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Gestational diabetes in women living with HIV in Botswana: Lower rates with dolutegravir- than efavirenz-based antiretroviral therapy

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Abstract

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AUTHOR CONTRIBUTIONS

JJ and KP conceptualized the study. KM wrote the first draft of the manuscript. JJ and SS analyzed the data, and JL was involved in data manipulation and data analysis. SS made edits to the Methods. JJ made significant edits to the Results and Discussion. KM finalized the manuscript. KP, SS, JM, MM, SK, GM, SM, MG, TM, JL, EJA, IJK, MEG and JJ all reviewed the manuscript and revisions.

DECLARATION OF INTERESTS

The authors have no financial disclosures to report.

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Background: Little data exist on the prevalence of gestational diabetes (GDM) in pregnant women living with HIV (WLHIV) in sub-Saharan Africa, particularly those using integrase strand transfer inhibitors such as dolutegravir (DTG).

Methods: We prospectively enrolled pregnant WLHIV and pregnant women without HIV ≥18 years in Gaborone, Botswana, excluding those with pre-existing diabetes. We screened for GDM using a 75-g Oral Glucose Tolerance Test (OGTT) performed at 24–28 weeks gestation or at the earliest prenatal visit for those presenting after 28 weeks. Logistic regression models were fit to assess the association between maternal HIV infection and GDM. Subgroup analyses were performed among WLHIV to assess the association between maternal antiretroviral therapy (ART) in pregnancy [DTG vs. efavirenz (EFV) with tenofovir/emtricitabine] and GDM.

Results: Of 486 pregnant women, 66.5% were WLHIV. WLHIV were older than women without HIV (median age 30 vs 25 years, $p<0.01$). Among WLHIV, 97.8% had an HIV-1 RNA level <400 copies/mL at enrollment. Overall, 8.4% had GDM with rates similar between WLHIV and those without HIV (9.0% vs. 7.4%). WLHIV receiving DTG-based ART had a 60% lower risk for GDM compared to those on EFV-based ART (aOR=0.40, 95% CI=0.18, 0.92) after adjusting for confounders.

Conclusions: Pregnant WLHIV on ART in Botswana were not at increased risk for GDM compared to women without HIV. Among WLHIV, risk of GDM was lower with DTG- vs EFV-based ART. Further studies with larger cohorts are warranted to confirm these findings.

Keywords

Gestational diabetes; HIV; Dolutegravir; Efavirenz; Africa

INTRODUCTION

Gestational diabetes (GDM) is associated with future maternal risk for insulin resistance, Type 2 diabetes, and cardiovascular disease as well as obesity and insulin resistance in their offspring (1–5). The worldwide prevalence of GDM is estimated to be 1–28% depending on assessment methods (6). The prevalence is reported to be 4.6–9.2% in the United States and 3.8–7.8% in Europe (7, 8). Few studies have assessed the prevalence of GDM in Africa, where HIV prevalence is also high. In countries such as Botswana, approximately 25% of pregnant women are living with HIV, and overall rates of GDM have not been well studied (9).

Some smaller studies in Africa have shown no difference in rates of GDM between WLHIV and women without HIV, but few have evaluated GDM as optimized antiretroviral drugs (ARVs) are introduced in Africa (10, 11). While ARVs, in particular protease inhibitors (PIs), have been associated with adverse metabolic effects, studies have not been entirely consistent in demonstrating whether a particular ARV is associated with GDM. A recent meta-analysis concluded that the risk of GDM was increased with use of first-generation PIs compared to no PI use (12), while a study conducted in Spain reported a positive association between PI use and GDM (13).

In sub-Saharan Africa, the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs) (EFV in the last 5 years) during pregnancy has been the mainstay of first-line ART for adults living with HIV, including pregnant WLHIV. In 2016, Botswana's national guidelines recommended dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), plus a tenofovir and emtricitabine backbone, as the preferred regimen for first-line ART for adults and pregnant WLHIV.(14) The World Health Organization followed suit in 2019 (15), and today DTG use is expanding globally in non-pregnant and pregnant individuals. There are, however, reports of hyperglycemia with dolutegravir use in non-pregnant adults (16) as well as concerns around gestational and postpartum weight gain in WLHIV (17–20). No studies have been published evaluating the prevalence of GDM in Botswana or in WLHIV on DTG-based ART in general. In this study, we assessed the association of maternal HIV infection with GDM and, among WLHIV, whether DTG-based ART compared to efavirenz (EFV)-based ART with similar ART backbones was associated with GDM in Botswana.

