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*Clinical Infectious Diseases*

MAJOR ARTICLE

# Weight Changes and Adverse Pregnancy Outcomes With Dolutegravir- and Tenofovir Alafenamide Fumarate–Containing Antiretroviral Treatment Regimens During Pregnancy and Postpartum

**Risa M. Hoffman,[1] Sean Brummel,[2] Lauren Ziemba,[2] Lameck Chinula,[3] Katie McCarthy,[4] Lee Fairlie,[5] Patrick Jean-Philippe,[6] Nahida Chakhtoura,[7] Ben Johnston,[8] Chelsea Krotje,[8] Teacler G. Nematadzira,[9] Frances Nakayiwa,[10] Victoria Ndyanabangi,[11] Sherika Hanley,[12] Gerhard Theron,[13] Avy Violari,[14] Esau João,[15] Mario Dias Correa Jr,[16] Cristina Barroso Hofer,[17] Oranich Navanukroh,[18] Linda Aurpibul,[19] Neetal Nevrekar,[20] Rebecca Zash,[21] Roger Shapiro,[2] Jeffrey S. A. Stringer,[22] Judith S. Currier,[1] Paul Sax,[23] and Shahin Lockman[24]; on behalf of the IMPAACT 2010/VESTED Study Team[a]**

[1]Department of Medicine, University of California, Los Angeles, California, USA; [2]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; [3]UNC Chapel Hill Department of Obstetrics & Gynecology, UNC Project Malawi, Lilongwe, Malawi; [4]FHI 360, Durham, North Carolina, USA; [5]Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa; [6]Maternal Adolescent Pediatric Research Branch, Division of AIDS, National Institutes of Health, Rockville, Maryland, USA; [7]National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA; [8]Frontier Science Foundation, Amherst, New York, USA; [9]University of Zimbabwe–UCSF Collaborative Research Programme, Chitungwiza, Zimbabwe; [10]MUJHU Care Limited, Kampala, Uganda; [11]Baylor College of Medicine Children's Foundation Uganda, Kampala, Uganda; [12]Department of Family Medicine, Centre for the AIDS Programme of Research and University of KwaZulu-Natal, Durban, South Africa; [13]Stellenbosch University, Stellenbosch, South Africa; [14]Perinatal HIV Research Unit, University of the Witwatersrand, Soweto, South Africa; [15]Infectious Diseases Department, Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil; [16]Department of Obstetrics and Gynecology, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [17]Department of Preventive Medicine, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [18]Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [19]Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand; [20]Byramjee Jeejeebhoy Government Medical College–Johns Hopkins University, Pune, India; [21]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; [22]Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA; [23]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; and [24]Department of Medicine, Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

***Background.*** We evaluated associations between antepartum weight change and adverse pregnancy outcomes and between antiretroviral therapy (ART) regimens and week 50 postpartum body mass index in IMPAACT 2010.

***Methods.*** Women with human immunodeficiency virus (HIV)-1 in 9 countries were randomized 1:1:1 at 14–28 weeks' gestational age (GA) to start dolutegravir (DTG) + emtricitabine (FTC)/tenofovir alafenamide fumarate (TAF) versus DTG + FTC/tenofovir disoproxil fumarate (TDF) versus efavirenz (EFV)/FTC/TDF. Insufficient antepartum weight gain was defined using Institute of Medicine guidelines. Cox-proportional hazards regression models were used to evaluate the association between antepartum weight change and adverse pregnancy outcomes: stillbirth (≥20 weeks' GA), preterm delivery (<37 weeks' GA), small size for GA (<10th percentile), and a composite of these endpoints.

***Results.*** A total of 643 participants were randomized: 217 to the DTG + FTC/TAF, 215 to the DTG + FTC/TDF, and 211 to the EFV/FTC/TDF arm. Baseline medians were as follows: GA, 21.9 weeks; HIV RNA, 903 copies/mL; and CD4 cell count, 466/μL. Insufficient weight gain was least frequent with DTG + FTC/TAF (15.0%) versus DTG + FTC/TDF (23.6%) and EFV/FTC/TDF (30.4%). Women in the DTG + FTC/TAF arm had the lowest rate of composite adverse pregnancy outcome. Low antepartum weight gain was associated with higher hazard of composite adverse pregnancy outcome (hazard ratio, 1.44 [95% confidence interval, 1.04–2.00]) and small size for GA (1.48 [.99–2.22]). More women in the DTG + FTC/TAF arm had a body mass index ≥25 (calculated as weight in kilograms divided by height in meters squared) at 50 weeks postpartum (54.7%) versus the DTG + FTC/TDF (45.2%) and EFV/FTC/TDF (34.2%) arms.

***Conclusions.*** Antepartum weight gain on DTG regimens was protective against adverse pregnancy outcomes typically associated with insufficient weight gain, supportive of guidelines recommending DTG-based ART for women starting ART during pregnancy. Interventions to mitigate postpartum weight gain are needed.

**Keywords.** HIV; women's health; antepartum weight change; postpartum weight; adverse pregnancy outcomes.

Weight gain among people with human immunodeficiency virus (HIV) who initiate antiretroviral therapy (ART) has received significant attention in the era of global scale-up of dolutegravir (DTG), which is included as a component of first-line therapy in global guidelines owing to its efficacy, high barrier to resistance, and excellent safety and tolerability profile [1]. Changes in weight have been marked for women receiving integrase strand transfer inhibitor (INSTI)–based regimens,

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[a]Study group team members are listed in the Acknowledgments.

Correspondence: R. Hoffman, Department of Medicine and Division of Infectious Diseases, University of California, Los Angeles, 10833 Le Conte Ave, Los Angeles, CA 90095 (Rhoffman@mednet.ucla.edu).

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particularly DTG, with greater increases in limb and trunk fat compared with men [2]. Over 96 weeks, treatment-naive South African women gained significantly more weight after starting DTG + emtricitabine (FTC)/tenofovir alafenamide fumarate (TAF) compared with DTG + FTC/tenofovir disoproxil fumarate (TDF). Both DTG-based regimens resulted in more weight gain than efavirenz (EFV)/TDF/FTC [3], with the weight trajectory in the DTG arms continuing to increase over 144 weeks [4]. ART-associated weight gain for women on INSTI-based regimens has consequences for women's health and for pregnancy outcomes among the 1 million women with HIV who conceive every year [5].

Inadequate weight gain during pregnancy increases the risk of preterm delivery, stillbirth, and small size for gestational age (SGA) [6, 7]; preterm birth and SGA are primary risk factors for infant mortality and poor long-term health outcomes globally. In contrast, excessive antepartum weight gain is associated with large size for GA (LGA) and need for operative delivery [6], as well as with gestational diabetes [8] and hypertension [9]. Observational studies in women on INSTI-based regimens demonstrate a reduced risk of adverse pregnancy outcomes relative to women on EFV, with higher antepartum weight gain protective against adverse pregnancy outcomes [10, 11]. The complex interactions between HIV, ART, weight gain, and pregnancy outcomes remain understudied in the era of widespread INSTI use.

We sought to characterize weight changes and adverse pregnancy outcomes by randomized ART regimen in IMPAACT 2010 (VESTED: Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG), a phase III randomized trial comparing the virologic efficacy and safety of 3 ART regimens for cisgender pregnant women with HIV and their infants (NCT03048422): DTG + FTC/TAF versus DTG + FTC/TDF versus EFV/FTC/TDF. Previously published VESTED data showed that DTG-containing regimens initiated in pregnancy were associated with superior virologic suppression at delivery and that DTG + FTC/TAF had the lowest frequency of adverse pregnancy outcomes and EFV/FTC/TDF the highest frequency of neonatal and infant mortality [12]. In this article, we explore the relationship between antepartum weight gain and adverse outcomes, and characterize postpartum weight trajectories.

