ORIGINAL ARTICLE

Dolutegravir in Pregnancy as Compared with Current HIV Regimens in the United States

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ABSTRACT

BACKGROUND

Data on the effectiveness and safety of dolutegravir-based antiretroviral therapy (ART) for human immunodeficiency virus type 1 (HIV-1) infection in pregnancy as compared with other ART regimens commonly used in the United States and Europe, particularly when initiated before conception, are limited.

METHODS

We conducted a study involving pregnancies in persons with HIV-1 infection in the Pediatric HIV/AIDS Cohort Study whose initial ART in pregnancy included dolutegravir, atazanavir–ritonavir, darunavir–ritonavir, oral rilpivirine, raltegravir, or elvitegravir–cobicistat. Viral suppression at delivery and the risks of infants being born preterm, having low birth weight, and being small for gestational age were compared between each non–dolutegravir-based ART regimen and dolutegravir-based ART. Supplementary analyses that included participants in the Swiss Mother and Child HIV Cohort Study were conducted to improve the precision of our results.

RESULTS

Of the pregnancies in the study, 120 were in participants who received dolutegravir, 464 in those who received atazanavir–ritonavir, 185 in those who received darunavir–ritonavir, 243 in those who received rilpivirine, 86 in those who received raltegravir, and 159 in those who received elvitegravir–cobicistat. The median age at conception was 29 years; 51% of the pregnancies were in participants who started ART before conception. Viral suppression was present at delivery in 96.7% of the pregnancies in participants who received dolutegravir; corresponding percentages were 84.0% for atazanavir–ritonavir, 89.2% for raltegravir, and 89.8% for elvitegravir–cobicistat (adjusted risk differences vs. dolutegravir, –13.0 percentage points [95% confidence interval {CI}, –17.0 to –6.1], –17.0 percentage points [95% CI, –27.0 to –2.4], and –7.0 percentage points [95% CI, –13.3 to –0.0], respectively). The observed risks of preterm birth were 13.6 to 17.6%. Adjusted risks of infants being born preterm, having low birth weight, or being small for gestational age did not differ substantially between non–dolutegravir-based ART and dolutegravir. Results of supplementary analyses were similar.

CONCLUSIONS

Atazanavir–ritonavir and raltegravir were associated with less frequent viral suppression at delivery than dolutegravir. No clear differences in adverse birth outcomes were observed with dolutegravir-based ART as compared with non–dolutegravir-based ART, although samples were small. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and others.)

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For pregnant persons with human immunodeficiency virus (HIV) infection, a dolutegravir-based regimen is preferred as first-line antiretroviral therapy (ART).[1,2] Among nonpregnant adults, dolutegravir-based ART is more effective, is less likely to be discontinued because of side effects, has a higher barrier to resistance, and has fewer drug interactions than other types of ART.[3-9] The efficacy, effectiveness, and safety of dolutegravir in pregnancy have been compared with those of efavirenz,[10-17] including comparisons in three randomized trials.[13,14,17] The DolPHIN-1 and DolPHIN-2 trials[13,14] and the IMPAACT 2010/VESTED trial[17] reported better viral suppression at delivery and either no evidence of a difference or a lower frequency of adverse birth outcomes with dolutegravir that was initiated in early or late pregnancy than with efavirenz.

However, data are lacking on the efficacy, effectiveness, and safety of dolutegravir as compared with other integrase strand-transfer inhibitor (INSTI)–based, protease inhibitor (PI)–based, and nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based ART regimens commonly used in pregnancy in the United States and Europe; these include regimens with raltegravir, atazanavir–ritonavir, and darunavir–ritonavir, which are categorized alongside dolutegravir as "preferred" in U.S. perinatal guidelines.[1] In addition, many persons with HIV infection worldwide conceive while taking ART,[18] which makes results from trials evaluating the initiation of specific ART regimens during pregnancy difficult to translate into clinical recommendations for this population.

We evaluated viral suppression at delivery and adverse birth outcomes in persons with HIV infection whose initial regimen in pregnancy included dolutegravir as compared with those whose initial regimen included other contemporary ART drugs commonly prescribed in the United States and Europe. We evaluated differences in outcomes overall and according to the timing of ART initiation.

METHODS

STUDY POPULATIONS

In the Pediatric HIV/AIDS Cohort Study Surveillance and Monitoring for ART Toxicities (SMARTT) protocol, we evaluate the safety of prenatal exposure to ART among children who were perinatally exposed to HIV but not infected.[19] Since April 2007, a total of 22 sites in the United States and Puerto Rico have enrolled pregnant persons with HIV infection and their infants within 72 hours after birth into the SMARTT Dynamic cohort. The SMARTT protocol was approved by the institutional review board at each participating site and the Harvard T.H. Chan School of Public Health. Written informed consent was obtained from each participant or their authorized representative.

