Dolutegravir and pregnancy outcomes including neural tube defects in the USA during 2008–20: a national cohort study

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Summary

Background A study from Botswana identified an increased risk of neural tube defects (NTDs) in infants of mothers with HIV who were treated with dolutegravir around the time of conception. We aimed to examine associations of dolutegravir use with NTDs and pregnancy loss using large health-care claims databases from the USA, a country with folic acid fortification of food.

Methods In this cohort study, we analysed health-care claims data, recorded in the Merative MarketScan commercial database (MarketScan data) and Centers for Medicare & Medicaid Services Medicaid database (Medicaid data) from Jan 1, 2008, to Dec 31, 2020. We identified pregnancies with enrolment during their entire duration among women aged 15–49 years and we estimated time of conception. For each pregnancy, we determined HIV status and periconceptional exposure to dolutegravir or other antiretroviral agents. We estimated and compared the incidence rate of NTDs, stillbirths, and pregnancy loss (ie, spontaneous or induced abortions) by type of periconceptional antiretroviral exposure. We calculated adjusted risk ratios of the adverse outcomes using Poisson models adjusting for demographic and clinical factors.

Findings Of 4 489 315 pregnancies in MarketScan data and 14 405 861 pregnancies in Medicaid data that had full enrolment, we identified 69 pregnancies in MarketScan data and 993 pregnancies in Medicaid data that were associated with HIV and periconceptional dolutegravir exposure. For women without HIV, the NTD rate was 4·1 per 10 000 live births (95% CI 3·9–4·3) in MarketScan and 5·7 per 10 000 live births (5·6–5·8) in Medicaid. No NTD cases were found among those with dolutegravir or non- dolutegravir antiretroviral drug exposure in the MarketScan data; only one NTD case was identified among women with dolutegravir, and three among women with non-dolutegravir antiretroviral exposure in Medicaid. After adjusting for covariates, there were no significant differences in risk ratios of NTD between groups with periconceptional dolutegravir or non-dolutegravir antiretroviral exposure and the group without HIV. However, compared with women without HIV, the risk of pregnancy loss was higher among women exposed to antiretroviral therapy: for dolutegravir exposure the adjusted risk ratio was 1·73 (95% CI 1·20–2·49) in MarketScan data and 1·41 (1·30–1·54) in Medicaid data; for non-dolutegravir antiretroviral exposure the adjusted risk ratio was 1·23 (1·10–1·37) in MarketScan data and 1·11 (1·07–1·15) in Medicaid data.

Interpretation We studied the largest US cohort of women with periconceptional or early-pregnancy dolutegravir exposure. Our results do not show an increased risk of NTDs in exposed infants in the USA. Administrative databases can be used, with rigorous methodology, to study correlates of rare outcomes, such as NTDs, and to monitor for adverse pregnancy outcomes in women who receive antiretrovirals.

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Introduction

Integrase strand transfer inhibitors (INSTIs) are preferred antiretroviral drugs for treatment of HIV due to their potency, rapid and durable suppression of HIV, tolerability, once-daily dosing, and low risk of resistance development. These characteristics make them particularly advantageous for use in pregnancy, when rapid viral suppression is needed for optimal prevention of perinatal HIV transmission. Dolutegravir is an INSTI that has been recommended as a preferred antiretroviral drug for the treatment of adults and adolescents with HIV in the USA since 2014,[1] and a roll-out for its use in pregnant women with HIV was initiated worldwide.[2]

However, a prospective surveillance study of birth outcomes among pregnant women with HIV in Botswana reported a 0·94% risk of neural tube defects (NTDs) in 494 infants of mothers exposed to dolutegravir around the time of conception.[3] Subsequent reports from this study with a much larger number of periconceptional exposures (n=9260) reported an NTD rate with periconceptional dolutegravir use of 0·11%,[4] which was not statistically higher than that among infants born to women without HIV, or infants exposed to any non-dolutegravir antiretroviral drug.[4,5] On the basis of the initial findings from Botswana, in 2018, WHO issued a warning about dolutegravir use in pregnancy, which led to disruptions in its roll-out in

Research in context

Evidence before this study

This cohort study was designed after the release of several reports from a Botswana study. In the initial report, of 426 women taking dolutegravir around the time of conception, four gave birth to infants with neural tube defects (NTDs) (0·94%), compared with 0·10% of those exposed to other antiretroviral agents. Subsequent reports from the same site, with an increasing number of infants with dolutegravir exposure at conception, revealed a much lower rate of NTDs (0·11% at last report presented at the International AIDS Society Conference in July, 2022), which is not different from infants of mothers with HIV and those exposed to other antiretrovirals, or from infants of mothers without HIV. However, in the intervening time, multiple public health authorities, including WHO and many countries' ministries of health, had issued guidance to avoid use of dolutegravir among women of childbearing potential not taking effective contraception. The US Panel on Treatment of HIV in Pregnancy and Prevention of Perinatal Transmission also issued similar guidance; however, with subsequent evidence these recommendations have now been revised. Data from North America and Europe using the Antiretroviral Pregnancy Registry observed one (0·14%) NTD event in 669 dolutegravir-exposed women. On April 16, 2022, we did a literature search in PubMed without language or date restrictions, including the terms "dolutegravir", "pregnancy", "stillbirth", "spontaneous abortion", "induced abortion", "early pregnancy loss", and "neural tube defects." We supplemented this search with reviewing the proceedings of relevant conferences in 2021 and 2022.

