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Effects of initiating raltegravir-based versus efavirenz-based antiretroviral regimens during pregnancy on weight changes and perinatal outcomes: NICHD P1081

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Contributions

ECJ, NC, TLF, DES, and MM designed the study. CMC, GD, AS, AV, CBH, JD, JHP, JSN and ECJ, implemented the interventions and collected data. All coauthors helped to oversee study conduct, reviewed, and commented on the manuscript. MGW and DES analyzed the data. CMC wrote the first version of the report with the help of MGW, TLF and ECJ. CMC made the final independent decision to submit the manuscript for publication. All authors had full access to all the data in the study and approved the final version of the manuscript.

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Abstract

Background: Integrase inhibitors have been associated with excess gestational weight gain that may lead to adverse pregnancy outcomes (APOs). This post-hoc analysis of NICHD P1081 compared antepartum changes in weight and body mass index (BMI) in pregnant women initiating raltegravir or efavirenz-based combined antiretroviral therapy (cART) and examined associations between rates of weight gain and APOs.

Setting: NICHD P1081 enrolled antiretroviral naive pregnant women living with HIV in the second and third trimester in Brazil, Tanzania, South Africa, Thailand, Argentina, and the US.

Methods: 281 women enrolled between 20–31 gestational weeks were randomized to raltegravir- or efavirenz-based cART and followed for ≥4 weeks. Low rate of weight gain was defined as <0.18 kg/week and high as >0.59 kg/week. We compared weight gain and BMI increase between treatment arms using Kruskal Wallis tests. Logistic regression was used to investigate the association between weight gain and APOs.

Results: Raltegravir-based cART was associated with significantly higher antepartum weight gain (median 0.36 kg/week versus 0.29 kg/week, p=0.01) and BMI increase (median 0.14 kg/m^2/week versus 0.11 kg/m^2/week, p=0.01) compared to efavirenz-based treatment. Women on raltegravir had less low weight gain (18% versus 36%) and more high weight gain (21% versus 12%) (p=0.001). Women with low weight gain were more likely than those with normal weight gain to have small for gestational age infants or a composite of APOs.

Conclusions: A raltegravir-based antiretroviral regimen was associated with significantly higher antepartum rate of weight gain and BMI increase compared to efavirenz-based treatment in antiretroviral-naive pregnant women.

Keywords

Raltegravir; Efavirenz; Weight Gain; Body Mass Index; Pregnancy; Pregnancy Outcomes

Introduction

Human Immunodeficiency Virus (HIV) suppression is critical during pregnancy for maintenance of maternal health and prevention of both secondary sexual and perinatal HIV transmission. Initiation of combined antiretroviral therapy early in pregnancy with a potent and safe pregnancy regimen is of paramount importance.[1] The integrase inhibitors raltegravir and dolutegravir are currently recommended as part of preferred initial antiretroviral regimens for pregnant women based on their demonstrated efficacy, straightforward posology and acceptability, available pharmacokinetic data and low toxicity.[1] Raltegravir was the first integrase inhibitor to be studied during pregnancy. Pregnancy pharmacokinetic data demonstrate adequate plasma exposures with use of standard adult doses of 400 mg twice daily, its use is known to result in rapid viral load decline in antiretroviral-naive late presenters compared to efavirenz- or lopinavir/ritonavir-based regimens, and raltegravir has a favorable safety profile, with no concerns regarding teratogenicity described to date.[2–4]

Mounting experience with integrase inhibitor use in non-pregnant populations has raised concern of potential adverse metabolic effects. Increases in weight, body fat, and body mass index (BMI) and greater risk for diabetes have been reported both following integrase inhibitor initiation in treatment-naive adolescents and adults[5–8] or after switching to integrase inhibitors in suppressed individuals when compared to non-nucleoside reverse transcriptase inhibitors and protease inhibitors.[9,10] These associations appear greater for patients receiving dolutegravir and tenofovir alafenamide. However, these same effects have not been observed by other researchers in similar studies.[11–13] With regards to pregnancy, increased antepartum and postpartum weekly weight gain was reported for dolutegravir compared to efavirenz in an African population, but still below the average weight gain of women not living with HIV.[14,15]