We evaluated participants enrolled in the SMARTT Dynamic cohort through January 1, 2020, whose initial ART in pregnancy included dolutegravir, atazanavir–ritonavir, darunavir–ritonavir, oral rilpivirine, raltegravir, or elvitegravir–cobicistat, in combination with abacavir–lamivudine, tenofovir disoproxil fumarate–emtricitabine, tenofovir disoproxil fumarate–lamivudine, or tenofovir alafenamide fumarate–emtricitabine. For the analysis of oral rilpivirine, pregnancies in which the earliest HIV viral load was greater than 100,000 copies per milliliter or the earliest CD4 cell count was less than 200 per cubic millimeter in pregnancy were excluded, since rilpivirine is contraindicated at these thresholds. Analyses were based on unique pregnancies and were limited to those for which birth-outcome information was available.

Supplementary analyses included participants who were enrolled in the Swiss Mother and Child HIV Cohort Study (MoCHiV)[20] through January 2019, in order to increase precision. In MoCHiV, a standardized protocol is used to collect pregnancy data on persons with HIV infection and clinical data on their children.

All the authors were involved in the study design, data analyses, writing of the manuscript, and decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data in this report.

EXPOSURES AND OUTCOMES

Initial ART in pregnancy was defined as the first ART regimen recorded in pregnancy, initiated either before conception or during pregnancy. Outcomes included viral suppression at delivery (viral load, <200 copies per milliliter), preterm and very preterm birth (at <37 weeks' and <32 weeks' gestation, respectively), low birth weight and very low birth weight (<2500 g and <1500 g,

respectively), status of being small for gestational age (birth weight <10th percentile for gestational age[21]), and neonatal death within 14 days after birth. Two composite outcomes were evaluated: any adverse birth outcome (preterm birth, low birth weight, status of being small for gestational age, or neonatal death) and any severe adverse birth outcome (very preterm birth, very low birth weight, or neonatal death). For multiple-gestation pregnancies, an adverse birth outcome in any twin or triplet was included in the analyses.

STATISTICAL ANALYSIS

Pregnancy characteristics, the observed percentages of pregnancies in which viral suppression was present at delivery, and the risks of adverse birth outcomes with 95% confidence intervals were summarized according to initial ART. Model-based probability and risk differences for each outcome were estimated for each non–dolutegravir-based ART regimen as compared with dolutegravir with the use of doubly robust estimation, including a propensity-score model for the probability of receiving a specific ART and a logistic model for the mean of the counterfactual outcome, given a set of covariates.[22] Inverse-probability weights were used to account for missing data on viral load at delivery (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Repeat pregnancies (3 to 8% of pregnancies across pairwise samples) were included. We report 95% percentile-based bootstrap confidence intervals with a minimum of 1000 bootstrap samples.

Pairwise ART comparisons with dolutegravir were adjusted for age at conception, participant-reported race and ethnic group, level of educational attainment, timing of maternal HIV infection diagnosis, trimester at the first prenatal care visit, preconception or postconception initiation of ART, use of tobacco during pregnancy, use of alcohol during pregnancy, use of other substances during pregnancy, and any sexually transmitted infection or vaginitis during pregnancy. Race and ethnic group were used as proxies for the influence of racism on ART taken during pregnancy and the risk of adverse birth outcomes.[23,24] For clinical relevance in the comparison of dolutegravir with rilpivirine, pregnancies in which the earliest HIV viral load was greater than 100,000 copies per milliliter or the earliest CD4 cell count was less than 200 per cubic millimeter were excluded.

To evaluate whether comparisons of non–dolutegravir-based ART with dolutegravir were modified by the timing of ART initiation, analyses were repeated within subgroups of participants who started ART before conception or during pregnancy. Because of the smaller samples, these prespecified analyses were not adjusted for confounding. Results of the 50 subgroup analyses are reported without correction for type I error; 2.5 false positive results would be expected by chance. Analyses were repeated with participants from MoCHiV. Because of missing data in that cohort, adjusted analyses excluded adjustment for trimester at first prenatal care visit and alcohol use during pregnancy. All analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