METHODS

Study Population

The Tshilo Dikotla Study is a prospective cohort examining metabolic outcomes of *in utero* HIV/ARV exposure. Pregnant WLHIV and pregnant women without HIV ≥18 years of age were enrolled between 16 – 36 weeks gestational age (GA) from antenatal clinics in Gaborone, Botswana between August 2016 and May 2019. In June 2016, Botswana National HIV Clinical Care guidelines recommended DTG be part of 1st-line ART in all adults living with HIV, including pregnant women (14). Hence, the Tshilo Dikotla study protocol required that all enrolled pregnant WLHIV should be receiving an ART regimen of DTG or EFV, with a backbone of tenofovir and emtricitabine for at least 4 weeks prior to delivery. Women with documented pre-existing diabetes mellitus or a multi-fetal pregnancy confirmed via ultrasound were excluded. Institutional Review Boards at the Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern Feinberg School of Medicine, Massachusetts General Hospital, and the Health Research and Resource Development Committee in Botswana approved the protocol. All women provided written informed consent for their study participation and that of their infant prior to participating.

Primary Outcome

Women were screened for GDM using a 75-g Oral Glucose Tolerance Test (OGTT), performed at 24–28 weeks GA or at the earliest prenatal visit for those presenting after 28 weeks GA. Fasting, 1-hour, and 2-hour plasma glucose levels were measured. GDM was defined as meeting any of the following criteria: fasting glucose ≥92 mg/dL, 1-hr glucose ≥180 mg/dL, or 2-hr glucose ≥153 mg/dL (21).

Predictors of Interest

The primary predictor of interest was maternal HIV infection which was confirmed through medical record review, including documented evidence of ART prescription from the participant's local Infectious Disease Care Clinic. Women who presented without documentation of HIV seronegativity within 3 months prior to enrollment underwent confirmatory HIV testing at enrollment. All HIV testing was performed using Unigold

Recombigen HIV-1/2 (Trinity Biotech, Ireland) and Alere® Determine™ HIV-1/2 (Alere Inc., Waltham, MA, USA) tests in parallel. HIV testing was repeated again after 32 weeks GA if the initial test during pregnancy was negative and occurred at <32 weeks GA in accordance with Botswana national guidelines (14). Among WLHIV, the predictor of interest was DTG- vs. EFV-based ART. Information on maternal ART history was obtained through questionnaires and confirmed through medical record review as described above.

Covariates

Sociodemographic data were obtained via questionnaire and included age, income, education level, and employment status. GA dating was confirmed via ultrasound. Maternal medical (including information on chronic hypertension), obstetric, and HIV histories were obtained through questionnaire and medical record review. Chronic hypertension was defined as documented hypertension or receipt of hypertensive medications prior to pregnancy. Height and weight were measured in a standardized fashion with duplicate measurements at each study visit using the same stadiometer and scale, respectively. Blood pressure was also measured in a standardized fashion using a digital sphygmomanometer. HIV RNA levels were measured using Abbott RealTime® HIV-1 RNA assays, and CD4 cell counts using Facs Calibur™ flow cytometry at enrolment. Infant birth data, including anthropometrics, were abstracted from delivery records.

Statistical Methods

Characteristics between pregnant WLHIV and pregnant women without HIV were compared using Wilcoxon, Chi-square, or Fisher Exact tests, as appropriate. Infant birth weight and length Z scores were calculated using INTERGROWTH 21st standards (22). Logistic regression models were fit to estimate the unadjusted (OR) and adjusted Odds Ratios (aOR) with 95% Confidence Intervals (CI) for the association between the predictor of interest (maternal HIV status or maternal ART) and GDM. Variables considered to be potential confounders were those associated with both the outcome and predictor of interest at $p \leq 0.10$, and these included maternal age, gravidity, body mass index (BMI), and CD4 cell count, as well as ART duration during pregnancy. Subgroup analyses were performed among WLHIV to assess the association between maternal HIV treatment regimen use in pregnancy (DTG- vs. EFV-based ART]) and GDM. We also introduced an interaction term to determine whether being on ART prior to pregnancy modified the relationship between ART use in pregnancy (DTG- vs. EFV-based ART) and GDM. Lastly, sensitivity analyses were performed to assess whether results were similar when we adjusted for the cumulative duration of ART during the pregnancy at the time of OGTT. All statistical analyses were performed using SAS® version 9.4.

