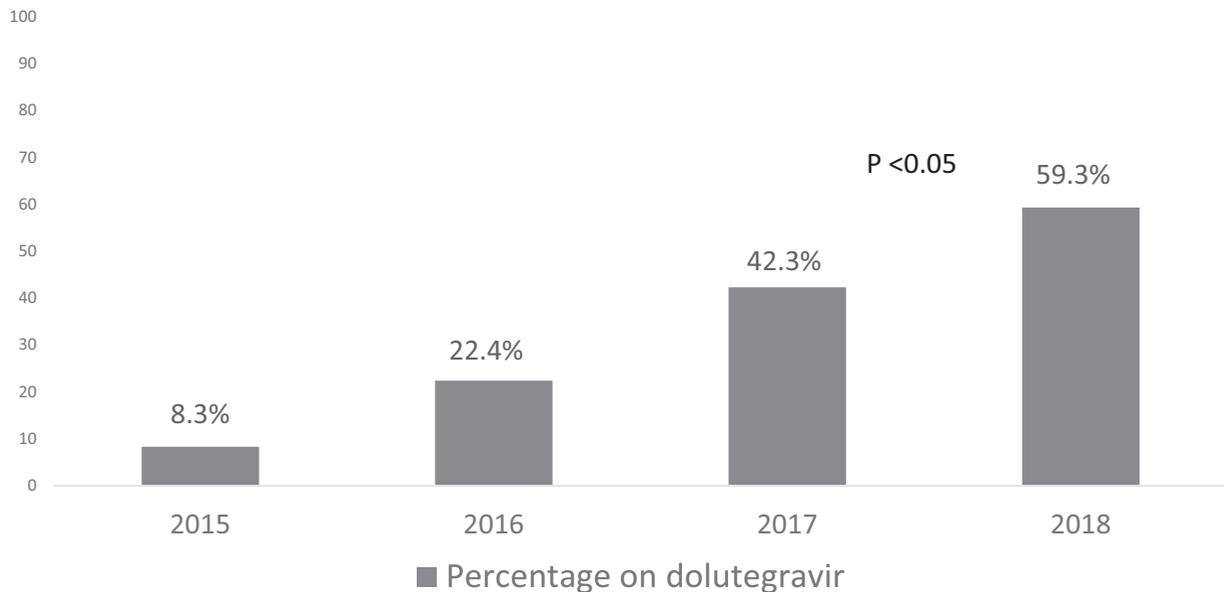


Fig. 1. The proportion of women with HIV using dolutegravir during pregnancy, 2015–2018. The total number of pregnancies was 60 in 2015, 67 in 2016, 71 in 2017 and 27 in 2018. 2018 includes January to May data only.

we collected study variables available up to the time of chart abstraction. Descriptive analyses included using mean and SD for continuous variables and proportion and associated SD for categorical variables. A trend analysis was performed to assess whether or not the proportion of women on DTG during pregnancy increased significantly over time.

Results

A total of 66 women used DTG during pregnancy and 57 had a live delivery during the study period. As demonstrated in Fig. 1, the proportion of women receiving DTG-based versus other regimens increased significantly by calendar year: 5/60 (8.3%) women in 2015, 15/67 (22.4%) in 2016, 30/71 (42.3%) in 2017, and 16/27 (59.3%) from January to May 2018 ($P < 0.05$). Demographic and clinical variables are presented in Table 1. The majority of women were US born (80.3%), black, non-Hispanic (84.8%) with a mean age of 28 (SD 6) years and with preserved immunologic function (84.8% had a $CD4^+ > 200$ cells/ μ l). About 9% of women were diagnosed with HIV during pregnancy. Many women were on DTG before pregnancy and remained on DTG during pregnancy ($n = 28$, 42.4%); 16 (24.2%) initiated DTG and 22 (33.3%) switched to DTG during pregnancy. The average gestational age for DTG initiation was 18.1 (SD 8.9) weeks and for regimen change was 21.1 (SD 10) weeks. The reasons for switching to DTG were to experience lower pill burden, lower side effects, or to achieve viral suppression before delivery. Once switched to DTG, women remained on it for the remainder of the pregnancy.