Among the pregnancies included in the study, 120 were in participants who received dolutegravir as part of their initial ART in pregnancy, 464 were in participants who received atazanavir–ritonavir, 185 were in participants who received darunavir–ritonavir, 243 were in participants who received oral rilpivirine, 86 were in participants who received raltegravir, and 159 were in participants who received elvitegravir–cobicistat (Fig. 1). In 51%, ART had been initiated before conception. Among the pregnancies in participants who received dolutegravir-based ART, the regimen included abacavir–lamivudine in 52%, tenofovir disoproxil fumarate–emtricitabine in 32%, and tenofovir alafenamide fumarate–emtricitabine in 17% (Table S1 in the Supplementary Appendix). Tenofovir disoproxil fumarate–emtricitabine was the primary backbone in regimens including atazanavir–ritonavir (94%), darunavir–ritonavir (90%), rilpivirine (86%), or raltegravir (94%). Among the pregnancies in participants who received elvitegravir–cobicistat–based regimens, the regimens in 48% included tenofovir alafenamide fumarate–emtricitabine. The initial ART regimen was changed during 27% of pregnancies, including changes only to the nucleoside or nucleotide reverse-transcriptase inhibitor backbone or booster drug. In 17% of pregnancies, the core drug that was included in the initial ART regimen was

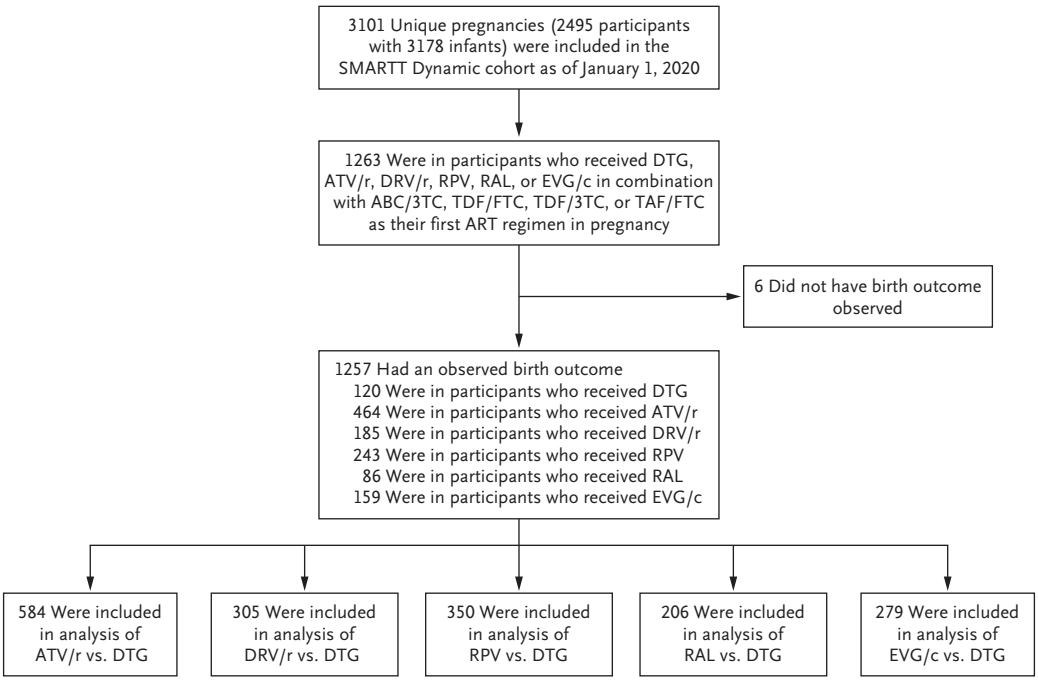

Figure 1. Selection of the Study Population.

The analysis of rilpivirine (RPV) as compared with dolutegravir (DTG) included only pregnancies in which the earliest human immunodeficiency virus (HIV) viral load was no greater than 100,000 copies per milliliter and the earliest CD4 cell count was at least 200 cells per cubic millimeter. 3TC denotes lamivudine, ABC abacavir, ART antiretroviral therapy, ATV/r atazanavir–ritonavir, DRV/r darunavir–ritonavir, EVG/c elvitegravir–cobicistat, FTC emtricitabine, RAL raltegravir, TAF tenofovir alafenamide fumarate, and TDF tenofovir disoproxil fumarate.

changed. Details on initial ART switches are provided in Tables S2 and S3.