Gestational weight gain is a potentially modifiable risk factor for immediate adverse pregnancy outcomes and has long-term implications. Low gestational weight gain has been linked to fetal growth restriction, preterm birth and perinatal mortality,[16,17] while increased weight gain has been associated with diabetes during pregnancy, hypertensive disorders, preterm birth, macrosomia, labor dystocia, Cesarean delivery, postpartum weight retention and offspring obesity.[17–21] Moreover, women living with HIV are also at risk for non-communicable diseases during reproductive age and throughout their lives, due to the intricate interactions between the virus, antiretrovirals and chronic inflammation, adding to the burden of possible integrase inhibitor-induced metabolic adverse events.[22,23] Therefore, it is of utmost importance to understand the potential impacts of integrase inhibitor use in pregnant women and in their offspring.

Weight gain related to integrase inhibitor use in pregnancy and its consequences have not yet been described for raltegravir. This study is a secondary analysis of a subset of

participants in the NICHD P1081 trial. The parent study compared clinical outcomes of antiretroviral-naive pregnant women randomized to receive a raltegravir- or efavirenz-based antiretroviral regimen starting between 20 and 36 weeks of gestation. This sub study only included those who started between 20 and 31 weeks' gestation and were on study for at least four weeks. The objectives of this analysis are to compare antepartum changes in body weight and BMI between treatments and to assess the associations between weight gain and adverse pregnancy outcomes.

Methods

Study population and design

NICHD P1081 was a phase 4, multicenter, two-arm, open-label, randomized clinical trial comparing the ability to achieve virologic suppression at delivery, tolerability, and safety in pregnant women living with HIV with a gestational age between 20 and 36 weeks who were antiretroviral-naive or had received short-course zidovudine (for a maximum of 8 weeks) only for prevention of perinatal HIV transmission in previous pregnancies, and their infants.[3] Women were randomized to receive one of two triple antiretroviral regimens, containing either raltegravir, the first licensed integrase inhibitor, or efavirenz, a non-nucleotide reverse transcriptase inhibitor, in combination with two nucleoside reverse transcriptase inhibitors. Patients were enrolled from 19 clinic and hospital facilities in Argentina (two), Brazil (seven), South Africa (one), Tanzania (one), Thailand (three) and the United States of America (five). Additional information about the original study can be found elsewhere.[3]

The study population for these secondary analyses is women with singleton pregnancies enrolled in NICHD P1081 in the 20-<28 weeks and 28-<31 weeks' gestation enrollment strata who were on study for at least four weeks and have available weight measurements within 30 days prior to or at entry and within 14 days prior to delivery, and delivery date data. Postpartum, women were switched to a local standard of care combined antiretroviral regimen. Data from infants born to enrolled women were included in the pregnancy outcome analysis.

Definitions and procedures

Documentation of HIV-1 infection was defined as positive results from two samples collected at different time points. Gestational age was determined by last menstrual period or ultrasound. Infant birth weight percentiles for gestational age with adjustment for sex were determined using the INTERGROWTH-21st tables.[24] Studied pregnancy outcomes included mode of delivery, preterm birth <37 completed gestational weeks, preterm birth <34 completed gestational weeks, small for gestational age (SGA, <10th percentile), large for gestational age (LGA, >90th percentile), stillbirth (>20 weeks) and neonatal death (death of a live-born infant within 28 days after birth) and a composite of four of these outcomes (stillbirth, neonatal death, preterm birth and SGA).

All pregnant participants had their weight measured at each study visit. BMI was calculated using the formula weight/height^2. Changes in weight and BMI were analyzed as the rates of change per week to account for the varying lengths of follow-up. Standards for weekly

weight gain during pregnancy were based on the Institute of Medicine 2009 guidelines on gestational weight gain,[25] modified due to the unavailability of weight and BMI from before study entry. Low rate of weight gain was defined as a weekly gain below 0.18 kg/week, normal rate of weight gain as a weekly gain between 0.18 kg/week and 0.59 kg/week, and high rate of weight gain as a weekly gain above 0.59 kg/week.