Infant outcomes

At birth, infants ($n = 57$) had a mean APGAR score of 8 (SD 1.5) at 1 min and 9 (SD 0.8) at 5 min; 18 (31.6%) were preterm deliveries and 9 (15.8%) were SGA. A total of two infants had a birth defect: one, from a twin pregnancy, developed nonimmune hydrops fetalis, and the second had a congenital heart abnormality (endocardial fibroelastosis versus ventricular septal defect). There were no cases of neural tube defects. All infants tested negative for HIV.

Maternal outcomes

Among women who delivered, 44 (77.2%) had undetectable viral load at delivery. When considering the entire cohort, including those who had not yet delivered, 49 (74.2%) had undetectable viral load. Two women in the cohort did not have delivery data because one moved out of the country while pregnant and the other had an elective termination of her pregnancy in the second trimester. A total of 16 women had pre-existing resistance to non-INSTIs; of these 16 women, six did not achieve viral suppression even after adding DTG to their regimen. However, no new resistance developed while on DTG, even among women with a history of prior ART resistance. There were no documented side effects from DTG during pregnancy.

Discussion

This study adds to the limited literature on DTG use among mother–infant pairs from resource-rich countries and provides some evidence for its safety and ‘real world’ effectiveness during pregnancy. We found no cases of

Table 1. Characteristics of mother–infant pairs using dolutegravir during pregnancy from two large urban academic centers, January 2015 to May 2018.

Maternal characteristics	Total, <i>n</i> = 66	Philadelphia, <i>n</i> = 35	Atlanta, <i>n</i> = 31
Age, mean (SD)	28.5 (6)	29 (6)	28 (6)
Race/ethnicity, <i>n</i> (%)			
Black, non-Hispanic	56 (84.8)	27 (77.1)	29 (93.5)
White, non-Hispanic	1 (1.5)	1 (2.9)	0 (0.0)
Hispanic	8 (12.1)	6 (17.1)	2 (6.5)
Asian, Pacific Islander	1 (1.5)	1 (2.9)	0 (0.0)
Non-US born	13 (19.7)	6 (17.1)	7 (22.6)
Years with HIV diagnosis, mean (SD) ^a	9.9 (7.7)	9.8 (8.4)	10 (7.0)
CD4 ⁺ greater than 200 at entry in prenatal care, <i>n</i> (%)	56 (84.8)	31 (88.6)	25 (80.6)
HIV diagnosed before current pregnancy, <i>n</i> (%)	60 (90.9)	30 (85.7)	30 (96.8)
DTG used before pregnancy, <i>n</i> (%)	28 (42.4)	17 (48.6)	11 (35.5)
Women not on ART at the beginning of pregnancy who initiated DTG during pregnancy, <i>n</i> (%)	16 (24.2)	11 (31.4)	5 (16.1)
Gestational age at DTG initiation, mean weeks (SD)	18.1 (8.9)	17.1 (8.5)	20.4 (10.4)
Change in regimen during pregnancy to include DTG, <i>n</i> (%)	22 (33.3)	7 (20.0)	15 (48.4)
Gestational age of ART change, mean weeks (SD)	21.1 (10.0)	17.6 (8.7)	23 (10.5)
Preexisting HIV resistance, <i>n</i> (%)	16 (24.2)	7 (20)	9 (29.0)
Resistance developed while on DTG, <i>n</i> (%)	0 (0)	0 (0)	0 (0)
^b Viral load less than 20 copies/ml using last available viral load, <i>n</i> (%)	49 (74.2)	27 (77.1)	22 (71.0)
Viral load less than 20 copies among women who delivered, <i>n</i> (%)	44/57 (77.2)	27/31 (87.1)	17/26 (65.4)
Baseline viral load among women who either initiated or switched to DTG, copies/ml	14 363	15 192	13 617
Average time to viral suppression, days (SD)	48 (23)	40.4 (18.6)	59.7 (27.3)
Infant characteristics	<i>n</i> = 57	<i>n</i> = 31 (includes two sets of twins)	<i>n</i> = 26
APGAR score at 1 min, mean (SD)	8 (1.5)	8 (1.4)	8 (2)
APGAR score at 5 min, mean (SD)	9 (0.8)	8.7 (1)	9 (1)
^c Preterm birth, <i>n</i> (%)	18 (31.6)	9 (29.0)	9 (34.6)
^d Small for gestational age, <i>n</i> (%)	9 (15.8)	5 (16.1)	4 (15.4)
Birth defect, <i>n</i> (%)	2 (3.5)	2 (6.5)	0 (0)
Infant HIV-positive status, <i>n</i> (%)	0 (0)	0 (0)	0 (0)