## METHODS

Women were enrolled in VESTED between 19 January 2018 and 8 February 2019. All primary outcomes have been published, with detailed methods and Consolidated Standards of Reporting Trials (CONSORT) diagrams [12, 13]. Ante- and postpartum weight change and the association between antepartum weight change and adverse pregnancy outcomes were prespecified secondary analyses.

### Study Population and Procedures

Pregnant women aged ≥18 years with confirmed HIV-1 infection were enrolled from 14–28 weeks' gestational age (GA) at 22 sites in Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the United States, and Zimbabwe. Participants were ART naive but could have received up to 14 days of ART during the current pregnancy; prior TDF or TDF/FTC preexposure prophylaxis; or ART during prior pregnancies and breastfeeding.

Baseline data were obtained at study enrollment (which occurred in the second or third trimester). Following randomization, antepartum study visits occurred every 4 weeks, at pregnancy outcome, and at 6, 14, 26, 38, and 50 weeks postpartum. Weight and height were measured at baseline, and weight was measured at every follow-up visit. For exploratory weight analyses, women were asked to report their prepregnancy weight at baseline, if known. Women who had ≥2 measurements for weight in their antepartum period before pregnancy outcome were included in antepartum analyses of change in weight.

### Outcomes and Outcome Definitions

In our main prespecified analysis, we evaluated weight change between enrollment and delivery. These antepartum weight changes were analyzed in 2 ways. First, using low and high weight gain (defined as <0.18 kg/wk and >0.59 kg/wk, respectively, based on Institute of Medicine (IOM) guidelines for weekly weight gain in the second and third trimesters [14]) and second, as average weekly gain in maternal weight. The main outcome was the parent trial's prespecified composite adverse pregnancy outcome: spontaneous abortion (<20 weeks' GA), stillbirth (≥20 weeks' GA), preterm delivery (<37 weeks' GA), or SGA (<10th percentile, adjusted for sex) [15]. Individual components of the composite pregnancy outcome and neonatal death were also analyzed.

Post hoc analyses were performed to evaluate additional adverse pregnancy outcomes, including the following: (1) LGA (>90th percentile); (2) macrosomia (>4000 g); (3) a composite of LGA, macrosomia, or cesarean delivery for any indication; (4) a nonsevere pregnancy outcome, defined as preterm (32 to <37 weeks' GA) or SGA (3rd to <10th percentile); (4) a severe pregnancy outcome, defined as stillbirth, very preterm delivery (<32 weeks' GA), very small size for GA (<3rd percentile), and/or neonatal death; and (5) first grade ≥3 maternal adverse event through pregnancy and up to 14 days postpartum. First occurring maternal adverse events were summarized by MedDRA system organ class and preferred term. Additional post hoc analyses included factors associated with body mass index (BMI) ≥25 to <30 (calculated as weight in kilograms divided by height in meters squared) (overweight category) or ≥30 (obese category) at 50 weeks postpartum; causal mediation analysis of weight change and the composite



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adverse pregnancy outcome. Women's self-reported prepregnancy weight was used for an exploratory analysis of the association of prepregnancy weight and adverse pregnancy outcomes and to describe the frequency of BMI categories comparing prepregnancy and 50 weeks postpartum.

#### Statistical Analysis

By-arm differences in the average weekly change in maternal weight were estimated and tested using generalized estimating equations with an identity link and an exchangeable working correlation matrix. Average weekly weight change was described over the antepartum period (from enrollment through delivery), the postpartum period (from delivery through 50 weeks postpartum), and overall. The change in weight for each time period was summarized within each country and overall. When prepregnancy weight was not available, it was imputed. For estimating weight change over the antepartum period and overall, models were adjusted for a participant's baseline weight as a sensitivity analysis. A sensitivity analysis for estimating differences in antepartum maternal weight change was conducted to account for possible by-arm differences in antepartum follow-up time owing to loss to follow-up, fetal loss, or preterm delivery. Standardized mortality ratio weights were used to standardize the GA distributions in the DTG arms to the observed GA distribution in the EFV/FTC/TDF arm at each study visit during the antepartum period. For the postpartum period, models were adjusted for delivery weight in a sensitivity analysis.

Treatment arm, baseline age, baseline CD4 cell count, baseline weight, ethnicity, change in antepartum weight, and region were explored as factors associated with BMI $\geq$25 to <30 or BMI $\geq$30 at 50 weeks postpartum. Relative risks were estimated using modified Poisson regression with robust variance estimator. Factors were analyzed using separate univariate models and one multivariable model with all factors included. Because antepartum weight change is a potential mediator for postpartum weight, a multivariable model without adjustment for antepartum weight change was also presented. The interactions between treatment arm and potential factors were evaluated using a Wald test.

We fit the Cox proportional hazards model to compare the hazard of adverse pregnancy events and maternal grade $\geq$3 adverse events by IOM weight gain categories (low vs normal and high vs normal). A similar analysis was conducted using weight as a continuous variable (for a 1-unit change in time-varying weekly change in weight) and prepregnancy weight. For preterm deliveries, censoring was applied at the last antepartum visit through 37 weeks' GA or the last antepartum visit before pregnancy outcome, whichever occurred first. Mother-infant pairs were censored at pregnancy outcome or the last antepartum visit for analyses of SGA, LGA, and macrosomia if they did not have a live birth pregnancy outcome or if infant birthweight data were missing. For all outcomes, models were adjusted for baseline GA stratum: 14–18, 19–23, or 24–28 weeks.

For exploratory analyses using prepregnancy weight, multiple imputation was used for missing prepregnancy weights and BMI. The imputation models were fit using linear mixed effect models, with antepartum weight as the dependent variable and GA as a predictor. GA was modeled with random intercepts, random slopes, and polynomial smoothing splines. The level of smoothness was chosen using Bayesian information criteria. The percentage of missing information was calculated [16].

Causal mediation analysis was used to separate the estimated effect of study arm on the risk of the composite pregnancy outcome into 2 effects, one mediated through the change in weight (indirect effect) and the other not mediated through the change in weight (direct effect). A linear regression model estimating the study arm effect on weight change and a logistic regression model estimating the effect of study arm and weight change on adverse pregnancy outcomes were used to estimate total, indirect, and direct effects. The proportion mediated was also estimated, which indicates how much of the by-arm risk difference for having an adverse pregnancy outcome can be explained by the indirect effect of changes in weight. Mediation models were adjusted for baseline variables of GA, BMI, CD4 cell count, country, and age. For all analyses, treatment arm comparisons were performed with the principle of intent to treat.

#### Ethical Considerations and Oversight

The study was approved by institutional review boards at each site. All maternal participants provided written informed consent.

## RESULTS

#### Study Population and Weight Changes by Arm

Baseline characteristics among 643 randomized women are summarized in Table 1, with no major differences between treatment arms. The median (interquartile range) age, GA, and baseline weight were 26.6 (22.5–31.7) years, 21.9 (18.3–25.3) weeks, and 63.0 (56.2–73.0) kg, respectively. A similar proportion of women in each arm had pre-pregnancy BMIs in the normal and overweight categories, but slightly more women in the EFV/FTC/TDF arm were underweight before pregnancy (10.7% vs 7% in each of the DTG arms), and slightly more women in the DTG + FTC/TAF arm were obese before pregnancy (17.7% vs 14.4% in the DTG + FTC/TDF and 12.6% in the EFV/FTC/TDF arm).