Added value of this study

In this cohort study, we analysed 2008–20 health-care claims data from the Merative MarketScan commercial database (MarketScan data) and the Centers for Medicare & Medicaid Services Medicaid database (Medicaid data). We identified pregnancies with enrolment during their entire duration, and we estimated time of conception. We estimated and compared the incidence rate of NTDs, stillbirths, and pregnancy loss (spontaneous or induced abortions) by type of periconceptional antiretroviral drug exposure. There were 69 pregnancies with HIV and periconceptional dolutegravir exposure in MarketScan data and 993 in Medicaid data. No NTD cases were found among those with dolutegravir exposure in MarketScan data; only one NTD case was identified among women with dolutegravir exposure in Medicaid data. There were no significant differences in risk ratios of NTD between groups with periconceptional dolutegravir or non-dolutegravir antiretroviral exposure and the group without HIV. However, periconceptional dolutegravir and non-dolutegravir antiretroviral exposure groups had higher risk ratios for pregnancy loss compared with the group without HIV. These data add information from the largest cohort of dolutegravir-exposed pregnancies in the USA, by utilising timely health claims data with the use of a detailed algorithm to identify the periconceptional period of relevant exposures. This methodology can be applied to monitor for gestational outcomes of other pharmacological exposures, including rare outcomes.

Implications of all the available evidence

Our study substantially adds to the evidence base on women exposed to dolutegravir around the time of conception from the largest cohort, so far, in the USA, a setting that uses folic acid supplementation of food. We report no excess risk of NTD events. These data add reassurance and support the current WHO and US HIV treatment recommendations that include dolutegravir as a preferred agent for treatment of people who are of childbearing potential, trying to conceive, or pregnant. Possible effects of dolutegravir on other adverse pregnancy outcomes need to be prospectively monitored and confirmed.

many countries. The US Department of Health and Human Services Guideline Panel also recommended that dolutegravir not be used in first-line antiretroviral drug regimens for women who are or might become pregnant, and recommended switching to an alternative regimen.[6] This recommendation was lifted 18 months later when the updated lower estimates of NTD risk from Botswana became available.

The rate of NTDs varies across countries. The median prevalence in African countries is 0·12%.[7] In the USA, folic acid fortification is mandated for some food items (enriched cereal grains), and people who plan to conceive or who are pregnant are recommended to take folic acid supplements.[8] The overall risk of NTDs in the US general population is very low (0·07%).[9] Most NTDs occur before the neural tube closes at around 4 weeks after conception (approximately 6 weeks after the last menstrual period, often before the pregnancy has been detected). NTDs might be associated with fetal loss and result in stillbirth or pregnancy loss. Unlike in the USA, there is no folic acid food fortification in Botswana, and it is unknown whether folate concentrations affect any association between periconceptional dolutegravir exposure and NTDs. In 2021, a retrospective national cohort study in Brazil (where wheat and maize flour are fortified with folic acid) reported no association between prenatal dolutegravir use and risk of NTDs.[10]

In this study, we analysed clinical health services and prescription data from two large US public and commercial health insurance claims databases to examine associations between periconceptional dolutegravir exposure and adverse pregnancy outcomes and NTDs in the USA.

Methods

Study design and data sources

In this cohort study, we analysed data in the Centers for Medicare & Medicaid Services Medicaid database

(referred to as Medicaid data hereafter) and Merative MarketScan Commercial database (referred to as MarketScan data hereafter), from Jan 1, 2008, to Dec 31, 2020, which include the years since INSTIs were introduced into clinical practice in the USA, and specifically dolutegravir in 2013, as well as the change in HIV treatment recommendations in 2018.[6]

Medicaid data included all available claims data of health-care services from state Medicaid programmes, representing almost all people in the USA with Medicaid insurance, with the following exceptions: data of Maine in 2008–09, Idaho in 2009, Children's Health Insurance Program data in 2008–15 in Iowa, Pennsylvania, and Wyoming, and part of Montana data (Third Party Agreement) in 2014 and 2015 were not available in the Medicaid data systems.

MarketScan data included health-care claims data for about 30–50 million enrolees each year, representing about 20% of all people with employer-sponsored commercial health insurance in the USA. Both databases included enrolment records, inpatient and outpatient medical records, and outpatient prescriptions that were dispensed. Both databases contained linking variables that enable matching some infants' records to mothers' records. Race and ethnicity information were available in Medicaid data but not in MarketScan data.