Most pregnancies (66%) were in participants who identified as non-Hispanic Black, and the median age at conception was 29 years (interquartile range, 25 to 33), which is representative of persons with HIV infection who are of childbearing potential in the United States (Table S4). The percentage of pregnancies in participants who received care in the U.S. South was higher among those who received elvitegravir–cobicistat or atazanavir–ritonavir than among those who received dolutegravir (58% and 46%, vs. 38%). Participants who received raltegravir in pregnancy were older than those who received dolutegravir (percentage of pregnancies in participants ≥35 years of age, 24% vs. 12%) and more often identified as non-Hispanic White or other (16% vs. 11%), received the diagnosis of HIV infection during pregnancy (24% vs. 13%), had an STI or vaginitis during pregnancy (52% vs. 44%), and started receiving prenatal care and ART in the third trimester (8% vs. 2% and 14% vs. 6%, respectively) (Table 1). The percentage of pregnancies in participants with at least a high school education was lower among those who received oral rilpivirine than among those who received dolutegravir (66% vs. 72%). Alcohol use and other types of substance use were less common among participants who received non–dolutegravir-based ART than among those who received dolutegravir-based ART in pregnancy.

VIRAL SUPPRESSION AT DELIVERY

The observed percentage of pregnancies in which viral suppression was present at delivery was 96.7% among participants who received dolutegravir; the corresponding percentages of pregnancies among participants who received other types of ART were 84.0% for atazanavir–ritonavir, 90.1% for darunavir–ritonavir, 89.2% for raltegravir, and 89.8% for elvitegravir–cobicistat

Table 1. Selected Characteristics of the Study Population.*

Participant Characteristic	Dolutegravir (N=120)	Atazanavir–Ritonavir (N=464)	Darunavir–Ritonavir (N=185)	Rilpivirine (N=243)	Raltegravir (N=86)	Elvitegravir–Cobicistat (N=159)
	number of pregnancies (percent)					
Timing of initiation of initial ART						
Before conception	58 (48)	205 (44)	107 (58)	130 (53)	45 (52)	94 (59)
First trimester	32 (27)	111 (24)	39 (21)	61 (25)	17 (20)	31 (19)
Second trimester	23 (19)	122 (26)	35 (19)	43 (18)	12 (14)	29 (18)
Third trimester	7 (6)	26 (6)	4 (2)	9 (4)	12 (14)	5 (3)
Race or ethnic group†						
Non-Hispanic Black	74 (62)	320 (69)	121 (65)	155 (64)	45 (52)	113 (71)
Non-Hispanic White or other	13 (11)	30 (6)	17 (9)	17 (7)	14 (16)	13 (8)
Hispanic	33 (28)	113 (24)	47 (25)	70 (29)	27 (31)	33 (21)
Age at conception						
<25 yr	32 (27)	120 (26)	51 (28)	64 (26)	15 (17)	31 (19)
25–34 yr	73 (61)	257 (55)	97 (52)	138 (57)	50 (58)	97 (61)
≥35 yr	15 (12)	87 (19)	37 (20)	41 (17)	21 (24)	31 (19)
Timing of first prenatal care visit						
First trimester	78 (65)	324 (70)	128 (69)	167 (69)	54 (63)	112 (70)
Second trimester	33 (28)	97 (21)	51 (28)	54 (22)	22 (26)	37 (23)
Third trimester	2 (2)	9 (2)	2 (1)	9 (4)	7 (8)	7 (4)
Labor or delivery	2 (2)	0	0	0	0	0
Education level of at least high school graduation	86 (72)	318 (69)	138 (75)	160 (66)	62 (72)	115 (72)
Diagnosis of HIV infection received during pregnancy	16 (13)	64 (14)	23 (12)	23 (9)	21 (24)	11 (7)
Use of tobacco during pregnancy	20 (17)	87 (19)	36 (19)	31 (13)	16 (19)	29 (18)
Use of alcohol during pregnancy	12 (10)	38 (8)	16 (9)	16 (7)	6 (7)	13 (8)
Use of other substances during pregnancy‡	24 (20)	42 (9)	25 (14)	25 (10)	9 (10)	25 (16)
Diagnosis of STI or vaginitis received during pregnancy§	53 (44)	207 (45)	76 (41)	96 (40)	45 (52)	75 (47)

* Table S1 shows distributions of all characteristics in the study population evaluated according to initial antiretroviral therapy (ART), as well as distributions of missing values. HIV denotes human immunodeficiency virus.
† Race and ethnic group were reported by the participants.
‡ Other substances included marijuana, heroin, ecstasy, cocaine or crack, methamphetamine, opium, inhalants, phencyclidine, ketamine, lysergic acid diethylamide, and other hallucinogen.
§ Sexually transmitted infection (STI) and vaginitis diagnoses included gonorrhea, chlamydia, trichomoniasis, syphilis, genital herpes, human papillomavirus, genital warts, and bacterial vaginosis.

Table 2. Observed Outcomes.