Statistical analysis

Kruskal-Wallis tests were used to compare rates of weight and BMI change from entry to delivery between treatment arms. Univariate linear regression was used to estimate differences in rates of change by treatment arm and by time between first and last weight measurements. The associations between treatment arms and weight change category, and between treatment arms and weight loss were assessed using Fisher's exact test.

For the analyses of pregnancy outcomes by categories of antepartum rates of weight gain, separate analyses compared (1) women with low versus normal rates of weight change and (2) women with high versus normal rates of weight change. For each set of comparisons, exact logistic regression was used to estimate the association between weight gain rate category and the odds of having stillbirth, neonatal death, preterm delivery, SGA, or a composite of these four outcomes. Other pregnancy outcomes included mode of delivery or LGA.

All statistical tests used a two-sided 5% significance level, without adjustment for multiple comparisons; significant results were interpreted with caution, with emphasis on magnitudes of effect sizes. This is an exploratory, post hoc analysis for objectives not included in the protocol. All data analysis was done using SAS version 9.4 (SAS Institute, Cary NC).

Role of the funding source

Staff of NICHD, which provided funding for the protocol, were full study team members involved in study design, data collection, data analysis, data interpretation, and writing of the report. Companies that supplied study drug (Merck, Bristol Myers-Squibb, and ViiV Healthcare) had no other role during the study. The corresponding author had full access to all the data related to this secondary analysis study and had final responsibility for the decision to submit for publication.

Ethics approval

All versions of the trial protocol and amendments were approved by each hospital institutional review board or regulatory entities. All pregnant women who agreed to participate gave written informed consent.

Results

Of the 408 participants enrolled and randomized into NICHD P1081, 105 were excluded from these analyses due to enrolling at 31 weeks' gestation or later and 22 others were excluded due to discontinuing study participation prior to delivery, not having singleton pregnancies, or having less than four weeks between their first and last weight

measurements. A total of 281 women were included in these analyses, with 137 on the efavirenz arm and 144 on the raltegravir arm (Figure 1).

Baseline characteristics of the study population are shown in Table 1. Participants had a median age of 26.2 years at study entry. Forty-five percent were Hispanic/Latino, 42% Black, 12% Asian, and 1% White. The distributions of weight and BMI at study entry were very similar between the arms. Only 5% of women were virally suppressed (HIV-1 RNA <200 copies/mL) at study entry. Fifty-two percent had viral load ≥10,000 copies/mL and 65% had CD4 counts less than 500 cells/mm^3. The median gestational age at entry was 25 weeks, with 67% in the 20-<28 weeks stratum and 33% in the 28-<31 stratum. The median weight at entry was 66.4 kg and median BMI was 26 kg/m^2. All participants started treatment within seven days of study entry; 98% started within a day of entry. The median time from entry to the last weight measured before delivery was 12.3 weeks, with a minimum of 4.0 and maximum of 21.9 weeks.

The rates of change for weight and BMI by treatment arm are shown in Table 2 and Supplemental Figure S1. The median rate of weight change in the raltegravir arm was 0.36 kg/week versus 0.29 kg/week in the efavirenz arm. The rate of change in BMI was also higher in the raltegravir arm, with women gaining a median of 0.14 kg/m^2/week versus 0.11 kg/m^2/week on the efavirenz arm.

Results of univariate linear regression analyses are shown in Supplemental Table S1. The parameter estimates show the differences in rates of change between the two arms. The average rate of weight change for women on raltegravir was 0.08 kg/week (95% confidence interval [CI] 0.02 – 0.15) greater than those on efavirenz. For BMI, the rate of change on raltegravir was 0.03 kg/m^2/week (95% CI 0.01 – 0.06) greater than on efavirenz. However, the length of time participants were on treatment (weeks from entry to delivery weight) was not a significant predictor of rates of change for either weight or BMI; that is, those on treatment longer had similar rates of change to those who started treatment closer to delivery.