As the study is an analysis of medical claims data, consent of study participants was not required. Ethics review was waived because the use of de-identified data did not involve human participants.

Participants and exposure type

We first extracted all pregnancy records among women aged 15–49 years, the reproductive age range commonly used in many studies, and linked to infants' records if available. For each pregnancy, we used a previously developed algorithm to estimate the first day of the pregnant person's last menstrual period and gestational age.[11] To ensure data quality, we restricted our analysis to pregnancies with continuous insurance enrolment over the entire pregnancy period (4 489 315 [72%] of all 6 047 882 pregnancies in Medicaid; 14 405 861 [74%] of 19 964 197 pregnancies in MarketScan). All analyses were done at the pregnancy level.

For each pregnancy, we identified women with HIV status if they had at least one inpatient or two outpatient records of an HIV diagnosis in addition to an antiretroviral drug prescription at any time before or during pregnancy. We determined periconceptional exposure to dolutegravir or non-dolutegravir antiretroviral drugs if a prescription was observed during the 8 weeks before the last menstrual period to end of first trimester

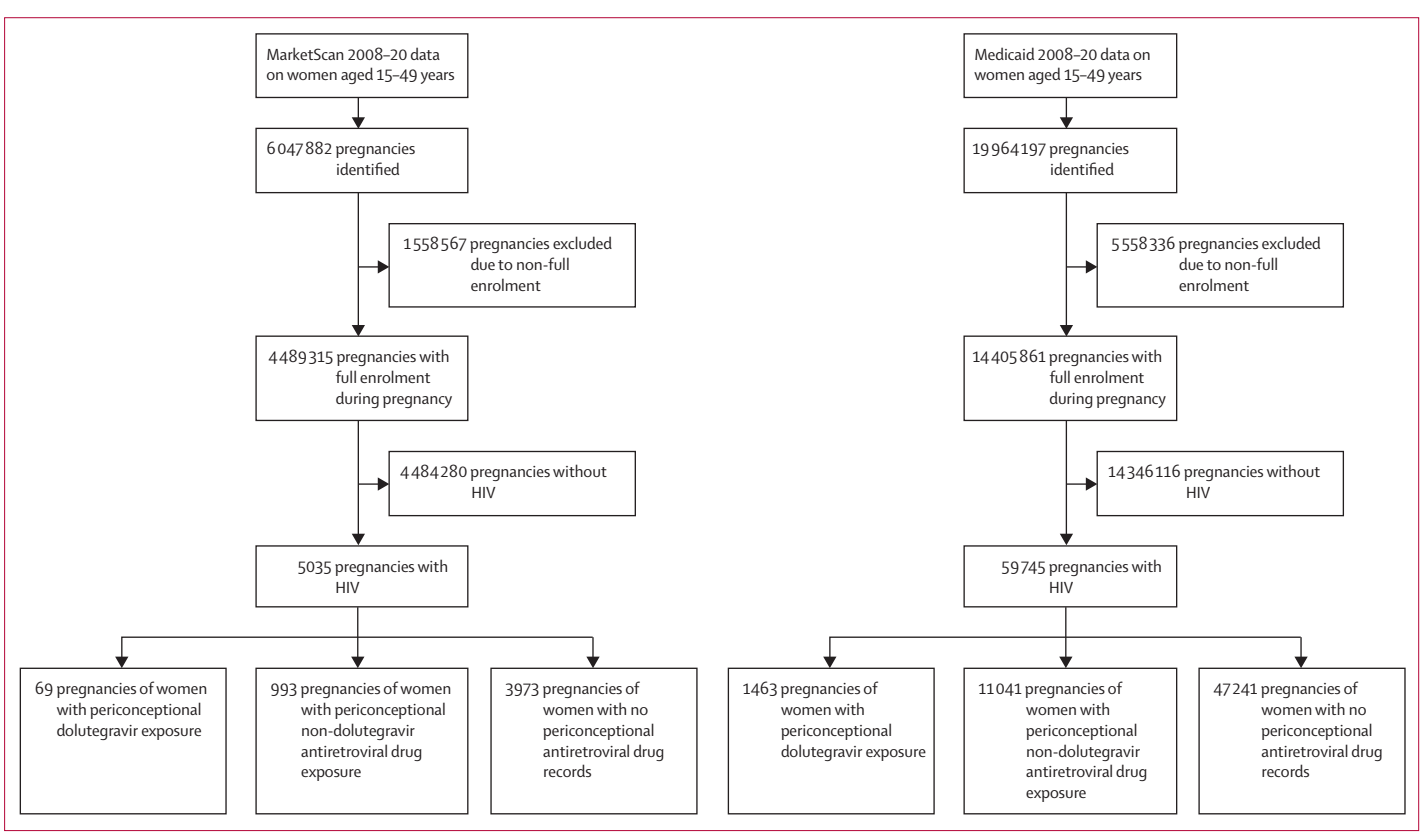

Figure: **Data selection flow in women aged 15–49 years fully enrolled during pregnancy in commercial health insurance or Medicaid, by type of antiretroviral exposure and timing of such exposure, in the USA during 2008–20**