The estimated average antepartum weight gain in the second and third trimesters was lower than the recommended IOM standard for average weekly weight gain in pregnancy in all treatment arms; however, participants in the DTG + FTC/TAF arm had higher antepartum weekly weight gain (0.378 kg/wk), which approached the IOM standard of

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**Table 1. Maternal Baseline Characteristics by Arm and Overall**

| Characteristic | Treatment Group, No. (%) of Women[a] | | | |
|---|---|---|---|---|
| | DTG + FTC/TAF (n = 217) | DTG + FTC/TDF (n = 215) | EFV/FTC/TDF (n = 211) | Total (n = 643) |
| Age | | | | |
| Range, y | 18.1–44.5 | 18.1–44.0 | 18.3–42.7 | 18.1–44.5 |
| Median (IQR), y | 26.8 (22.3–31.5) | 26.0 (22.3–31.4) | 26.6 (23.1–32.1) | 26.6 (22.5–31.7) |
| Country | | | | |
| Botswana | 16 (7.4) | 18 (8.4) | 17 (8.1) | 51 (7.9) |
| Brazil | 21 (9.7) | 19 (8.8) | 17 (8.1) | 57 (8.9) |
| India | 2 (0.9) | 1 (0.5) | 0 (0.0) | 3 (0.5) |
| South Africa | 37 (17.1) | 37 (17.2) | 37 (17.5) | 111 (17.3) |
| Tanzania | 15 (6.9) | 13 (6.0) | 15 (7.1) | 43 (6.7) |
| Thailand | 5 (2.3) | 4 (1.9) | 6 (2.8) | 15 (2.3) |
| Uganda | 37 (17.1) | 37 (17.2) | 36 (17.1) | 110 (17.1) |
| United States | 2 (0.9) | 2 (0.9) | 0 (0.0) | 4 (0.6) |
| Zimbabwe | 82 (37.8) | 84 (39.1) | 83 (39.3) | 249 (38.7) |
| Race | | | | |
| Asian | 7 (3.2) | 5 (2.3) | 6 (2.8) | 18 (2.8) |
| Black or African American | 195 (89.9) | 196 (91.2) | 194 (91.9) | 585 (91.0) |
| Other | 10 (4.6) | 6 (2.8) | 4 (1.9) | 20 (3.1) |
| Unknown | 0 (0.0) | 1 (0.5) | 0 (0.0) | 1 (0.2) |
| White | 5 (2.3) | 7 (3.3) | 7 (3.3) | 19 (3.0) |
| Ethnicity | | | | |
| Hispanic or Latina | 21 (9.7) | 21 (9.8) | 17 (8.1) | 59 (9.2) |
| Not Hispanic or Latina | 194 (89.4) | 192 (89.3) | 191 (90.5) | 577 (89.7) |
| Unknown | 2 (0.9) | 2 (0.9) | 3 (1.4) | 7 (1.1) |
| GA, wks[b] | | | | |
| Mean (SD) | 21.6 (4.2) | 21.4 (4.2) | 21.8 (4.2) | 21.6 (4.2) |
| Range | 13.1–28.8 | 13.7–31.3 | 12.4–30.0 | 12.4–31.3 |
| Median (IQR) | 22.1 (18.4–25.0) | 21.3 (18.1–25.1) | 22.1 (18.3–25.4) | 21.9 (18.3–25.3) |
| GA category | | | | |
| 14–18 wks | 58 (26.7) | 64 (29.8) | 59 (28.0) | 181 (28.1) |
| 19–23 wks | 93 (42.9) | 83 (38.6) | 77 (36.5) | 253 (39.3) |
| 24–28 wks | 66 (30.4) | 68 (31.6) | 75 (35.5) | 209 (32.5) |
| Weight, kg | | | | |
| Mean (SD) | 67.7 (15.1) | 66.3 (16.8) | 64.5 (13.3) | 66.2 (15.2) |
| Range | 35.8–124.2 | 44.2–206.3 | 43.9–126.4 | 35.8–206.3 |
| Median (IQR) | 65.0 (56.7–77.1) | 63.0 (56.3–72.0) | 61.4 (55.470.8) | 63.0 (56.2–73.0) |
| Prepregnancy weight recorded | 66 (30.4) | 54 (25.1) | 52 (24.6) | 172 (26.7) |
| Prepregnancy BMI category[c] | | | | |
| Underweight (<18.5) | 7.1 | 7.7 | 10.7 | 8.5 |
| Normal (18.5 to <25) | 53.7 | 53.5 | 53.6 | 53.6 |
| Overweight (25 to <30) | 21.4 | 24.4 | 23.2 | 23.0 |
| Obese (≥30) | 17.7 | 14.4 | 12.6 | 14.9 |
| Hepatitis B status | | | | |
| Missing | 1 | 0 | 2 | 3 |
| Negative | 213 (98.6) | 209 (97.2) | 205 (98.1) | 627 (98.0) |
| Positive | 3 (1.4) | 6 (2.8) | 4 (1.9) | 13 (2.0) |
| WHO clinical stage | | | | |
| 1 | 213 (98.2) | 211 (98.1) | 208 (98.6) | 632 (98.3) |
| 2 | 4 (1.8) | 4 (1.9) | 3 (1.4) | 11 (1.7) |
| $Log_{10}$ HIV-1 RNA, copies/mL | (n = 216) | (n = 215) | (n = 209) | (n = 640) |
| Mean (SD) | 3.0 (1.1) | 2.9 (1.1) | 3.1 (1.0) | 3.0 (1.1) |
| Range | 1.3–5.6 | 1.3–6.1 | 1.3–5.6 | 1.3–6.1 |
| Median (IQR) | 2.9 (2.2–3.8) | 2.9 (2.1–3.6) | 3.1 (2.3–3.7) | 3.0 (2.2–3.7) |

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**Table 1. Continued**

| Characteristic | Treatment Group, No. (%) of Women[a] DTG + FTC/TAF (n = 217) | DTG + FTC/TDF (n = 215) | EFV/FTC/TDF (n = 211) | Total (n = 643) |
|---|---|---|---|---|
| CD4 cell count, cells/μL | (n = 215) | (n = 215) | (n = 208) | (n = 638) |
| Mean (SD) | 491 (233) | 505 (250) | 477 (251) | 491 (244) |
| Range | 51–1492 | 60–1571 | 68–1431 | 51–1571 |
| Median (IQR) | 467 (324–624) | 481 (332–642) | 439 (300–616) | 466 (308–624) |
| CD4 cell count category | | | | |
| Missing | 2 | 0 | 3 | 5 |
| 50–349/μL | 64 (29.8) | 60 (27.9) | 73 (35.1) | 197 (30.9) |
| 350–499/μL | 56 (26.0) | 54 (25.1) | 50 (24.0) | 160 (25.1) |
| 500–750/μL | 68 (31.6) | 67 (31.2) | 59 (28.4) | 194 (30.4) |
| >750/μL | 27 (12.6) | 34 (15.8) | 26 (12.5) | 87 (13.6) |

Abbreviations: BMI, body mass index; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; GA, gestational age; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization.

[a]Data represent no. (%) of women unless otherwise specified.

[b]Sites used the best available method to determine whether a woman met the inclusion criteria for gestational age (GA) at entry. The GA reported above was recalculated based on the American College of Obstetricians and Gynecologists algorithm [17], which uses information from ultrasonography and the last menstrual period. Ultrasounds were permitted to be performed up to 14 days after randomization.