RESULTS

A total of 486 pregnant women were enrolled (323 WLHIV and 163 women without HIV). WLHIV were older than those without HIV (median age 30 vs 25 years, p<0.01), were more likely to have only completed secondary school as their highest education level (88.2 vs 66.9% p<0.01), and had higher gravidity (median 3 vs 1, p<0.01) (Table 1a). BMI and rates of chronic hypertension prior to pregnancy between the two groups were similar (26.1 vs

25.9% p=0.76, 11 vs 2% p=0.24 respectively). Infant GA at delivery, infant birth weight and length, and rates of stillbirths did not differ between groups.

Among WLHIV, 39% were on EFV- and 61% on DTG-based ART. At the time of the OGTT 47% had a CD4 cell count >500 cells/mm^3, while 97.8% had an HIV-1 RNA level <400 copies/mL (Table 1a). WLHIV receiving EFV-based ART were older than those receiving DTG- based ART (median 32 vs 28 years, p<0.01) (Table 1b). BMI and rates of chronic hypertension prior to pregnancy were similar between groups. Fewer women conceived on DTG-based ART (31.5 vs 87.3%, p<0.01), and the duration of ART during pregnancy was shorter among women on DTG-based ART compared to EFV-based ART (16.7 vs 27.6 weeks, p< 0.01). Proportions of stillbirths, infant GA at delivery, and birth weight and length did not differ between WLHIV on DTG-based vs. EFV-based ART. Among WLHIV, two stillbirths occurred, and both were in WLHIV receiving TDF/FTC/DTG: one was secondary to gestational hypertension/pre-eclampsia and the other secondary to a nuchal cord. Neither of the WLHIV who had a stillbirth had GDM.

Overall, 8.4% of women had GDM, with rates similar between WLHIV and women without HIV (9.0% vs. 7.4%, p=0.61). This relationship persisted even after adjusting for age, highest education level, BMI and gravidity [adjusted Odds Ratio (aOR)=0.83, 95% CI=0.37, 1.85] (Table 2a). BMI (aOR= 1.12, 95% CI=1.05, 1.18) and maternal age (aOR=1.10, 95% CI=1.04, 1.17) were also positively associated with risk of GDM.

In a subgroup analysis of WLHIV, rates of GDM were lower among women receiving DTG- vs EFV-based ART (6.1% vs 13.5%, p=0.03). After adjusting for age, BMI, gravidity, CD4 and whether ART had been started prior to pregnancy, WLHIV receiving DTG-based ART had a 66% lower risk for GDM compared to those on EFV-based ART (aOR=0.34, 95% CI=0.12, 0.97) (Table 2b). BMI was also associated with increased risk for GDM (aOR=1.13, 95% CI=1.04, 1.22). When we introduced an interaction term to assess whether ART initiation prior to pregnancy modified the relationship between ART group (DTG- vs. EFV-based ART) and GDM, we found no effect modification (p=0.57), and therefore this interaction term was removed. In a sensitivity analysis where we also adjusted for the cumulative duration of ART during the pregnancy at the OGTT, this variable was not significant (aOR=0.97, 95%CI=0.93, 1.02) and did not change our finding of lower risk for GDM with DTG vs. EFV use (aOR=0.40, 95%CI: 0.18, 0.92). (Data not shown)

DISCUSSION

Our study is the first to compare GDM rates between pregnant WLHIV and pregnant women without HIV infection in Botswana as well as between pregnant WLHIV receiving DTG- vs EFV-based ART. We observed an overall GDM prevalence of 8.4%, with similar rates between WLHIV and HIV-uninfected women. However, compared to WLHIV receiving EFV-based ART, those receiving DTG-based ART had a significantly lower risk for GDM.