(13 weeks, or 91 days). We compared data from three groups: pregnancies among women with HIV and periconceptional dolutegravir exposure; pregnancies among women with HIV and periconceptional non-dolutegravir antiretroviral drug exposure; and pregnancies among women without HIV, defined as having neither a HIV diagnosis nor an antiretroviral drug prescription observed any time before or during the pregnancy.

Outcomes

We searched for NTD cases among pregnancy records with a livebirth outcome. We defined NTD cases when a diagnosis of an NTD (defined according to International Classification of Diseases, ninth edition [ICD-9], and International Classification of Diseases, tenth edition [ICD-10] codes; appendix p 1) was observed in one inpatient or two separate outpatient records and occurred during the time from last menstrual period to the delivery date plus 30 days in mothers' records, or linked infants with any record for NTD.

Given that severe congenital defects can lead to fetal loss, we included two additional pregnancy outcomes: stillbirth (defined according to ICD-9, IC-10, and Current Procedural Terminology codes; appendix p 1) and pregnancy loss (spontaneous or induced abortions, defined according to ICD-9, IC-10, and other codes; appendix p 1). We identified stillbirth and pregnancy loss, respectively, when at least one diagnosis or procedure indicating stillbirth or pregnancy loss (appendix p 1) was observed in pregnancy records. The details of methods of assigning the pregnancy outcome of each pregnancy are described elsewhere.[11]

Statistical analysis

Given that MarketScan data and Medicaid data were collected with different sampling processes, we analysed the data separately. We estimated rates of NTDs per 10 000 livebirths and estimated 95% CIs, assuming a Poisson distribution. Rates of stillbirth and pregnancy loss were calculated among all pregnancies. Although weights are available in the MarketScan data, we did not weight the estimates because weighting a rare outcome might result in exaggeration or suppression of its effect in the sample. We calculated adjusted risk ratios (aRRs) of the adverse outcomes by antiretroviral drug exposure type, using generalised Poisson regression models, adjusting for delivery year, age of mother at delivery, US census region, race and ethnicity (Medicaid only), and maternal comorbidities. We selected 12 comorbidities related to maternal health: alcohol use, asthma, chronic obstructive pulmonary disease, autoimmune diseases, cancer, cardiovascular diseases, diabetes, epilepsy, hypertension, mental health-related conditions, sexually transmitted diseases, and tobacco use[12] (appendix pp 5–14). Given the large sample size and rare outcome, we constructed a dichotomous comorbidity variable to be included in the models so that the models could converge. We did sensitivity analyses to include maternal comorbidities separately in the models with an outcome that could converge (diagnosis codes are in the appendix [p 15]).

Additionally, we did three sensitivity analyses: we compared demographic characteristics between women with pregnancies that were fully enrolled and those with intermittent enrolment (appendix p 16), we estimated the effect on NTD rates assuming a proportion of NTDs resulted in pregnancy losses (appendix p 17), and we estimated NTD among all pregnancies, to include pregnancy losses, stillbirths, and live births (appendix p 17). All analyses were done with SAS (version 9.4). All ICD-9 and ICD-10 diagnoses and procedure codes used

See Online for appendix

	Women without HIV	Periconceptional* dolutegravir exposure	Periconceptional* non-dolutegravir ART exposure
MarketScan data			
Total	4 484 280	69	993
Age of mother at delivery, years			
15–24	627 518 (14·0%)	8 (11·6%)	68 (6·8%)
25–34	2 610 826 (58·2%)	31 (44·9%)	400 (40·3%)
35–44	1 212 171 (27·0%)	26 (37·7%)	496 (49·9%)
45–49	33 765 (0·8%)	4 (5·8%)	29 (2·9%)
US census region			
Northeast	785 945 (17·5%)	8 (11·6%)	190 (19·1%)
Midwest	1 005 078 (22·4%)	8 (11·6%)	128 (12·9%)
South	1 788 735 (39·9%)	46 (66·7%)	565 (56·9%)
West	846 664 (18·9%)	7 (10·1%)	101 (10·2%)
Unknown	57 858 (1·3%)	0 (0·0%)	9 (0·9%)
Medicaid data			
Total	14 346 116	1463	11 041
Age of mother at delivery, years			
15–24	6 074 003 (42·3%)	269 (18·4%)	2543 (23·0%)
24–34	6 626 646 (46·2%)	819 (56·0%)	5840 (52·9%)
35–44	1 610 139 (11·2%)	364 (24·9%)	2512 (22·8%)
45–49	35 328 (0·2%)	11 (0·8%)	146 (1·3%)
Race or ethnicity			
White	5 400 672 (37·6%)	210 (14·4%)	1839 (16·7%)
Black	3 295 275 (23·0%)	849 (58·0%)	6698 (60·7%)
Hispanic†	4 103 849 (28·6%)	272 (18·6%)	1750 (15·9%)
Other‡	758 828 (5·3%)	21 (1·4%)	235 (2·1%)
Unknown	787 492 (5·5%)	111 (7·6%)	519 (4·7%)
US census region			
Northeast	2 799 573 (19·5%)	603 (41·2%)	4108 (37·2%)
Midwest	1 973 077 (13·8%)	164 (11·2%)	1023 (9·3%)
South	5 201 299 (36·3%)	423 (28·9%)	4528 (41·0%)
West	4 372 167 (30·5%)	273 (18·7%)	1382 (12·5%)