Outcome	Dolutegravir (N=120)	Atazanavir–Ritonavir (N=464)	Darunavir–Ritonavir (N=185)	Raltegravir (N=86)	Elvitegravir–Cobicistat (N=159)	Dolutegravir vs. Rilpivirine*	
						Dolutegravir (N=107)	Rilpivirine (N=243)
Viral suppression at delivery — no./total no. (%)†	87/90 (96.7)	326/388 (84.0)	128/142 (90.1)	58/65 (89.2)	115/128 (89.8)	77/80 (96.3)	182/188 (96.8)
Preterm birth — no. (%)‡	20 (16.7)	68 (14.7)	26 (14.1)	13 (15.1)	28 (17.6)	19 (17.8)	33 (13.6)
Very preterm birth — no. (%)‡	4 (3.3)	7 (1.5)	4 (2.2)	0	4 (2.5)	4 (3.7)	1 (0.4)
Low birth weight — no. (%)§	20 (16.7)	75 (16.2)	27 (14.6)	14 (16.3)	22 (13.8)	17 (15.9)	29 (11.9)
Very low birth weight — no. (%)§	5 (4.2)	7 (1.5)	2 (1.1)	0	5 (3.1)	5 (4.7)	1 (0.4)
Small for gestational age — no. (%)§	15 (12.5)	58 (12.5)	20 (10.8)	10 (11.6)	17 (10.7)	14 (13.1)	22 (9.1)
Neonatal death within 14 days after birth — no. (%)¶	0	0	0	0	0	0	0
Any adverse birth outcome — no. (%)¶	33 (27.5)	128 (27.6)	49 (26.5)	24 (27.9)	42 (26.4)	30 (28.0)	55 (22.6)
Any severe adverse birth outcome — no. (%)¶	5 (4.2)	10 (2.2)	4 (2.2)	0	5 (3.1)	5 (4.7)	1 (0.4)

* Only pregnancies in which the earliest HIV viral load was no greater than 100,000 copies per milliliter or the earliest CD4 cell count was at least 200 per cubic millimeter were included in this comparison.

† Viral suppression at delivery was defined as an HIV viral load of less than 200 copies per milliliter. Percentages of participants with viral suppression at delivery were calculated among pregnancies with data on viral load at delivery.

‡ Preterm birth was defined as birth before 37 weeks' gestation, and very preterm birth was defined as birth before 32 weeks' gestation.

§ Low birth weight was defined as a birth weight of less than 2500 g, and very low birth weight was defined as a birth weight of less than 1500 g. Small for gestational age was defined as a birth weight below the 10th percentile for gestational age.

¶ An adverse birth outcome was defined as preterm birth, low birth weight, status of being small for gestational age, or neonatal death within 14 days after delivery. A severe adverse birth outcome was defined as very preterm birth, very low birth weight, or neonatal death within 14 days after delivery.

(Table 2). In the analysis of oral rilpivirine as compared with dolutegravir, the percentage of pregnancies in which viral suppression was present at delivery was 96.8% among participants who received rilpivirine and 96.3% among those who received dolutegravir.

Model-based unadjusted and adjusted differences in the estimated probability of viral suppression at delivery are shown in Figure 2. In adjusted analyses, the estimated probability of viral suppression at delivery was lower among pregnancies in participants taking atazanavir–ritonavir than among those in participants taking dolutegravir (adjusted risk difference, –13.0 percentage points; 95% confidence interval [CI], –17.0 to –6.1); the probability of viral suppression at delivery was also lower with raltegravir than with dolutegravir (adjusted risk difference, –17.0 percentage points; 95% CI, –27.0 to –2.4) and lower with elvitegravir–cobicistat than with dolutegravir (adjusted risk difference, –7.0 percentage points; 95% CI, –13.3 to –0.0001).

Among pregnancies in participants who conceived while taking ART, the probability of viral suppression at delivery was lower with raltegravir than with dolutegravir (86.0% vs. 96.0%; risk difference, –10.0 percentage points; 95% CI, –22.0 to 1.9) and was higher with rilpivirine than with dolutegravir (99.6% vs. 92.3%; risk difference, 7.3 percentage points; 95% CI, 4.1 to 20.9) (Table S5). Among pregnancies in participants who started ART during pregnancy, the percentages in which viral suppression was present at delivery were lower among participants who started taking a PI-based regimen than among those who started taking dolutegravir (risk difference, –21.2 percentage points [95% CI, –26.9 to –16.0] for atazanavir–ritonavir and –14.0 percentage points [95% CI, –23.1 to –5.7] for darunavir–ritonavir). In addition, the percentages of pregnancies in which viral suppression was present at delivery were lower among participants who started taking rilpivirine, raltegravir, or elvitegravir–cobicistat during pregnancy than among participants who started taking dolutegravir during pregnancy (risk difference, –7.5 percentage points [95% CI, –13.7 to –1.9] for rilpivirine, –7.4 percentage points [95% CI, –18.3 to –3.1] for raltegravir, and –14.2 [95% CI, –24.5 to –6.0] for elvitegravir–cobicistat) (Table S5).