Out of 66 pregnancies (35 in Philadelphia and 31 in Atlanta), so far, 57 have resulted in live deliveries. Two women in the cohort did not have delivery data because one moved out of the country while pregnant and the other had an elective termination of her pregnancy in the second trimester. ART: antiretroviral therapy; DTG: dolutegravir.

^aThere were a total of 12 (18%) women who acquired HIV perinatally.

^bThe HIV viral load used was the one closest to delivery if delivery occurred or the last available lab value at the time of chart abstraction if the woman had not yet delivered.

^cPreterm births: birth before 37 weeks.

^dSmall for gestational age: weight less than 10th percentile.

neural tube defects; however, the risk of neural tube defects needs to be assessed using provider reporting of pregnancies to the Antiretroviral Pregnancy Registry (APR) in the US and respective pregnancy registries used in other countries. We observed a significant increase in the proportion of women using DTG during pregnancy with rates of viral suppression at delivery that are similar to those previously reported from other US cohorts [12,13]. However, with the change of recent treatment guidelines, the number of women entering pregnancy on DTG or women who initiate DTG during pregnancy might significantly decrease.

Infants generally appeared healthy at birth based on APGAR scores. The percentage of birth defects we observed is similar to that reported in the APR [14] and in Europe [15]. Our cohort demonstrated a relatively high proportion of preterm births (31.6%) and a similar proportion of SGA infants (15.8%) compared to other cohorts of WLWH [3,8]; the proportion of preterm deliveries and SGA infants among pregnant WLWH

receiving DTG-based therapy from other cohorts has ranged between 11–22% [14,16] and 17–25% [3,17], respectively, in resource-rich and resource-limited settings. Because of the short-term and long-term consequences of both preterm birth and SGA, future studies need to assess the safety profile of DTG for infants, and explore potential mechanisms of adverse outcomes, such as the role of DTG in reducing estradiol in pregnancy [17].

This cohort had a viral suppression rate of 74.2%. Studies using INSTIs late in pregnancy showed mixed results for viral suppression, but all resulted in reduced viral load at delivery [9,18]. A DTG pharmacokinetic study (*n* = 21) reported 100% viral suppression [19]; however, patients with poor adherence are usually excluded from pharmacokinetic studies. In our study, a substantial number of women were diagnosed with HIV during pregnancy, had viral resistance, or switched regimens, all known predictors of viral nonsuppression at delivery [2,20]. Even with these barriers, most women achieved viral suppression, highlighting the potency of DTG during

pregnancy. Furthermore, no resistance to DTG developed, which is consistent with findings in nonpregnant populations [21]. Although many women with preexisting resistance did not achieve suppression, this failure could potentially relate to issues of medication access or adherence.

Although we offered a larger cohort than most previous studies, limitations include the retrospective nature of data collection. Our study adds to the current literature by providing evidence from a real-world cohort that DTG is effective at suppressing plasma viral load. However, specific effects on infants should be explored further.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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