Our overall GDM rates are consistent with reported rates in the United States (7). In sub-Saharan Africa, there is minimal data on GDM using standardized or uniform screening

procedures. Our rates were consistent with those reported in Cameroon (6.3%), Nigeria (4.5–13.4%), Tanzania (4.5–7.7%), and South Africa (3.8–8.8%) (10, 11, 23, 24).

Our study found that rates of GDM did not differ between WLHIV and pregnant women without HIV. This is consistent with findings from a recent meta-analysis which showed no association between HIV infection and GDM (12) and a cross-sectional study conducted in Cameroon which reported similar GDM rates between WLHIV and HIV-uninfected women (11). In addition, an older study in Spain reported a GDM rate among WLHIV of 7% (25) which is congruent with the recently reported GDM rates of 8.6% (8) in the general population in Spain. However, other studies have reported higher rates of GDM in WLHIV compared to women without HIV, including a smaller German study that observed a GDM rate of 11% (26). This rate has not changed over the last decade, but appeared somewhat higher than rates (8–9%) (8) in neighboring European countries such as Austria, France, and Belgium. In addition, a recent study from India showed higher rates of GDM in WLHIV compared to HIV-uninfected women (27). It is important to note that both of these studies had more women on PI-based ART than ours (35% in the German study and 14% in the Indian study vs none in ours).

Among WLHIV, we found a GDM rate of 9.0% in Botswana, similar to that in WLHIV in Cameroon where the same GDM screening method was used. We also observed that women receiving DTG-based ART had significantly lower risk for GDM compared to those receiving EFV-based ART after adjustment. No current published data exist on GDM rates among WLHIV receiving DTG. Our observed rate of GDM among WLHIV on EFV-based ART was similar to rates observed in WLHIV receiving nevirapine-based ART in Cameroon (11).

Data on DTG (or other INSTIs) and dysglycemia currently are conflicting (16, 28, 29). In non-pregnant populations of adults living with HIV, switching to integrase strand transfer inhibitors (INSTI), such as DTG or raltegravir (RAL,) from a regimen containing a protease inhibitor, has been associated with improvement in insulin sensitivity (28). This may explain our observation of lower risk for GDM with DTG- vs. EFV-based ART. However, other reports have shown hyperglycemia with switch to DTG or a trend towards increased risk for diabetes with initiation of INSTIs compared to NNRTIs in non-pregnant adults (16, 29). It is also interesting to note that the observed lower risk of GDM with DTG-based vs. EFV-based ART appears somewhat paradoxical to some studies which recently reported higher gestational weight gain with DTG vs. EFV use (17, 18). One explanation may be that the lower risk for GDM in WLHIV on DTG indicates higher first-phase insulin secretion during the third trimester in WLHIV receiving DTG compared to EFV. Improved insulin sensitivity is associated with higher first-phase insulin secretion (30) both of which likely enhance lipogenesis and the weight gain observed in pregnant WLHIV on DTG. It is unclear whether the gestational weight gain seen in WLHIV on DTG compared to EFV is primarily from increased subcutaneous adipose tissue and protective against ectopic fat deposition in the liver, but, even so, expanding or dysregulated subcutaneous adipose may, over the long term, adversely influences insulin sensitivity well after pregnancy despite a lower risk for GDM in pregnancy with DTG use.

The association of EFV-based ART with higher risk for GDM could also be explained by mitochondrial toxicity reported with the use of NNRTIs, particularly EFV (31, 32). This mitochondrial dysfunction likely contributes to abnormalities in adipose tissue, including lipotoxicity in hepatic cells (31), and inflammatory pathways which are linked to GDM and type 2 diabetes (33).

Consistent with literature outlining traditional risk factors for type 2 diabetes and GDM in non-HIV populations, we observed that BMI was positively associated with GDM in all models (34, 35). In the United States, studies have observed that this association may be even more pronounced in African American women (34), underscoring the importance of our female African study population.