There was an association between treatment arm and rate of weight gain category (Table 2 and Figure 2; Fisher's exact test, p=0.001). Women on raltegravir were less likely than those on efavirenz to have low rates of weight gain (18% versus 36%) and were more likely to have high rates of weight gain (21% versus 12%). Ten percent of women experienced weight loss over the study period; however, the proportion of women in each arm who lost weight during the study did not differ significantly between study arms (efavirenz 12%, raltegravir 8%, Table 2).

The frequencies of pregnancy outcomes by rate of weight gain category are shown in Table 3. A few outcomes have some missing data due to unknown gestational age at birth.

The results of the exact logistic regression analyses are also shown in Table 3. For the comparisons between women with low and normal rates of weight gain, those with low rates of weight gain were significantly more likely to have SGA infants (30% versus 13%, odds ratio 3.0 [95% CI 1.4 – 6.4], p=0.003) or to have a composite adverse outcome event (44% versus 22%, odds ratio 2.7 [95% CI 1.4 – 5.2], p=0.002). Women with low rates of

weight gain were less likely to have Cesarean sections (24% vs. 46%, odds ratio 0.4 [95% CI 0.2 – 0.7], p=0.001). There were no significant differences in rates of outcomes between the women with high versus normal rates of antepartum weight gain (Table 3). Rates of most pregnancy outcomes were low, meaning there was low precision as seen in the wide confidence intervals for the estimates of the odds ratios for possible associations between weight gain category and outcomes.

Discussions

A raltegravir-based antiretroviral regimen was associated with significantly higher antepartum rate of weight gain and BMI increase compared to efavirenz-based treatment in antiretroviral-naive pregnant women. Women on raltegravir were less likely to have low rates of weight gain and more likely to have high rates of weight gain than women on efavirenz. Women with low rates of weight gain were significantly more likely to have SGA infants or to have composite adverse pregnancy outcomes than women with normal rates of weight gain, but there were no significant differences in these rates for women with high versus normal rates of weight gain.

The IMPAACT 2010 trial randomly assigned pregnant women living with HIV between 14 and 28 weeks of gestational age into two dolutegravir-based arms and one efavirenz-based arm.[26] A secondary analysis of this study found greater weight gain in the dolutegravir-based arms than the efavirenz-based arm and higher rates of adverse pregnancy outcomes in women with low weight gain.[27] Another randomized clinical trial, DolPHIN-2, examined late antenatal and postpartum weight gain through 72 weeks after delivery in Uganda and South Africa among women who enrolled after 28 weeks' gestational age and initiated dolutegravir- or efavirenz-based regimens.[28] Postpartum weight gain among women using dolutegravir-based regimens was also greater than among those using efavirenz-based regimens. In the Tsepamo observational cohort in Botswana, the rate of high weight gain in women initiating dolutegravir during pregnancy was higher than among those initiating efavirenz, but lower than women not living with HIV. Also, fewer women in the dolutegravir arm had weight loss.[14] In a cohort of women living with HIV in Rio de Janeiro who used integrase inhibitor-based combined antiretroviral therapy, when women who conceived in use of such treatment were compared to those who initiated the regimen during pregnancy, there was greater weight gain in women who initiated during pregnancy[29]. However, this study only compared integrase inhibitors and no other antiretroviral regimens. A study of an Italian national pregnancy cohort did not find an association between different antiretroviral regimens, including integrase inhibitors, and excessive absolute weight increase during pregnancy. However, the comparison of the influence of individual drugs on weight gain was hindered by the limited number of cases.[30] Our findings were similar to those of the two randomized clinical trials and the Tsepamo cohort, showing that both raltegravir and dolutegravir, when started during pregnancy, result in increased antenatal weight gain compared to efavirenz-based treatments.

Few studies have investigated the impact of different rates of weight gain associated with distinct antiretroviral regimens on pregnancy outcomes. IMPAACT 2010 reported that a low rate of weight gain, more common among those on efavirenz than dolutegravir regimen, was

associated with increased risk for SGA and a composite of adverse pregnancy outcomes including stillbirth, preterm delivery, SGA, and neonatal death,[27] very similar to this study's findings. Neither DolPHIN-2 analysis nor the Tsepamo study investigated these outcomes.[14,28] High rate of weight gain during pregnancy has been previously associated with increased risk of LGA, preterm birth, labor dystocia and Cesarean delivery.[17] However, this study's results are concordant with IMPAACT 2010, showing that raltegravir initiation during pregnancy might be less associated with adverse pregnancy outcomes related to low rate of weight gain when compared to efavirenz-based regimens. Although low rates of weight gain were associated with fewer Cesarean sections, further analysis of this finding was limited by the fact that there was considerable variation among sites with respect to the medical reason for Cesarean delivery.