[c]BMI was calculated as weight in kilograms divided by height in meters squared. Prepregnancy BMI was imputed for 73% of participants for whom prepregnancy weights were not available. Imputed values were used to estimate the percentage of participants in each BMI category.

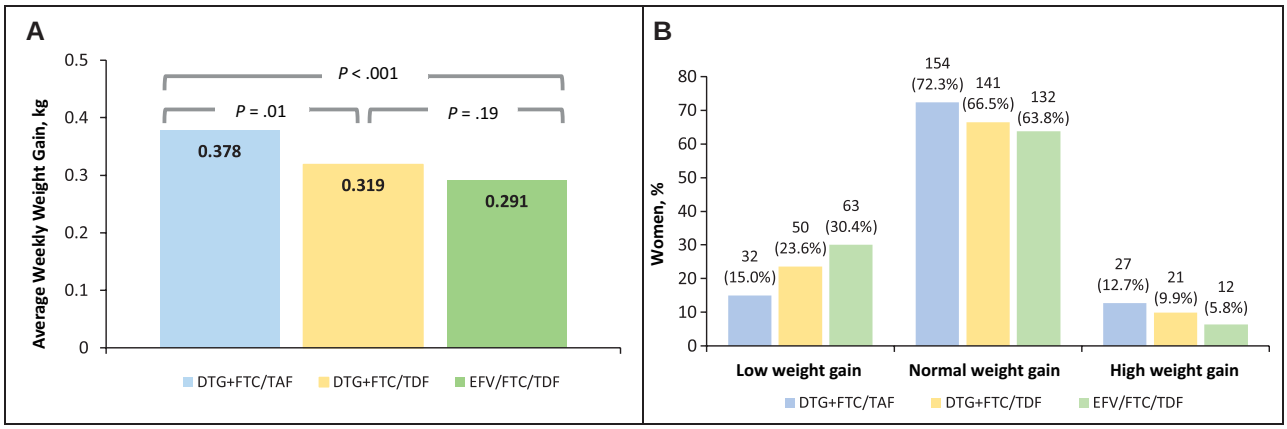



**Figure 1.** Weight changes antepartum. *A,* Average weekly rate of change antepartum relative to Institute of Medicine (IOM) standard. *B,* Low, normal, and high weight gain based on IOM definitions by treatment arm. Abbreviations: DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

0.42 kg/wk, compared with the DTG + FTC/TDF arm (0.319 kg/wk; difference, 0.058 [95% confidence interval (CI), .013–.102 kg/wk]) and the EFV/FTC/TDF arm (0.291 kg; difference, 0.086 [95% CI, .40–.132 kg/wk]) (Figure 1*A*). After standardizing for GA, the results were similar. There was marked variability between mean weight gain within country and treatment arm, but comparisons were limited by small sample size (Supplementary Table 1).

Low weight gain (0.18 kg/wk) was observed in 15.0% (95% CI, 10.2%–19.8%) of women in the DTG + FTC/TAF, 23.6% (17.9%–29.3%) in the DTG + FTC/TDF, and 30.0% (24.2%–36.7%) in the EFV/FTC/TDF arm. The opposite pattern was seen for high weight gain (>0.59 kg/wk), which was observed in 12.7% (95% CI, 8.2%–17.1%) of women in the DTG + FTC/TAF arm, 9.9% (5.9%–13.9%) in the DTG + FTC/TDF arm, and 5.8% (2.6%–9.0%) in the EFV/FTC/TDF arm (Figure 1*B*).

More women in the DTG + FTC/TAF arm had BMI in the overweight or obese category at 50 weeks postpartum (55%), relative to the DTG + FTC/TDF (45%) and EFV/FTC/TDF (34%) arms, with a more marked shift into BMI ≥25 among women in the DTG + FTC/TAF arm and minimal change



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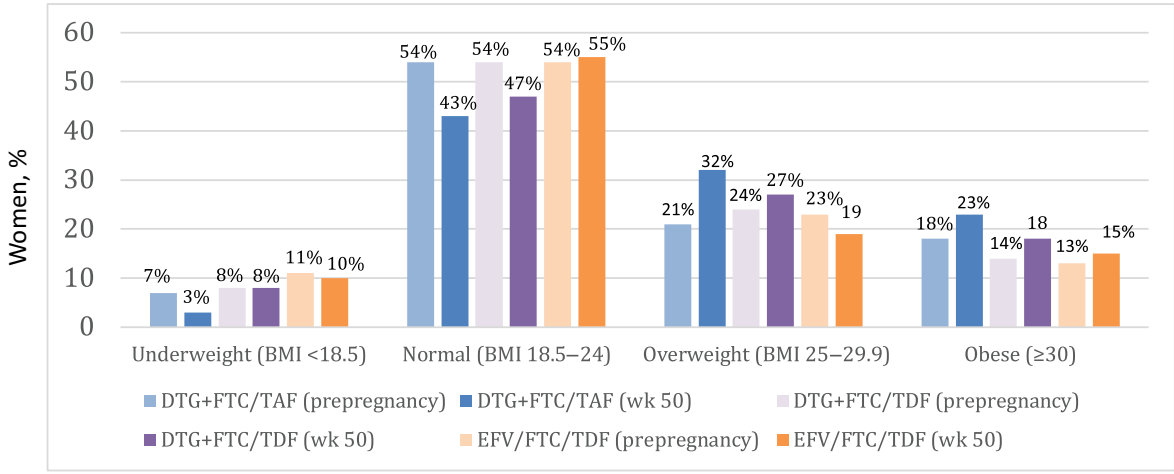



**Figure 2.** Body mass index (BMI) from before pregnancy to 50 weeks postpartum by study arm (BMI calculated as weight in kilograms divided by height in meters). Note that prepregnancy BMI was imputed for 73% of participants when prepregnancy weight data were not available. Abbreviations: DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

**Table 2. Predictors of Being Overweight or Obese at 50 Weeks Postpartum**

| | Unadjusted RR | | | Adjusted RR | | Adjusted RR Without Antepartum Weight Change | |
|---|---|---|---|---|---|---|---|
| Variable[a] | Estimate (95% CI) | *P* Value | Interaction With Arm *P* Value | Estimate (95% CI) | *P* Value | Estimate (95% CI) | *P* Value |
| DTG + FTC/TAF vs DTG + FTC/TDF | 1.21 (.99–1.48) | .07 | … | 1.08 (.90–1.29) | .43 | 1.09 (.91–1.31) | .32 |
| DTG + FTC/TDF vs EFV/FTC/TDF | 1.32 (1.03–1.70) | .03 | … | 1.31 (1.04–1.65) | .02 | 1.33 (1.05–1.67) | .02 |
| DTG + FTC/TAF vs EFV/FTC/TDF | 1.60 (1.27–2.02) | <.001 | … | 1.42 (1.15–1.77) | .001 | 1.46 (1.18–1.81) | <.001 |
| Age (y) | 1.04 (1.02–1.05) | <.001 | .42 | 1.02 (1.00–1.03) | .02 | 1.01 (1.00–1.03) | .051 |
| Rate of antepartum weight gain (kg/wk) | 1.09 (.70–1.69) | .70 | .85 | 1.54 (1.03–2.31) | .04 | … | |
| Baseline weight (kg) | 1.04 (1.03–1.04) | <.001 | .09 | 1.04 (1.03–1.04) | <.001 | 1.04 (1.03–1.04) | <.001 |
| Baseline CD4 cell count, (cells/μL) | 1.00 (1.00–1.00) | .92 | .26 | 1.00 (1.00–1.00) | .47 | 1.00 (1.00–1.00) | .33 |
| Hispanic/Latina vs not Hispanic/Latina | 1.73 (1.43–2.11) | <.001 | .90 | 2.19 (1.21–3.96) | .01 | 2.15 (1.43–3.23) | <.001 |
| Race | … | | .99 | … | | … | |
| Asian vs black or African American | 0.93 (.50–1.74) | .82 | | 9.50 (2.64–34.11) | <.001 | 1.34 (.75–2.38) | .32 |
| White vs black or African American | 1.45 (.98–2.15) | .06 | | 0.93 (.53–1.63) | .81 | 0.83 (.51–1.33) | .44 |
| Other vs black or African American | 1.71 (1.28–2.28) | <.001 | | 0.88 (.50–1.57) | .68 | 0.85 (.49–1.50) | .58 |
| Region | … | | .84 | … | | … | |
| Americas vs Africa | 1.74 (1.44–2.11) | <.001 | | 0.53 (.25–1.11) | .09 | 0.50 (.28–.90) | .02 |
| Asia vs Africa | 0.96 (.51–1.80) | .89 | | 1.42 (.78–2.57) | .25 | 1.42 (.78–2.57) | .25 |