Data are n or n (%). ART=antiretroviral therapy. *Periconceptional exposure was defined as exposure from 8 weeks before the last menstrual period through to 13 weeks (end of first trimester) of gestation. †Hispanic persons can be of any race. ‡Other includes American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, and other.

Table 1: **Characteristics of pregnant women aged 15–49 years fully enrolled in commercial health insurance and Medicaid in the USA during 2008–20**

to define the conditions in this study are listed in the appendix (appendix pp 1–4, 5–15).

Role of the funding source

The funder had a role in study design and data analysis. The study was funded by the US Centers for Disease Control and Prevention (CDC) and was conducted by CDC scientists who designed the study, performed the analysis, interpreted the data, and wrote the report.

Results

Between Jan 1, 2008, and Dec 31, 2020, we identified 4 489 315 fully enrolled pregnancies of women aged 15–49 years in MarketScan data; 69 pregnancies were among women with HIV and periconceptional dolutegravir exposure and 993 among women with HIV and periconceptional non-dolutegravir antiretroviral drug exposure. There were 14 405 861 fully enrolled pregnancies of women aged 15–49 years in Medicaid data; 1463 pregnancies were among women with HIV and periconceptional dolutegravir exposure and 11 041 among women with HIV and periconceptional non-dolutegravir antiretroviral drug exposure (figure). Compared with women without HIV, most women with HIV and periconceptional dolutegravir or non-dolutegravir antiretroviral drug exposure were older at delivery. In Medicaid data, about 60% of the pregnancies with dolutegravir or non-dolutegravir antiretroviral drug exposure were among Black women. For pregnancies among women without HIV, 23·0% were Black (table 1).

In MarketScan data, there were 1352 infant NTD cases among 3 316 459 live births to women without HIV, with a rate of 4·1 per 10 000 live births (95% CI 3·9–4·3 (table 2). No NTD cases were found in the dolutegravir or non-dolutegravir antiretroviral drug exposure groups. In Medicaid data, 6639 NTD cases were found among 14 346 116 live births to women without HIV (5·7 per 10 000 [95% CI 5·6–5·8]). Only one NTD case was found in the dolutegravir group and three were found in the non-dolutegravir antiretroviral drug group (table 2). No significant difference in risk of NTD was observed between the groups with early dolutegravir versus non-dolutegravir antiretroviral drug exposure in either dataset (table 3).

In MarketScan data, we identified a rate of pregnancy loss of 4200 per 10 000 pregnancies (95% CI 2810–3520) among women with HIV and periconceptional dolutegravir exposure and 3510 per 10 000 pregnancies (2810–6040) among women with HIV and periconceptional non-dolutegravir antiretroviral drug exposure. The pregnancy loss rate was 2460 per 10 000 pregnancies (2450–2460) in women without HIV (table 2). In Medicaid data, rates of pregnancy loss were 3510 per 10 000 pregnancies (95% CI 3210–3820) in the group with HIV and periconceptional dolutegravir exposure and 2610 per 10000 pregnancies (3210–3820) among women with HIV and periconceptional non-dolutegravir antiretroviral drug exposure. The pregnancy loss rate for women without HIV was 1780 per 10 000 (1780–1780). For women without HIV, rates of stillbirth were 58·8 per 10 000 pregnancies (95% CI 58·1–59·5) in MarketScan data and 56·2 per 10 000 pregnancies (55·9–56·6) in Medicaid data. Very few stillbirths were found in the dolutegravir exposure group (0·0 [95% CI 0·0–534·6] in MarketScan; 27·3 per 10 000 pregnancies [7·4–70·0] in Medicaid), whereas 14 in MarketScan (141·0 per 10 000 pregnancies [77·1–236·6]) and 53 in Medicaid (48·0 per 10 000 pregnancies [36·0–62·8]) were found in the non-dolutegravir antiretroviral drug exposure group (table 2).