This study was limited by our inability to accurately measure the pre-pregnancy BMI or gestational weight gain. However, we adjusted for BMI measured at the time of the OGTT. In addition, due to the manner in which DTG was scaled up as 1st-line ART in 2016, women receiving DTG-based ART were less likely to have conceived on DTG-based ART. Therefore, we may not have been able to definitively disentangle the effects of ART from duration of HIV/ART. However, we adjusted for ART use at conception and also found no effect modification by this variable on the overall relationship between DTG vs. EFV use in pregnancy and lower risk for GDM. In addition, a sensitivity analysis showed similar results when we adjusted for the cumulative duration of ART during the pregnancy at the OGTT. These findings together lend support to the notion that differences in ART use at conception or cumulative duration of ART in pregnancy between WLHIV on DTG-based ART and those on EFV-based ART do not categorically invalidate our overall findings. Lastly, all of our study participants were black African, limiting the worldwide generalizability of our findings. Nonetheless, our results bridge an important gap in information on GDM in sub-Saharan Africa where currently the vast majority of WLHIV reside. In addition, among WLHIV in our study, the homogeneity in ART backbone allowed us to more accurately measure true differences in GDM between DTG and EFV.

In conclusion, overall rates of GDM in Botswana are similar to those in United States, with no differences between WLHIV and HIV-uninfected women. Among WLHIV, GDM risk was lower in WLHIV on DTG-based ART compared to those on EFV-based ART. Further and larger longitudinal studies are warranted to confirm our findings and monitor the long-term metabolic health of WLHIV after pregnancy.

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Table 1a.

Characteristics of Pregnant Women at Enrollment and their Infants at Birth by Maternal HIV Status

	Women living with HIV (n=323)	Women without HIV (n=163)	*p*-value
WOMEN			
Sociodemographic			
Age (years)	30.0 (25.0 – 35.0)	25.0 (21.0 – 29.0)	<0.01
Gestational age at OGTT (weeks)	28 (26 – 32)	27 (25 – 32)	<0.01
Annual income (USD)			0.62
>$1200	150 (46.4)	82 (50.3)	
$240 – $1199	33 (10.2)	20 (12.3)	
<$240	132 (40.9)	57 (35.0)	
Unsure/Unknown	8 (2.5)	4 (2.5)	
Highest education secondary school or less	285 (88.2)	109 (66.9)	<0.01
Married	19 (5.9)	18 (11.0)	0.05
Employed	163 (50.5)	76 (46.6)	0.44
Past Obstetric History			
Gravidity	3 (2 – 4)	1 (1 – 3)	<0.01
Chronic hypertension prior to pregnancy	11 (3.4)	2 (1.2)	0.24
Height (cm)	161 (156 – 165)	161 (157 – 165)	0.74
BMI$^{\$}$ (kg/m^2)	26.1 (23.6 – 29.8)	25.9 (22.9 – 30.7)	0.76
Hypertensive at OGTT *	14 (4.3)	3 (1.8)	0.20
Preeclampsia	3 (1.0)	0 (0.0)	0.55
HIV Clinical Disease at OGTT			
CD4 cell count >500 (cells/mm^3)	153 (47.4)	---	---
HIV RNA level <400 (copies/mL)	316 (97.8)	---	---
On ART at conception	172 (53.3)	---	---
ART regimen			
TDF/FTC/DTG	197 (61.0)	---	---
TDF/FTC/EFV	126 (39.0)	---	---
INFANTS			
Stillborn	2 (0.6)	3 (1.8)	0.34
Gestational age at delivery (weeks)	39 (37 – 40)	39 (37 – 40)	0.54
Birth weight z score	−0.2 (−0.9 – 0.6)	−0.1 (−0.8 – 0.5)	0.60
Birth length z score	1.2 (0.0 – 2.0)	1.3 (−0.0 – 2.4)	0.22

Table 1b.

Characteristics of Pregnant Women Living with HIV at Enrollment and their Infants at Birth by Maternal ART Regimen in Pregnancy