Abbreviations: CI, confidence interval; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; RR, risk ratio; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

[a]Categorical variables are presented with the group of interest on the left and the reference group on the right (eg, Africa is the reference group for regional comparisons).

over follow-up in the EFV/FTC/TDF arm (Figure 2). The risk of BMI ≥25 (obese or overweight categories) at 50 weeks after pregnancy was higher in the DTG + FTC/TAF than in the EFV/FTC/TDF arm (risk ratio, 1.60 [95% CI, 1.27–2.02]) and in the DTG + FTC/TDF than the EFV/FTC/TDF arm (1.32 [1.03–1.70]). Older age (RR, 1.04), Hispanic/Latina ethnicity (1.73), and higher baseline weight (1.04) were associated with a higher risk of BMI ≥25 at 50 weeks postpartum (Table 2).

### Association of IOM Antepartum Weight Change Category and Adverse Pregnancy Outcomes and Adverse Events

Overall, 111 mother-infant pairs (18%) experienced a nonsevere adverse pregnancy outcome (preterm [32 to <37 weeks' GA] or SGA [3rd to <10th percentile]), and 12% (n = 78) experienced a severe pregnancy outcome (spontaneous abortion, stillbirth, very preterm [<32 weeks' GA], very small for GA [<3rd percentile], or neonatal death). Among women with low antepartum weight gain, 17% (n = 25) had a severe



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pregnancy outcome, compared with 11% (n = 47) with normal and 10% (n = 6) with high weight gain (Table 3).

Across all treatment arms, low weight gain was associated with an increased hazard of the composite adverse pregnancy outcome (hazard ratio [HR], 1.44 [95% CI, 1.04–2.00]) with a trend toward an association with a severe adverse pregnancy outcome (1.58 [.97–2.57]) and with SGA alone (1.48 [.99–2.22]) (Figure 3*A*). When comparing high with normal average weekly antepartum weight gain, there were no clear associations with adverse pregnancy outcomes, including macrosomia, cesarean delivery, and LGA (Figure 3*B*). For 21 women with high antepartum weight gain who delivered by cesarean, 3 (14%) had the procedure because of preeclampsia or eclampsia and 2 (10%) because of suspected macrosomia. There were 14 neonatal deaths, with no observed associations between neonatal deaths and high or low weight gain categories.

In the by-arm analysis of weight gain by IOM category, low weight gain on DTG + FTC/TAF was associated with a higher hazard of the composite adverse pregnancy outcome (HR, 2.69 [95% CI, 1.39–5.21]), with a similar trend for EFV/TDF/FTC, which did not reach statistical significance (Figure 3*C*). There were no clear associations between high weight gain and arm (Figure 3*D*).

Of 632 women, 143 experienced at least one grade ≥3 adverse event through 14 days postpartum. The most common first occurrences of these adverse events were a decrease in hemoglobin (in 30 women), hypertensive disorders (in 24 women; including chronic hypertension, gestational hypertension, preeclampsia, and eclampsia), and infections (in 12 women). Detailed grade ≥3 adverse events are described in Supplementary Table 2. Women with low compared with normal weight gain were more likely to have a grade ≥3 adverse event (39 of 145 vs 87 of 427 women, respectively; HR 1.43 [95% CI, .98–2.10]). There was variability in the association by treatment arm, with low versus normal weight gain on DTG + FTC/TAF (Figure 4*A*) and high versus normal weight gain on EFV/FTC/TDF showing stronger associations with a grade ≥3 event (HRs, 2.54 [95% CI, 1.21–5.32] and 3.89 [1.62–9.32], respectively) (Figure 4*B*).

### Association of Continuous Weekly Antepartum Weight Change and Adverse Pregnancy Outcomes

Across all treatment arms, higher weekly antepartum weight gain was associated with a 66% reduction in the risk of SGA (HR, 0.34 [95% CI .15–.80]), a 59% reduction in the risk of the composite adverse pregnancy outcome (0.41 [.21–.81]), and a 68% reduction in the risk of a severe pregnancy outcome (0.32 [.12–.86]). In the DTG + FTC/TAF arm, higher weekly antepartum weight gain was associated with lower hazards of preterm delivery (HR, 0.02 [95% CI, .00–.24]) and of the composite adverse pregnancy outcome (0.09 [.02–.36]) and stillbirths (0.02 [.00–.085]) (Supplementary Table 3). Higher

**Table 3. Pregnancy Outcomes Overall and by Treatment Arm Based on Institute of Medicine Weight Categories**

| Adverse Pregnancy Outcome[a] | Women by Weight Gain Category, No. (%) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Low Weight Gain | | | | Normal Weight Gain | | | | High Weight Gain | | | | Total | | |
| | DTG + FTC/ TAF | DTG + FTC/ TDF | EFV/ FTC/ TDF | All Arms | DTG + FTC/ TAF | DTG + FTC/ TDF | EFV/ FTC/ TDF | All Arms | DTG + FTC/ TAF | DTG + FTC/ TDF | EFV/ FTC/ TDF | All Arms | DTG + FTC/ TAF | DTG + FTC/ TDF | EFV/ FTC/ TDF | All Arms |
| Severe | 7 (22) | 8 (16) | 10 (16) | 25 (17) | 10 (7) | 20 (14) | 17 (13) | 47 (11) | 2 (7) | 3 (15) | 1 (8) | 6 (10) | 19 (9) | 31 (15) | 28 (14) | 78 (12) |
| Nonsevere | 6 (19) | 9 (18) | 17 (27) | 32 (22) | 23 (15) | 27 (19) | 22 (17) | 72 (17) | 2 (7) | 2 (10) | 3 (25) | 7 (12) | 31 (15) | 38 (18) | 42 (20) | 111 (18) |
| No adverse outcome | 19 (59) | 32 (65) | 36 (57) | 87 (60) | 120 (78) | 94 (67) | 93 (70) | 307 (72) | 23 (85) | 15 (75) | 8 (67) | 46 (78) | 162 (76) | 141 (67) | 137 (66) | 440 (70) |
| **Total** | **32 (100)** | **49 (100)** | **63 (100)** | **144 (100)** | **153 (100)** | **141 (100)** | **132 (100)** | **426 (100)** | **27 (100)** | **20 (100)** | **12 (100)** | **59 (100)** | **212 (100)** | **210 (100)** | **207 (100)** | **629 (100)** |

Abbreviations: DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

[a]Severe pregnancy outcomes included spontaneous abortion, stillbirth, very preterm delivery (<32 weeks' gestational age [GA]), very small size for GA (<3rd percentile), and neonatal death; nonsevere pregnancy outcomes, preterm delivery (32 to <37 weeks' GA) ad small size for GA (3rd to <10th percentile).