As the present sub study followed participants during gestation, we did not investigate trends in weight change associated with integrase inhibitor use before pregnancy. In a modeling study[31] based on the findings of the ADVANCE trial[5], among women who used integrase inhibitor for 96 weeks prior to gestation, the rate of treatment-associated obesity was 14.1% for the tenofovir alafenamide/emtricitabine+dolutegravir arm and 7.9% for the tenofovir disoproxil fumarate/emtricitabine+dolutegravir arm, and such obesity was predicted to increase the risk of adverse pregnancy outcomes. These findings suggest that further studies are needed regarding obesity associated with long-term integrase inhibitor use in women of child-bearing age.

Gorwood et al. showed that integrase inhibitors cause weight gain by elevating adipogenesis, which leads to fibrosis and lipid accumulation.[32] However, due to the multifactorial nature of weight regulation mechanisms, other factors may also contribute to weight gain associated with integrase inhibitor exposure. On the other hand, many reasons have been described to explain why efavirenz compromises adipogenesis: a dose-dependent suppression of adipocyte differentiation, a decreased production of lipoprotein lipase, leptin and adiponectin via down-regulation of regulator genes, and a significant increase in the release of pro-inflammatory cytokines.[33] Additionally, slow efavirenz metabolizers, carriers of loss-of-function polymorphisms detectable by CYP2B6 genotyping, which are more prevalent among African descendants, have increased blood concentrations of efavirenz, what may further decrease weight gain.[34] The aforementioned mechanisms could possibly explain why pregnant women using raltegravir had a higher rate of weight gain compared to efavirenz in this study.

Strengths of this exploratory analysis of the NICHD P1081 study data include its randomized design with participants from multiple centers in Asia, Africa, and the Americas. Furthermore, this secondary analysis was the first prospective study to evaluate the effect of raltegravir on weight gain during gestation in antiretroviral-naive pregnant women. Among the limitations of the study are the lack of pre-pregnancy weight and BMI, and the fact that the study sample was almost exclusively composed of participants from low- and middle-income countries, precluding generalization to other populations. It will be useful to further examine the relationship between weight gain and adverse pregnancy outcomes, regardless of regimen, in future studies.

In conclusion, integrase inhibitors have long been recognized for their capacity to suppress viral load during pregnancy with good tolerability,[3,26] which were important considerations for their designation as a component of the preferred antiretroviral regimens for pregnant women living with HIV. In this study, we also found that raltegravir is more effective at promoting weight gain than efavirenz. This may possibly reduce adverse pregnancy outcomes since low rate of weight gain was associated with adverse pregnancy outcomes. These results may be important for counselling and management of pregnant women living with HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interests

DES reports grants from US National Institute of Allergy and Infectious Diseases (NIAID) and US Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), during the conduct of the study, and grants from NIAID and NICHD, outside the submitted work. MW reports grants from NIAID and NICHD, during the conduct of the study, and grants from NIAID, outside the submitted work. AS reports grants from NICHD and NIAID during the conduct of the study. AV reports grants from NICHD during the conduct of the study. MM reports grants from NICHD and NIAID during the conduct of the study, and grants from Merck & Co, ViiV Healthcare, and Gilead Sciences, outside the submitted work. All other authors declare no competing interests.

Data sharing

The primary data for this study has been de-identified and is publicly available through the NICHD Data and Specimen Hub (DASH). Study specimens will be made available through the NICHD DASH at a later time.