	Women without HIV		Periconceptional* dolutegravir exposure		Periconceptional* non-dolutegravir antiretroviral drug exposure	
	Number	Rate per 10 000 (95% CI)	Number	Rate per 10 000 (95% CI)	Number	Rate per 10 000 (95% CI)
MarketScan data						
Total pregnancies	4 484 280	..	69	..	993	..
Pregnancy loss†	1 102 863	2460 (2450–2460)	29	4200 (2810–3520)	313	3510 (2810–6040)
Stillbirth	26 355	58·8 (58·1–59·5)	0	0·0 (0·0–534·6)	14	141·0 (77·1–236·6)
Livebirth	3 316 459	..	39	..	647	..
NTDs‡	1352	4·1 (3·9–4·3)	0	0·0 (0·0–940·5)	0	0·0 (0·0–56·7)
Medicaid data						
Total pregnancies	14 346 116	..	1463	..	11 041	..
Pregnancy loss†	2 555 854	1780 (1780–1780)	513	3510 (3210–3820)	2885	2610 (2520–2710)
Stillbirth	80 687	56·2 (55·9–56·6)	4	27·3 (7·4–70·0)	53	48·0 (36·0–62·8)
Livebirth	11 642 251	..	940	..	7989	..
NTDs‡	6639	5·7 (5·6–5·8)	1	10·6 (0·3–59·3)	3	3·8 (0·8–11·0)

Data are n or n (95% CI). NTD=neural tube defect. *Periconceptional exposure was defined as exposure from 8 weeks before the last menstrual period through to 13 weeks (end of first trimester) of gestation. †Rounded to nearest 10 to prevent overstatement of accuracy. ‡Rate of NTD was calculated among livebirths.

Table 2: **NTDs and pregnancy outcomes among women aged 15–49 years fully enrolled in commercial health insurance and Medicaid, by type of antiretroviral exposure and timing of such exposure, in the USA during 2008–20**

After adjusting for demographic characteristics and maternal comorbidities, the groups with dolutegravir exposure or non-dolutegravir antiretroviral drug exposure had higher risk of pregnancy loss compared with those without HIV and in MarketScan Data (table 3). Similarly, in Medicaid data, the groups with dolutegravir exposure and with non-dolutegravir antiretroviral drug exposure had higher risk of pregnancy loss compared with women without HIV. Compared with the group with non-dolutegravir antiretroviral drug exposure, the group with dolutegravir exposure had a marginally higher risk of pregnancy loss in both MarketScan data) and in Medicaid data (table 3).

We did a sensitivity analysis, in which we assumed that one-third or one-half of all NTDs resulted in fetal loss and not in livebirth,[8,13] and another analysis where we looked at all recorded NTDs among all pregnancies, including those resulting in pregnancy loss or stillbirth. Under all three scenarios, the NTD rate in women with periconceptional dolutegravir exposure was not significantly higher than that in women with non-dolutegravir antiretroviral drug exposure or that in women without HIV (appendix p 17). We did additional analyses on women with HIV but no record of antiretroviral drug exposure periconceptionally and found no significantly different effect on infant NTDs in this subgroup (appendix p 18).

In MarketScan data, the group with non-dolutegravir antiretroviral drug exposure had an aRR of 2·10 (95% CI 1·24–3·55) for stillbirth, compared with the group without HIV. The group with dolutegravir exposure had zero stillbirths and could not be fit in the multivariable models. In Medicaid data, there was no significant difference in the risk of stillbirth between groups with dolutegravir or non-dolutegravir antiretroviral drug exposure compared with the group without HIV (table 3).

	Pregnancy loss* (aRR† (95% CI))	Stillbirth, (aRR† (95% CI))	NTDs among livebirths, (aRR† (95% CI))
MarketScan data			
HIV and dolutegravir exposure *vs* no HIV	1·73 (1·20–2·49)	··‡	··‡
HIV and non-dolutegravir ART exposure *vs* no HIV	1·23 (1·10–1·37)	2·10 (1·24–3·55)	··‡
HIV and dolutegravir exposure *vs* HIV and non-dolutegravir ART exposure	1·45 (0·99–2·13)	··‡	··‡
Medicaid data			
HIV and dolutegravir exposure *vs* no HIV	1·41 (1·30–1·54)	0·52 (0·20–1·39)	1·81 (0·26–12·89)
HIV and non-dolutegravir antiretroviral drug exposure *vs* no HIV	1·11 (1·07–1·15)	0·87 (0·66–1·14)	0·66 (0·21–2·06)
HIV and dolutegravir exposure *vs* HIV and non-dolutegravir ART exposure	1·27 (1·15–1·39)	0·63 (0·23–1·74)	2·97 (0·31–28·89)

aRR=adjusted risk ratio. NTD=neural tube defect. ART=antiretroviral therapy. *Pregnancy loss includes spontaneous and induced abortions. †Multivariable regression models were adjusted for delivery year, age of mother at delivery, US census region, race or ethnicity (Medicaid only), and maternal comorbidities. ‡aRRs cannot be calculated using multivariable regression models because of too few cases of the outcome.