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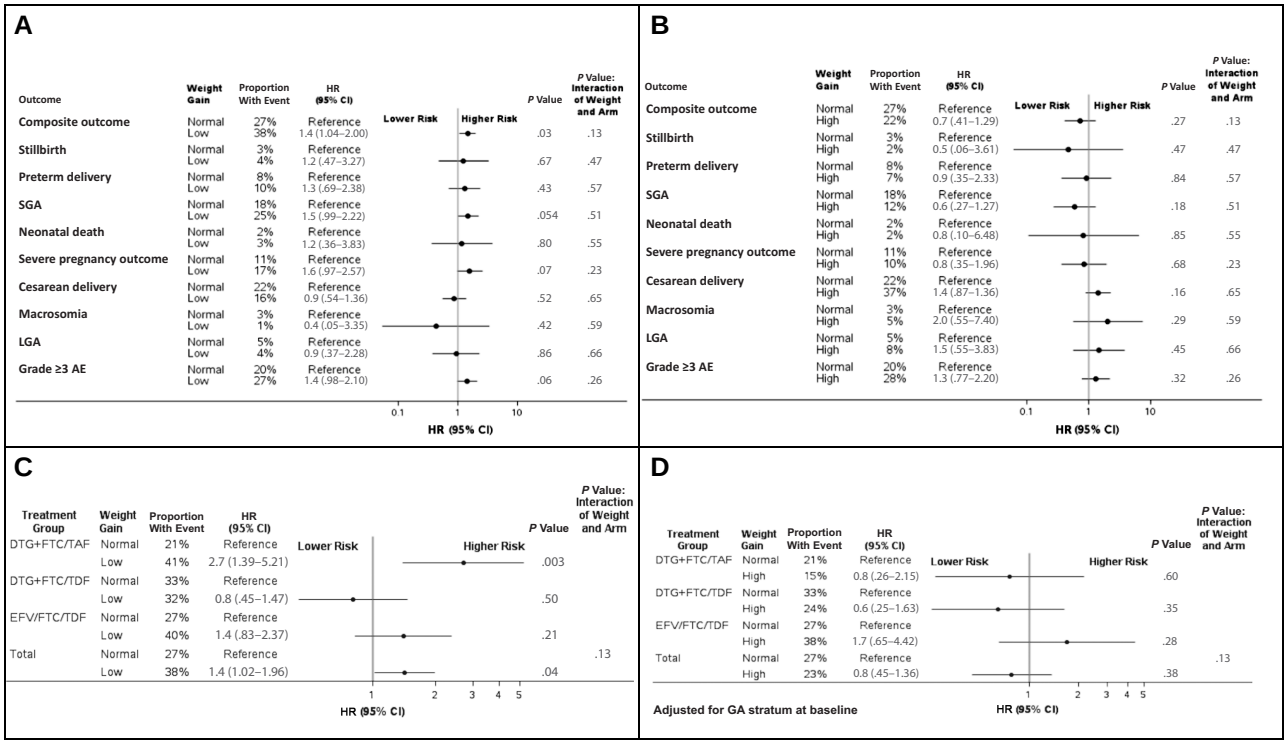



**Figure 3.** Associations between adverse pregnancy outcomes and Institute of Medicine weight gain categories. *A,* Low versus normal weight gain. *B.* High versus normal weight gain. *C,* Low versus normal weight gain by arm for the composite adverse pregnancy outcome. *D,* High versus normal weight gain by arm for the composite adverse pregnancy outcome. Models were adjusted for gestational age (GA) stratum at baseline. Abbreviations: AE, adverse event; CI, confidence interval; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; HR, hazard ratio; LGA, large size for GA; SGA, small size for GA; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

weekly antepartum weight gain was associated with a 30-fold increase in the hazard of macrosomia (HR, 30.6 [95% CI, 2.2–420]), although the CI was wide owing to the low number of events (occurring in 15 infants).

### Prepregnancy Weight and Adverse Pregnancy Outcomes

For the exploratory analysis of prepregnancy weight, retrospectively collected data were available for 27% of women and imputed for 73%. Since prepregnancy weight was strongly associated with weight at study entry, the percentage of missing information using the imputation model to assess the relationship between the pregnancy outcomes and prepregnancy weight was low and ranged from 0.12% to 1.18%. For every 10-kg increase in prepregnancy weight, the hazard of SGA was reduced (HR, 0.86 [95% CI, .76–.98]), while there was a trend toward a higher hazard of macrosomia, LGA, and cesarean delivery (Supplementary Table 4). Higher prepregnancy weight was associated with having a grade ≥3 adverse event (HR, 1.09 [95% CI, 1.00–1.18]).

### Causal Mediation Analysis

In causal mediation analysis, the percentage of the risk difference of adverse pregnancy outcome mediated by weight change was 31% for DTG + FTC /TAF versus EFV/FTC/TDF and 11% for DTG + FTC/TAF versus DTG + FTC/TDF. These results did not differ after adjustment for baseline GA, BMI, CD4 cell count, country, and age, and they suggest that up to one-third of observed differences in adverse pregnancy outcomes between randomized arms are mediated by ART-related weight change, with other factors accounting for the remainder of the effect (Supplementary Figure 1).

## DISCUSSION

In this randomized clinical trial of women with HIV starting ART in pregnancy, we found that insufficient weight gain during the second and third trimesters of pregnancy occurred in all treatment arms. However, greater weight gain was seen with DTG-based ART, in particular if combined with TAF/FTC. Furthermore, greater pregnancy weight gain was associated with a reduction in the hazard of adverse pregnancy outcomes typically associated with insufficient weight gain, including SGA, preterm delivery, and stillbirth.

The relationship between insufficient antepartum weight gain and adverse pregnancy outcomes is well established in women both with [10, 11] and without [6, 7, 18] HIV. Much of the HIV-related data have been collected from women receiving what was previously first-line ART with EFV/TDF