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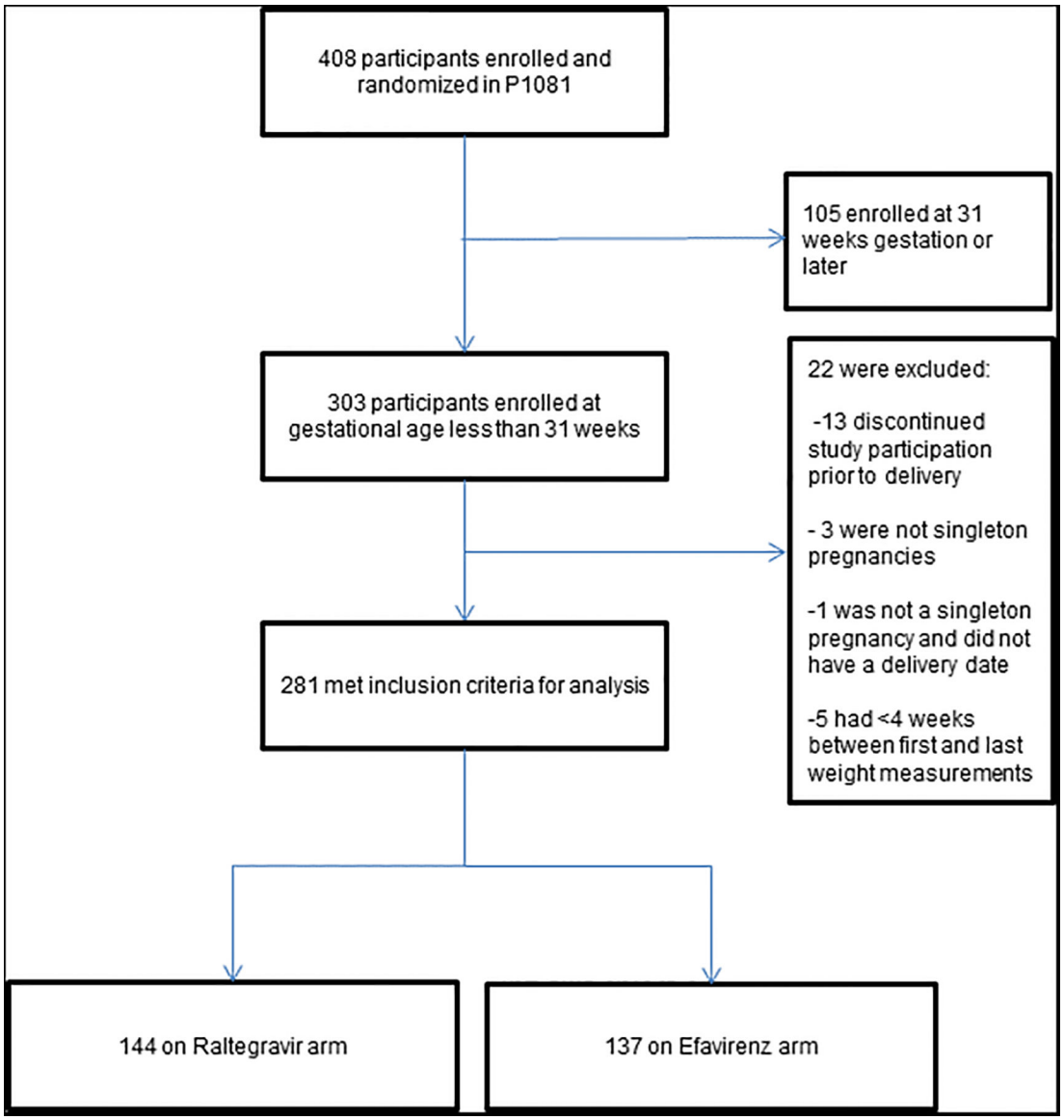

Figure 1:
CONSORT diagram.