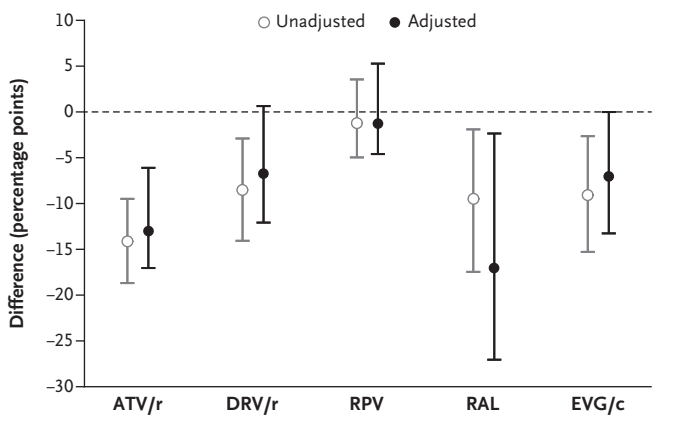

Figure 2. Differences as Compared with Dolutegravir in the Probability of Viral Suppression.

Differences above the dashed reference line indicate a lower probability of viral suppression at delivery (i.e., a viral load of <200 copies per milliliter) with dolutegravir-based ART, and differences below the dashed reference line indicate a higher probability of viral suppression at delivery with dolutegravir-based ART. I bars indicate the 95% confidence interval.

ADVERSE BIRTH OUTCOMES

The observed risks of infants being born preterm, having low birth weight, and being small for gestational age ranged from 13.6% to 17.6%, from 11.9% to 16.7%, and from 9.1% to 12.5%, respectively, across different initial ART regimens in pregnancy (Table 2). The observed risks of the composite of any adverse birth outcome and any severe adverse birth outcome ranged from 22.6% to 27.9% and from 0% to 4.2%, respectively, across initial ART regimens in pregnancy. Across all ART regimens, 20 very preterm births occurred, and in 15 of these births the infants had very low birth weight. No neonatal deaths occurred. Four instances of perinatal HIV transmission occurred — two in pregnancies in participants who were taking atazanavir–ritonavir, one in a pregnancy in a participant taking rilpivirine, and one in a pregnancy in a participant taking elvitegravir–cobicistat. (Additional data on perinatal HIV transmission are provided in Table S6.) Among the 95 infants born to participants who conceived while taking dolutegravir or received dolutegravir in the first trimester, 3 had major congenital anomalies reported: 1 case of syndactyly and 2 cases of polydactyly.

Model-based unadjusted and adjusted differences in the risk of adverse birth outcomes are shown in Figure 3. Adjusted risks of preterm