	TDF/FTC/DTG (n=197)	TDF/FTC/EFV (n=126)	*p*-value
Sociodemographic			
Age (years)	28.0 (25.0 – 33.0)	32.0 (27.0 – 36.0)	<0.01
Gestational age at OGTT (weeks)	28 (26 – 32)	28 (25 – 32)	0.68
Annual income (USD)			0.43
>$1,200	90 (45.8)	60 (47.6)	
$240 – $1,199	19 (9.6)	14 (11.1)	
<$240	85 (43.1)	47 (37.3)	
Unsure/Unknown	3 (1.5)	5 (4.0)	
Highest education secondary school or less	169 (85.8)	116 (92.1)	0.11
Married	7 (3.6)	12 (9.5)	0.03
Employed	96 (48.7)	67 (53.2)	0.49
Past Obstetric History			
Gravidity	3 (2–3)	3 (2–4)	0.01
Chronic hypertension prior to pregnancy	7 (3.6)	4 (3.2)	0.99
Height (cm)	161 (156 – 165)	161 (155 – 166)	0.75
BMI (kg/m^2)	26.9 (23.3 – 31.1)	25.8 (22.8 – 29.5)	0.19
Hypertensive at OGTT *	12 (6.1)	2 (1.6)	0.09
Preeclampsia	2 (1.1)	1 (0.8)	0.99
HIV Clinical Disease at OGTT			
CD4 cell count >500 (cells/mm^3)	85 (43.1)	68 (54.0)	0.16
HIV RNA level (copies/mL)	1.6 (1.6 – 1.6)	1.6 (1.6 – 1.6)	0.24
On ART at conception	62 (31.5)	110 (87.3)	<0.01
Duration on ART during pregnancy (weeks)	16.7 (10.6 – 25.7)	27.6 (25.3 – 31.6)	<0.01
INFANTS			
Stillborn	2 (1.0)	0 (0.0)	0.53
Gestational age at delivery (weeks)	39 (37 – 40)	39 (37 – 40)	0.40
Birth weight z score	−0.2 (−0.9 – 0.6)	−0.2 (−0.9 – 0.7)	0.72
Birth length z score	1.1 (0.0 – 2.2)	1.2 (−0.0 – 1.9)	0.81

Continuous variables shown as median (interquartile range) and categorical variables shown as n (%).

* Defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg.

$ BMI was obtained during pregnancy.

ART=Antiretroviral Therapy; BMI=Body Mass Index; DTG=dolutegravir; FTC=emcitritabine; GA=gestational age; OGTT=Oral Glucose Tolerance Test; TDF=tenofovir; USD=US Dollars

Table 2a.

Multivariable Model Showing the Unadjusted and Adjusted Odds Ratios for the Association between Maternal HIV Status and Gestational Diabetes

Factor	Unadjusted OR	95% CI	Adjusted OR	95% CI
Maternal HIV infection vs. no infection[a]	1.24	(0.62, 2.50)	0.83	(0.37, 1.85)
Age (years)	1.12	(1.06, 1.19)	1.10	(1.04, 1.17)
Highest education level				
Secondary school or less	0.82	(0.38, 1.87)	0.70	(0.31, 1.60)
Tertiary school or higher	Ref	---		
BMI (kg/m^2)	1.13	(1.07, 1.19)	1.12	(1.05, 1.18)
Gravidity	1.34	(1.08, 1.65)	0.96	(0.72, 1.28)

Table 2b.

Multivariable Model Showing the Unadjusted and Adjusted Odds Ratios for the Association of TDF/FTC/DTG vs. TDF/FTC/EFV use in Pregnancy with Gestational Diabetes Among Women Living with HIV

Factor	Unadjusted OR	95% CI	Adjusted OR	95% CI
TDF/FTC/DTG vs. TDF/FTC/EFV[b]	0.42	(0.19, 0.90)	0.34	(0.12, 0.97)
Age (years)	1.07	(1.00, 1.15)	1.04	(0.95, 1.14)
BMI (kg/m^2)	1.11	(1.04, 1.19)	1.13	(1.04, 1.22)
Gravidity	1.21	(0.93, 1.58)	0.96	(0.69, 1.34)
CD4>500 cells/mm^3	0.89	(0.42, 1.92)	1.09	(0.48, 2.49)
On ART at conception	1.27	(0.59, 2.75)	0.64	(0.22, 1.86)

[a] n=29 (9.0%) women living with HIV had GDM and n=12 (7.4%) women without HIV had GDM

[b] n=12 (6.1%) women living with HIV receiving TDF/FTC/DTG had GDM and n=17 (13.5%) women living with HIV receiving TDF/FTC/EFV

ART=Antiretroviral Treatment; BMI=Body Mass Index; CI=Confidence Interval; DTG=dolutegravir; EFV=efavirenz; FTC=emtricitabine; GDM=Gestational Diabetes Mellitus; OGTT=Oral Glucose Tolerance Test; OR=Odds Ratio