Table 3: **Multivariable models of pregnancy outcomes among women aged 15–49 years fully enrolled during pregnancy in commercial health insurance and Medicaid, by type of antiretroviral exposure and timing of such exposure, in the USA during 2008–20**

Discussion

In this study, which includes the largest-to-date US cohort of pregnant women with HIV who used dolutegravir periconceptionally, we did not find a higher rate of NTDs among dolutegravir-exposed women with HIV than among women without HIV or women with HIV exposed to other antiretroviral drugs. Our study included 16·4 million directly observed livebirths (unweighted data) during 2008–20, which represents approximately one-third of all livebirths in the USA during that period.

The rate of NTDs in women with HIV and periconceptional dolutegravir exposure in MarketScan data and Medicaid data we observed is consistent with the national US rate of 0·07%.[14] Our findings support previously reported data from two US-based surveillance systems for HIV and for birth defects during 2013–17 that included 15 participating US jurisdictions.[15] Our data are also in alignment with data from other settings that supplement their food staples with folic acid, such as Brazil[10] and Europe.[16] These results are reassuring and support the current Panel on Treatment of HIV in Pregnancy and Prevention of Perinatal Transmission recommendations that include dolutegravir-containing regimens as the preferred antiretroviral drug regimen for people of reproductive age, including those who are pregnant or who are considering pregnancy.[17] However, the dolutegravir drug label still contains information warning health-care providers about potential fetal toxicity.

As new antiretroviral drugs are approved for HIV treatment, it is essential to have surveillance systems capable of detecting rare but serious adverse outcomes, such as NTDs.[14] Such post-marketing surveillance needs to be prospective, accurate, and rapidly generated. Voluntary reporting databases, such as the Antiretroviral Pregnancy Registry and the European Pregnancy and Paediatric HIV Cohort Collaboration, have some drawbacks: reporting in these systems is initiated by clinicians and there is a long lag between the time of drug approval and obtaining sufficient numbers of first-trimester exposures necessary to detect an increase in overall birth defects, and an even longer lag to detect an increase in rarer birth defects (such as NTD). As of July 31, 2022, there were 669 periconceptional dolutegravir exposures prospectively reported to the Antiretroviral Pregnancy Registry,[18] providing an insufficient number of exposures to determine whether an elevated risk of NTDs exists in the USA.[18] Approximately 2000 exposures are needed to rule out a three-fold increase in risk of NTDs.[14,17]

Inclusion of data on stillbirth and pregnancy loss is important in studies of NTDs, because a third to a half of

all affected fetuses might be lost.[14,19] We found that all categories of antiretroviral drug exposure among women with HIV had higher rates of pregnancy loss, compared with women without HIV. Studies done before the wide availability of antiretroviral therapy had shown that women with HIV were at increased risk of adverse pregnancy outcomes, including miscarriages and stillbirths.[20] This difference was no longer present in the antiretroviral drug era in a study from Kenya,[21] whereas conditions associated with adverse pregnancy outcomes, such as older age, higher parity, higher frequency of sexually transmitted infections, and lower socioeconomic status, were more common among women with HIV than among those without HIV.[21] Many of these factors are also more common among women with HIV in the USA. Other studies have reported persistently increased risk of adverse pregnancy outcomes in women with HIV on antiretroviral therapy compared with women without HIV, including in Botswana,[22] Eswatini,[23] Ethiopia,[24] and South Africa[25,26] as well as in a recent meta-analysis.[27]

Few studies have estimated an association between periconceptional dolutegravir or other antiretroviral drug exposures with pregnancy loss. Our analysis indicated a marginally higher rate of pregnancy loss among women with periconceptional exposure to dolutegravir, compared with other antiretroviral drugs. The significance of this finding is unclear; however, in a sensitivity analysis in which we assumed half of all NTDs resulted in fetal loss, we still did not find a significant association of NTDs with periconceptional dolutegravir exposure. Additional studies and monitoring of pregnancy loss among women with HIV using antiretroviral therapy are needed.