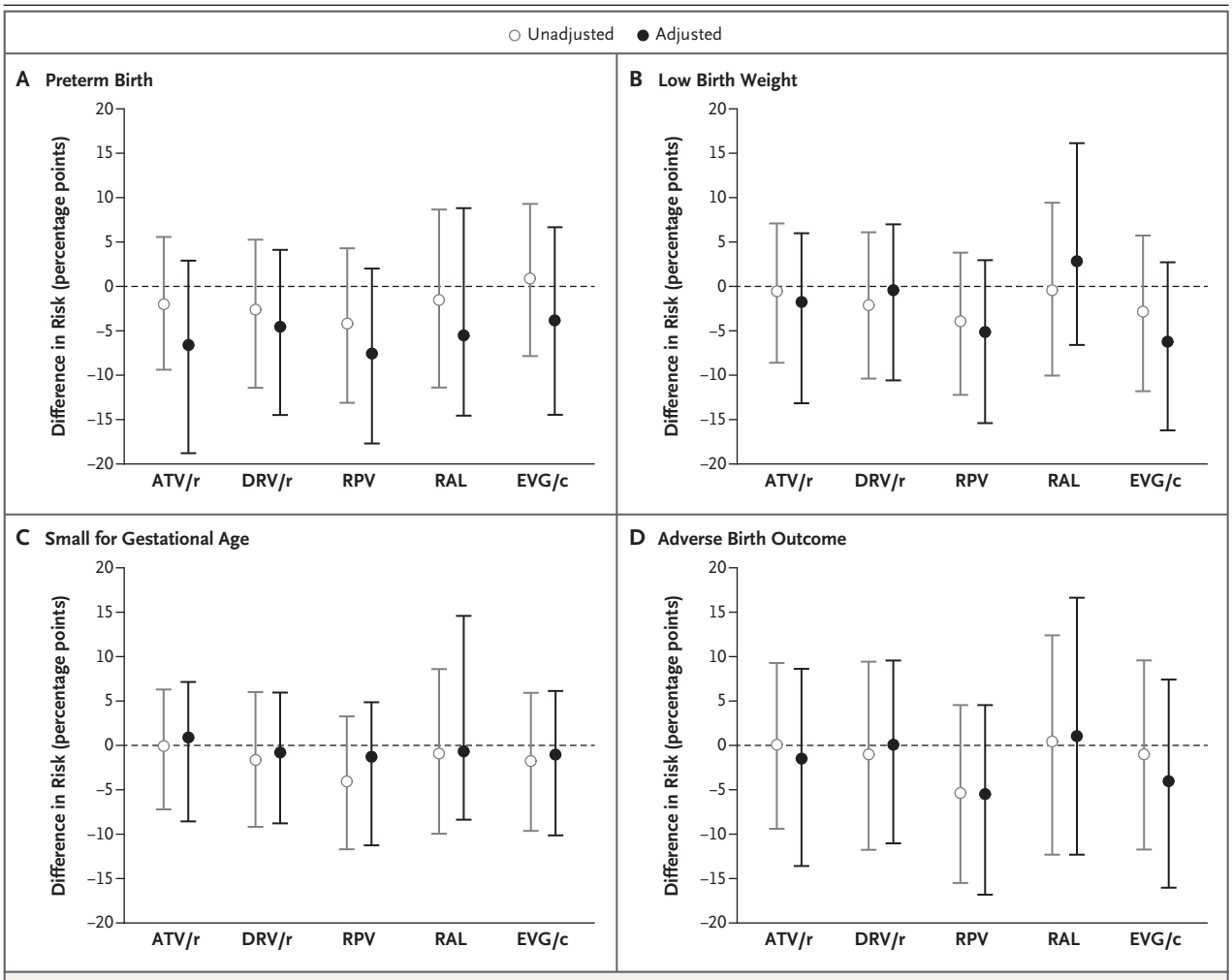

Figure 3. Differences as Compared with Dolutegravir in the Risks of Adverse Birth Outcomes.

Differences above the dashed reference line indicate a lower risk with dolutegravir-based ART, and differences below the dashed reference line indicate a higher risk with dolutegravir-based ART. Preterm birth was defined as birth before 37 weeks' gestation. Low birth weight was defined as a birth weight of less than 2500 g. Small for gestational age was defined as a birth weight below the 10th percentile for gestational age. An adverse birth outcome was defined as preterm birth, low birth weight, status of being small for gestational age, or neonatal death within 14 days after delivery. I bars indicate the 95% confidence interval.

birth were lower for all evaluated non–dolutegravir-based ART regimens than for dolutegravir, with risk differences ranging from –3.8 percentage points (elvitegravir–cobicistat vs. dolutegravir) to –7.6 percentage points (rilpivirine vs. dolutegravir); however, the variability around these estimated differences was large for all comparisons with dolutegravir, ranging from large decreases (risk differences as low as –18.8 percentage points, for atazanavir–ritonavir vs. dolutegravir) to large increases (risk differences as high as 8.8 percentage points, for raltegravir vs. dolutegravir). We also did not observe clear differences between any of the ART regimens and dolutegravir with respect to the other adverse birth outcomes.

We found no apparent patterns of differences in observed risks of adverse birth outcomes between any non–dolutegravir-based ART and dolutegravir stratified according to timing of ART initiation in pregnancy (Table S5). However, the observed risks of any adverse birth outcome were higher among participants who started taking dolutegravir, oral rilpivirine, raltegravir,

or elvitegravir–cobicistat during pregnancy than among participants who conceived while taking those drugs.

SUPPLEMENTARY ANALYSIS INCLUDING THE SMARTT AND MOCHIV COHORTS

Inclusion of the MoCHiV cohort added 170 pregnancies to our analysis. Comparisons of characteristics between the MoCHiV and SMARTT study populations are provided in Table S7. Distributions of observed outcome measures according to initial ART in pregnancy in the MoCHiV cohort are provided in Table S8. Unadjusted and adjusted results were similar when the MoCHiV cohort was included in analyses that had previously been restricted to the SMARTT population (Figs. S1 and S2).