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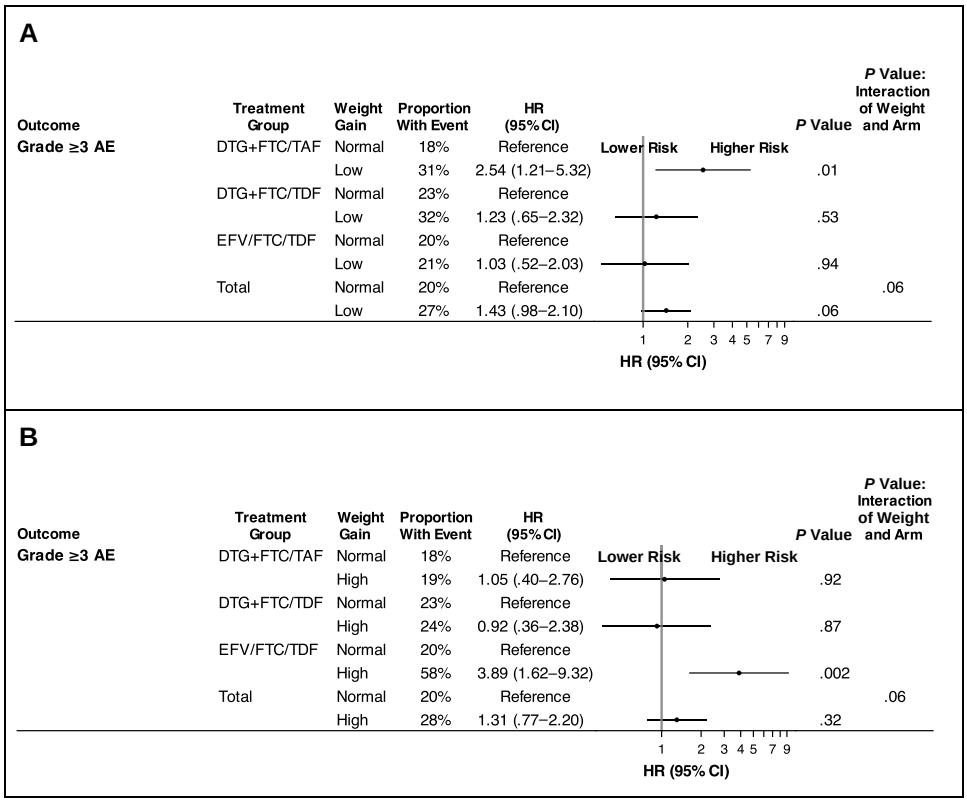



**Figure 4.** Associations between Institute of Medicine weight category and a maternal grade ≥3 adverse event (AE) overall and by arm, adjusted for baseline gestational age category. *A,* Low versus normal weight gain. *B,* High versus normal weight gain. Abbreviations: CI, confidence interval; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; HR, hazard ratio; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

(with FTC or lamivudine [3TC]), a regimen now known to have a weight-suppressive effect [19–21]. As global first-line ART shifts to DTG-based therapy, our study results have particular relevance for women with HIV of childbearing potential. Women in our study in the DTG + FTC/TAF arm achieved antepartum weight gain that approached (though was still lower than) IOM-recommended normal weekly weight gain, and they experienced the lowest rate of adverse pregnancy outcomes. Although weight gain with INSTI regimens has raised concern with regard to exacerbating an already significant global obesity epidemic [22–24], our data counter the dogma that INSTI-associated weight gain has only negative health effects. Our data are consistent with other recent observational studies comparing EFV and INSTI-based regimens in pregnancy showing that EFV versus DTG was associated with more insufficient antepartum weight gain in Botswana [25] and retrospective data from women initiating either raltegravir or EFV in pregnancy, in which women on raltegravir gained more weight and were less likely to have adverse pregnancy outcomes [10].

In our study population, higher weekly antepartum weight gain was associated with macrosomia. A study from Botswana among women conceiving on either EFV or DTG found that having a first pregnancy weight >90 kg (at a visit before 24 weeks' GA) was associated with a higher risk of macrosomia (adjusted risk ratio, 3.24 [95% CI, 2.36–4.44]) and hypertension (1.79 [1.62–1.97]) [11]. In this Botswana study, the risk of hypertension by weight strata was higher for women on DTG, an observation seen in people with HIV who are not pregnant [26]. At least one other study identified an association between INSTI regimens and hypertensive disorders in pregnancy [27], suggesting this is an important area for further study.

Of note, while EFV-based regimens have been largely phased out globally, high antepartum weight gain with EFV in our study was associated with adverse pregnancy outcomes, as well as with a higher rate of grade ≥3 adverse events, while low weight gain on DTG regimens was associated with grade ≥3 adverse events. These finding underscore the complexity of the interaction between HIV, ART regimen, baseline weight, weight change, and other factors that may influence pregnancy outcomes. This is reflected in our mediation analysis, in which up to one-third of the observed differences in the composite pregnancy outcome between randomized arms was attributed to antepartum weight gain. While this degree of contribution from weight is important, there remain significant gaps in our understanding of the mechanisms by which different ART regimens influence pregnancy outcomes [28].



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While both DTG-containing regimens were associated with improved antepartum weight gain and reduced risk for adverse pregnancy outcomes, more women on these regimens had BMIs in the overweight or obese category at 50 weeks postpartum, and this represented a shift from baseline, particularly for women on DTG/TAF/FTC. Similar data have been reported from DolPHIN-2, a randomized trial of DTG- versus EFV-containing regimens initiated late in pregnancy in South Africa and Uganda, in which women on DTG-based ART retained more weight through 72 weeks postpartum [29]. In DolPHIN-2, weight changes were more marked in South African women, suggesting regional variation in weight gain patterns. Outside of pregnancy and postpartum, weight gain among women has been consistently noted with the initiation of DTG- relative to EFV-containing regimens, including from Cameroon [30] and South Africa [4], and a recent study from South Africa demonstrated modest weight loss in people who switched from DTG/FTC/TAF to DTG/FTC/TDF [31]. Research suggests that EFV and TDF are weight suppressive in certain individuals, and this may contribute to the perception that INSTI and TAF are significantly obesogenic—although mechanisms of weight changes remain unclear and are likely to be multifactorial [32]. An in vitro study showed that DTG disrupts estrogen-mediated fat differentiation, providing one potential mechanism for greater ART-related weight gain in women than men [33]. More research is needed on the differential effects of INSTI-related weight gain in women, with representation from diverse populations to reflect the variability seen by race/ethnicity and region.

Taken together, our data portray a complex picture of weight gain. Increased antepartum weight gain on DTG regimens was protective for adverse pregnancy outcomes that are known to be associated with insufficient weight gain and are supportive of guidelines that recommend DTG-based ART for women starting ART during pregnancy. However, given that more women on the DTG regimens had BMIs in the overweight or obese categories approximately 1 year postpartum (representing a shift from prepregnancy category) and given the known association between prepregnancy weight and pregnancy outcomes [11] (replicated in our study), this pattern may ultimately be associated with adverse outcomes over time. Women with high BMI at conception are at risk of having LGA or macrosomic infants, gestational diabetes, or hypertensive disorders of pregnancy [34], and at least one risk prediction model showed excess risk of adverse pregnancy outcomes with DTG-based regimens, including gestational hypertension, with the excess risk most marked for DTG + FTC/TAF [35]. In the setting of high fertility rates in many high HIV prevalence regions (4.7 in sub-Saharan Africa [36]), pregnancy planning and preconception counseling can play an important role optimizing maternal weight between pregnancies, to improve both maternal and infant health outcomes. Future research should seek to understand weight change over recurrent pregnancies among women on DTG and DTG/TAF-containing regimens.

Important strengths of our study include randomization and enrollment from diverse global settings. However, the small number of adverse pregnancy events limited our exploration of antepartum weight change with individual components of the composite adverse pregnancy outcome endpoint as well as our precision in estimating the association of weight gain with adverse pregnancy outcomes by ART regimen. Prepregnancy weight was not available for many women, resulting in the need for imputation for weight and BMI categories, which could overestimate or underestimate our findings.