In our study, the rate of stillbirth among pregnant women with HIV and periconceptional exposure to dolutegravir or other antiretroviral drugs was similar to the overall rate of 0·6% in pregnancies in the USA.[28] HIV infection has been associated with stillbirth in several studies, particularly in the pre-antiretroviral drug era.[20] Antiretroviral therapy has resulted in better overall pregnancy outcomes among women with HIV, although adverse outcomes might still be more frequent among women with HIV than those without HIV.[12,20] Reported associations of stillbirth and antiretroviral drug regimens initiated before and during pregnancy differ by regimen, with scarce data from resource-rich settings.[29–32] A clinical trial that evaluated three antiretroviral drug regimens starting in pregnancy showed that dolutegravir-containing regimens exhibited a lower rate of composite adverse pregnancy outcomes and neonatal deaths compared with an efavirenz-containing regimen.[33]

We found dolutegravir was used more frequently among women insured with Medicaid than among commercially insured women. Because dolutegravir was the first INSTI with once-daily dosing and was well tolerated, one hypothesis for why women with Medicaid coverage were more likely to take dolutegravir is that people with lower incomes might have more adherence challenges, and they might be more likely to benefit from once-daily dosing of an INSTI. Another hypothesis is that health-care providers taking Medicaid payments probably see more patients with HIV and might be more attuned to updated clinical practice guidelines and more readily prescribe newer antiretroviral drugs.

Our study has several limitations. First, health-care claims data were created for billing purposes and recorded exposures or outcomes might be subject to coding errors. Second, the algorithm we used to estimate last menstrual period and gestational age depends on the availability of pregnancy or birth outcome data; thus, the estimated last menstrual period might be subject to error, which could affect the accuracy of the defined periconceptional exposure window. Third, to ensure constant data feed throughout a pregnancy, we restricted our analyses to pregnancies with continuous insurance enrolment during the observation period, which might result in selection bias. However, a sensitivity analysis comparing our study sample with a sample without the continuous enrolment restriction revealed similar distributions in demographic characteristics. Fourth, we did not include women with HIV diagnoses and no antiretroviral drug prescriptions because the current report focuses on the effect of different antiretroviral drug regimens. Fifth, because we treated each pregnancy independently, any dependency of multiple pregnancies from the same woman over time was not addressed. Sixth, given that our data sources were administrative databases, we did not have detailed information on several covariates that might influence pregnancy outcomes, such as BMI, tobacco, alcohol, or other substance use, or receipt of prenatal vitamins. This constraint restricted our ability to analyse the effects of factors such as folate supplementation or obesity. The two datasets we used included commercially versus publicly insured people, respectively, who probably have differences with regard to socioeconomic parameters and access to health care, which also influence outcomes. Lastly, one additional factor that could affect our results is the possibility that physicians ordered more screenings for NTDs in women prescribed dolutegravir after the initial Botswana report. This outcome could result in a higher likelihood of diagnosis among the dolutegravir-exposed individuals and might lead to an overestimate of the risk of NTDs, which indicates our non-positive findings might be even more reassuring.

Despite these limitations, our study adds important information from the currently largest cohort in the USA. Our incidence estimates provide reassuring evidence that an elevated risk of infant NTD among women with HIV who used dolutegravir around the time of conception is unlikely. Associations of dolutegravir use with risk of pregnancy loss were statistically marginal and need to be further investigated in prospective surveillance or large dedicated patient cohorts. Thus, our

study underscores the need for a comprehensive US system of prospective, systematic pharmacovigilance surveillance to monitor outcomes of periconceptional exposure to pharmacological agents, including antiretroviral drugs. In the absence of such a system, the pregnancy algorithm developed and used in this study with the administrative databases can still provide a robust and timely method to monitor for signals, including for rare outcomes, while minimising biases and misclassifications. Our findings are consistent with published estimates of rates of NTD and of stillbirths for the US population.[9,31] The algorithm provides a method to interrogate administrative data for birth outcomes associated with newer antiretroviral drug use,[11] and as such it fills a public health need that will become even more pressing as newer antiviral agents are licensed for use for treatment or prevention of HIV, as well as for treatment of other viral infections, such as hepatitis C or COVID-19. New antiretroviral drugs in the INSTI class, as well as in new antiretroviral drug classes, are being developed, tested, or marketed for use both as HIV treatment and pre-exposure prophylaxis. It is anticipated that millions of people worldwide might use these medications, which might have a duration of action of several months. Assuring adequate post-licensure monitoring of birth and infant outcomes for such newer antiviral agents should be a public health priority.

Contributors

APK conceptualised the analysis and drafted the manuscript, and decided to submit the manuscript for publication. WZ accessed the data, performed and verified the data analysis, and contributed to writing the manuscript. MAL contributed to the conceptualisation, analysis, and writing of the manuscript. Y-LAH contributed to the analysis, accessed the data and verified the analysis, and contributed to writing the manuscript. KWH contributed to the conceptualisation, analysis, and writing of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Restrictions apply to the availability of these data, which were used under licence for this study. The Centers for Medicare & Medicaid Services data is a closed database and CDC's data use agreement (DUA) with Centers for Medicare & Medicaid Services does not allow sharing of the data directly. Readers can apply for data access through https://resdac.org/research-identifiable-files-rif-requests. The MarketScan data is a commercial claims database and cannot be shared directly under the current DUA, either. Readers can contact https://www.merative.com/real-world-evidence for MarketScan data access.

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