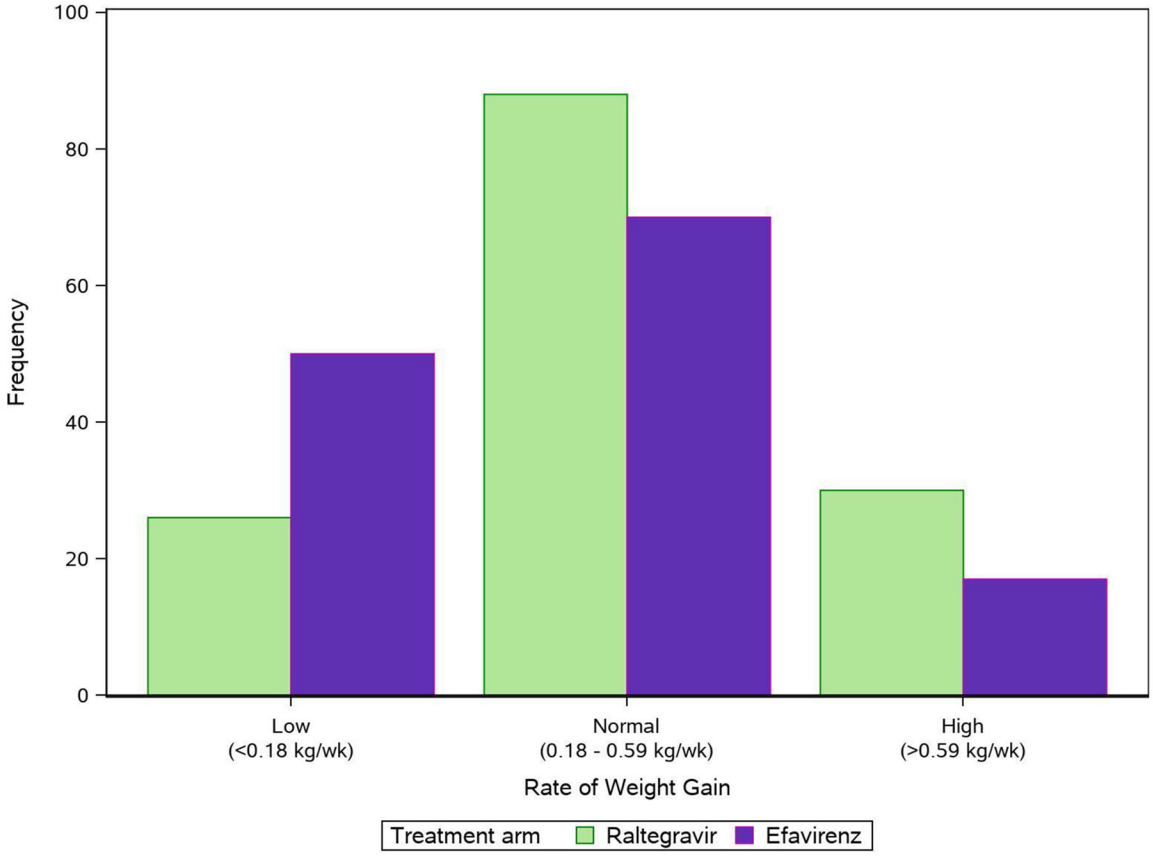

Figure 2:
Antepartum rate of weight gain by treatment

Table 1:

Baseline Characteristics of the Study Participants (N=281).