DISCUSSION

In a U.S.-based multisite cohort study involving pregnant persons with HIV infection and their infants in routine clinical care, dolutegravir-based ART was superior to ART with atazanavir–ritonavir, raltegravir, or elvitegravir–cobicistat and was similar to darunavir–ritonavir–based and oral rilpivirine–based ART in achieving viral suppression at delivery. No clear differences were observed in the risk of adverse birth outcomes between dolutegravir and any of these ART regimens.

A published study that compared dolutegravir with non–efavirenz-based ART in pregnancy matched 57 persons with HIV infection who received dolutegravir in pregnancy to persons who received darunavir–ritonavir and noted no differences in the risk of preterm birth and stillbirth.[16] We similarly did not detect a clear difference in the risk of preterm birth between pregnancies in participants taking dolutegravir and those in participants taking darunavir–ritonavir in our larger study. We also compared dolutegravir with other contemporary ART.

In U.S. perinatal guidelines, raltegravir, atazanavir–ritonavir, and darunavir–ritonavir are considered "preferred" in pregnancy, along with dolutegravir.[1] Rilpivirine is an "alternative" NNRTI, and elvitegravir–cobicistat is "not recommended" for use in pregnancy because of insufficient pharmacokinetic levels in the third trimester. However, oral rilpivirine and elvitegravir–cobicistat are still commonly used during pregnancy in the United States.[25] Previously available evidence to help categorize the use of these regimens in pregnancy as preferred, alternative, or not recommended was primarily from small pharmacokinetic studies and data from the Antiretroviral Pregnancy Registry, which relies on voluntary reporting of outcomes. Our observational study provides some systematic data on the effectiveness and safety of these regimens relative to dolutegravir in a prospective cohort of pregnant persons with HIV infection, which may help to inform guidelines and clinical practice.

One important finding was that viral suppression at delivery was less frequent with raltegravir and atazanavir than with dolutegravir, both overall and when ART was initiated during pregnancy. As new antiretroviral drugs and regimens (e.g., bictegravir and long-acting cabotegravir with rilpivirine) are introduced into clinical practice for nonpregnant adults, their effectiveness and safety in pregnancy will need to be evaluated in comparison with dolutegravir and other contemporary regimens commonly used to treat pregnant persons with HIV infection, as highlighted by our results.

We observed that among pregnancies in participants who took dolutegravir, oral rilpivirine, raltegravir, or elvitegravir–cobicistat, initiation of ART during pregnancy was associated with a higher risk of any adverse birth outcome than initiation of ART before pregnancy. This finding appears to contradict those in previous studies, which have shown higher risks of adverse birth outcomes among persons with HIV infection who conceive while taking ART than among those who start ART during pregnancy.[26] These previous associations, however, were found among persons with HIV infection who were primarily taking PI-based, nevirapine-based, or efavirenz-based ART. Our data suggest that the association between the timing of ART initiation and the risk of adverse birth outcomes may differ according to specific ART.

We acknowledge several limitations and assumptions of our study. First, we had limited information on some important predictors of preterm birth and low birth weight, including parity, previous preterm birth, and prepregnancy body-mass index. Our estimates therefore could

be confounded if the distribution of these predictors varied within comparisons of ART regimens. Second, our analyses included pregnancies that occurred before and after the warning about a potential increased risk of neural-tube defects associated with dolutegravir.[11] Comparison of the 23 pregnancies with exposure to dolutegravir after the warning on May 18, 2018, with the 97 pregnancies exposed to dolutegravir before May 18, 2018, showed higher risks of infants being born preterm (30.4% vs. 13.4%), having low birth weight (30.4% vs 13.4%), and being small for gestational age (17.4% vs. 11.3%) among the pregnancies exposed to dolutegravir after the warning. This suggests that there may be residual confounding within our comparisons of non–dolutegravir-based ART and dolutegravir. Third, despite the fact that our analyses involved participants from a large multisite cohort study, samples of participants receiving INSTIs were small, which limited our power to detect small differences in adverse birth outcomes between non–dolutegravir-based ART and dolutegravir and our ability to conduct adjusted analyses stratified according to timing of ART initiation. Our collaboration with MoCHiV aimed to increase sample size. Finally, our analyses compared initial ART regimens in pregnancy and did not consider ART switching.

Our study contributes data on the effectiveness and safety of contemporary, commonly used INSTIs, PIs, and NNRTIs during pregnancy. Our results provide evidence suggesting that atazanavir–ritonavir and raltegravir provide less HIV viral suppression at delivery than dolutegravir and support darunavir–ritonavir as a reasonable alternative when dolutegravir use is not feasible.

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