In conclusion, DTG-containing ART initiated in pregnancy resulted in healthier antepartum weight gain, with the lowest rates of adverse pregnancy outcomes in the DTG + FTC/TAF arm. More women in the DTG arms (particularly those on DTG/TAF but also those on DTG/TDF) had BMI ≥25 at 50 weeks postpartum, and the importance of prepregnancy BMI as a predictor of pregnancy outcomes raises important questions about how to balance benefits of antepartum weight gain with risks of excess weight gain over time in women of childbearing age, particularly in settings with high fertility rates. Given the importance of DTG-based ART as a well-tolerated and highly effective regimen globally, a focus on healthy body weight, particularly before conception, may help optimize outcomes over recurrent pregnancies as well as health over a woman's life span.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

***Author Contributions.*** Development of statistical analysis plan and analyses: R. M. H., S. B., L. Z., and S. H. Primary drafting of manuscript: R. M. H., and S. L. Editing of manuscript: S. B., L. Z., L. C., L. F., T. G. N., F. N., V. N., S. H., G. T., A. V., E. J., M. D. C., C. B. H., O. N., L. A., N. N., R. Z., R. S., J. S. A. S., J. S. C., and P. S. Direct support of research protocol implementation: L. C., K. M., L. F., P. J. P., N. C., T. G. N., F. N., V. N., S. H., G. T., A. V., E. J., C. B. H., O. N., L. A., N. N., J. S. A. S., and J. S. C. Data management and review of manuscript: B. J. and C. K.

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E. Murray, MD, Stuart Campbell Ray, MD, Haroon Saloojee, MBBCh, FCPaed, MSc, Anastasios A. Tsiatis, PhD, Paul A. Volberding, MD, David Glidden, PhD, and Valeria Cavalcanti Rolla, MD, PhD); the Safety Review Group members (N. C., Jeanna Piper, MD, Karin Klingman, MD, Debika Bhattacharya, MD, P. J. P., Lynne Mofenson, MD, S. B., L. Z., B. J., and C. K.); IMPAACT 2010 team members, in addition to coauthors (Scott McCallister, MD, Jean van Wyk, MBChB, MFPM, Mark Mirochnick, MD, Brookie Best, PhD, Kevin Robertson, PhD, Cheryl Blanchette, BS, Nagawa Jaliaah, Andi Fox, MPH, Frances Whalen, Kevin Knowles, and William Murtaugh, MPH); Mauricio Pinilla, MS; Yao Cheng, PhD; and Emmanuel Patras. The authors also acknowledge and thank Jim Rooney and Rich Clark from Gilead Sciences and Scott McCallister and Jean van Wyck from ViiV Heathcare.

***Additional study team members.*** IMPAACT Operations Center at FHI 360: Anne Coletti, MS; Division of AIDS, National Institutes of Health (NIH): Lynette Purdue, PharmD; University of Washington: Lisa Frenkel, MD; University of Michigan: K. Rivet Amico, PhD; Massachusetts General Hospital: Lewis Ball Holmes, MD; Botswana Harvard AIDS Institute: Gaerolwe Masheto, MD, and Sikhulile Moyo, MSc, MPH; University of California San Diego: Jeremiah Momper, PharmD; University of Zimbabwe College of Health Sciences Clinical Trials Unit: Lynda Stranix-Chibanda; Data Management Center at Frontier Science Foundation: Kevin Knowles, PhD; and Laboratory Center at UCLA: William Murtaugh, MPH, and Frances Whalen, MPH.

***Participating sites.*** **Botswana:** Botswana Harvard AIDS Institute Partnership, Gaborone and Molepolole—Ponego L. Ponatshego, MD, DTMH, Lesedi Tirelo, Dip Nursing, Boitshepo J. Seme, Dip Nursing, Georginah O. Modise, Dip Nursing, Mpho S. Raesi, BSN, PGDip HIV/AIDS Management, Marian E. Budu, MBBS, and Moakanyi Ramogodiri, Dip Nursing. **Brazil:** Instituto de Puericultura e Pediatria Martagão Gesteira, UFRJ, Rio de Janeiro—Ricardo Hugo Oliveira, MD, Mac, Thalita Fernandes de Abreu, MD, PhD, and Lorena Macedo Pestanha, MD; Hospital Federal dos Servidores do Estado, Rio de Janeiro—Leon Claude Sidi, MD, Trevon Fuller, PhD, and Maria Leticia Santos Cruz, PhD; Federal University of Minas Gerais—Jorge Pinto, MD, Flávia Ferreira, MD, M. D. C., and Juliana Romeiro, PhD; Hospital Geral de Nova Iguacu and AIDS and Molecular Immunology Laboratory/IOC—Jose Henrique Pilotto, MD, PhD, Luis Eduardo Barros Costa Fernandes, MD, MSc, Luiz Felipe Moreira, MD, and Ivete Martins Gomes, MD, MSc. **India:** Byramjee Jeejeebhoy Medical College CRS, Pune—Shilpa Naik, MD, Vidya Mave, MD, and Aarti Kinikar, MD. **South Africa:** Shandukani Research Centre, Wits Reproductive Health and HIV Institute, Johannesburg—Lee Fairlie, MBCHB (UCT), DCH (UK), FC Peads (Wits), Mmed (Wits), Elizea Horne, MBCHB(Pret), Faeezah Patel, MBBCh (Wits), and Hamisha Soma-Kasiram, MBBCh (Wits), B Pharm; Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg—Haseena Cassim, MBChB, Sisinyana Ruth Mathiba, MBChB, and Mandisa Nyati, MBChB; FAMCRU, Cape Town—Jeanne de Jager, MSc, Magdel Rossouw, MBChB, and Lindie Rossouw, MBChB; CAPRISA Umlazi CRS, University of Kwazulu Natal, Durban—Alicia Catherine Desmond, Mpharm, Rosemary Gazu, Dip Nursing, and Vani Govender, BSC Hon. **Thailand:** Siriraj Hospital, Mahidol University, Bangkok—Amphan Chalermchockcharoenkit, MD, Manopchai Thamkhantho, MD, Peerawong Werarak, MD, and Supattra Rungmaitree, MD; Chiangrai Prachanukroh Hospital, Chiangrai—Jullapong Achalapong, MD, and Lukkana Sitiritkawin, BSN; AMS-CMU & IRD Research Collaboration, Chiangrai—Tim R. Cressey, PhD, and Pra-ornsuda Sukrakanchana, BSN; Research Institute for Health Sciences, Chiang Mai University—Fuanglada Tongprasert, MD, Chintana Khamrong, MSc, and Sopida Kiattivej, BNS, RN. **Uganda:** Mujhu Care Ltd, Kampala—Deo Wabwire, MMED, Enid Kabugo, MSC, and Joel Maena, MPH; Baylor College of Medicine Children's Foundation–Uganda, Kampala—Beatrice Nagaddya, Dip Nus Mid, Rogers Sekabira, MPS, and Justus Ashaba, BCS. **United States:** University of Miami, Miami, Florida—Charles D. Mitchell, MD, Adriana Drada, CCRP, Grace A. Alvarez, MPH, and Gwendolyn B. Scott, MD; UF CARES, Jacksonville, Florida—Mobeen Rathore, MD, Saniyyah Mahmoudi, MSN, ARNP, Adnan Shabbir, BS, and Nizar Maraqa, MD. **Zimbabwe:** University of Zimbabwe Clinical Trials Research Centre, Harare—St Mary's—Patricia Fadzayi Mandima, MPH, Mercy Mutambanengwe, Bpharm Hons, Suzen Maonera, MSc, Nursing Science, and Gift Chareka, MSc, Clinical Trials; Seke North—Vongai Chanaiwa, Bpharm Hons, MSc Clin Epi, Taguma Allen Matubu, PhD, and Kevin Tamirepi, Bpharm Hons; Harare Family Care—Sukunena Maturure, DCN, Tsungai Mhembere, MPH, Tichaona Vhembo, MPH, and Tinashe Chidemo, MBA.

***Data availability.*** Data are not publicly available.

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