Characteristic		Treatment Arm Efavirenz (N=137)	Raltegravir (N=144)	Total (N=281)
Age at baseline (years)	Median (Q1-Q3)	25.5 (21.4–31)	26.7 (22.7–30.9)	26.2 (22.2–31)
Race/ethnicity	Asian, Pacific Islander	15 (11%)	19 (13%)	34 (12%)
	Black, Not Hispanic	58 (43%)	59 (41%)	117 (42%)
	Hispanic, Latino	62 (46%)	65 (45%)	127 (45%)
	White, Not Hispanic	1 (1%)	1 (1%)	2 (1%)
	Unknown	1	0	1
Log10 RNA (copies/mL)	Median (Q1-Q3)	4 (3.4–4.4)	4.1 (3.5–4.6)	4 (3.5–4.6)
HIV-1 RNA (copies/mL)	<200	7 (5%)	7 (5%)	14 (5%)
	200–999	12 (9%)	12 (8%)	24 (9%)
	1,000–9,999	49 (36%)	48 (34%)	97 (35%)
	≥10,000	69 (50%)	75 (53%)	144 (52%)
Absolute CD4 count (cells/mm^3)	Median (Q1-Q3)	391 (271.5–590.5)	363.5 (229–566.5)	385 (242.5–570)
	<200	20 (15%)	26 (19%)	46 (17%)
	200–499	63 (48%)	68 (49%)	131 (48%)
	≥500	49 (37%)	46 (33%)	95 (35%)
Gestational age (weeks)	Median (Q1-Q3)	25 (22–28)	24 (22–28)	25 (22–28)
Gestational age strata	20 - <28 weeks	93 (68%)	96 (67%)	189 (67%)
	28 - <31 weeks	44 (32%)	48 (33%)	92 (33%)
Entry weight (kg)	Median (Q1-Q3)	67.7 (58.5–78.4)	65 (58.8–77.8)	66.4 (58.7–77.9)
Entry body mass index (kg/m^2)	Median (Q1-Q3)	26.1 (23.6–30.3)	25.9 (23.1–29.3)	26 (23.3–29.9)
Days from entry to start of treatment	0	130 (95%)	138 (96%)	268 (95%)
	1	4 (3%)	5 (3%)	9 (3%)
	4	1 (1%)	0 (0%)	1 (0%)
	6	0 (0%)	1 (1%)	1 (0%)
	7	2 (1%)	0 (0%)	2 (1%)
Weeks from entry to delivery weight	Median (Q1-Q3)	12.1 (9.9–16.3)	12.6 (9.8–16)	12.3 (9.9–16)
	Min, Max	5.7, 21.7	4, 21.9	4, 21.9

Table 2:

Rates of weight and body mass index change and categories of weight changes by treatment arm.

	Efavirenz	Raltegravir	
	Median (IQR)	**Median (IQR)**	***p*-value***
Rate of weight change (kg/week)	0.29 (0.11–0.45)	0.36 (0.23–0.55)	0.01
Rate of BMI change (kg/m^2/week)	0.11 (0.04–0.17)	0.14 (0.09–0.2)	0.01
	N (%)	**N (%)**	***p*-value****
Rate of weight gain			
Low	50 (36%)	26 (18%)	0.001
Normal	70 (51%)	88 (61%)	
High	17 (12%)	30 (21%)	
Weight loss			
No	121 (88%)	132 (92%)	0.43
Yes	16 (12%)	12 (8%)	
Total	**137**	**144**	

*p-values calculated using Kruskal-Wallis test

**p-values calculated using Fisher's Exact test

BMI: body mass index, IQR: interquartile range

Table 3:

Association of rate of antenatal weight gain with pregnancy outcomes.

	Rate of Weight Gain			Odds ratios (95% Confidence Interval)			
Pregnancy Outcome	**Low (N=76)**	**Normal (N=158)**	**High (N=47)**	**Low vs. Normal**	***p*-value**	**High vs. Normal**	***p*-value**
Composite outcome **	32 (44%)	35 (22%)	13 (28%)	2.7 (1.4, 5.2)	0.002	1.3 (0.6, 3.0)	0.55
Stillbirth	3 (4%)	0 (0%)	0 (0%)	8.2 (1.2, >999.9)	0.07	N/A	N/A *
Neonatal death	1 (1%)	1 (1%)	0 (0%)	2.1 (0.0, 165.3)	>0.99	N/A	N/A *
Preterm <37 weeks	7 (10%)	15 (9%)	7 (15%)	1.1 (0.4, 3.0)	>0.99	1.7 (0.5, 4.7)	0.43
Preterm <34 weeks	2 (3%)	3 (2%)	4 (9%)	1.5 (0.1, 13.8)	0.96	4.8 (0.8, 33.7)	0.10
Small for gestational age	21 (30%)	20 (13%)	7 (15%)	3.0 (1.4, 6.4)	0.003	1.2 (0.4, 3.2)	0.85
Large for gestational age	4 (6%)	16 (10%)	2 (4%)	0.5 (0.1, 1.8)	0.43	0.4 (0.0, 1.8)	0.34

* N/A: Not available (odds ratios and confidence intervals could not be estimated well due to very small numbers of events)

** Composite includes the occurrence of any of: stillbirth, neonatal death, preterm (<37 weeks) or small for gestational age (<10th percentile)