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Associations of HIV and antiretroviral therapy with gestational diabetes: findings from a prospective cohort in South Africa

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Abstract

Objective: To estimate associations of HIV-status and antiretroviral (ART) regimen with gestational diabetes (GDM) and postpartum glucose metabolism.

Design: Prospective cohort study

Methods: We enrolled pregnant persons living with HIV(PHIV) and without HIV in Cape Town, South Africa who were ≥18 years of age at 24-28 weeks gestation and followed up to 26 months postpartum. Participants were tested for GDM in pregnancy and for diabetes postpartum using a 75 g 2-hour oral glucose tolerance test and diagnosed via WHO criteria. We estimated associations of HIV-status and ART regime (efavirenz (EFV) vs dolutegravir (DTG)) with GDM and postpartum impaired glucose metabolism using multivariable log binomial or linear regression models.

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Results: Among 397 participants (median age 30 (IQR 25,34; n=198 without HIV, n=199 PHIV), the prevalence of GDM was 6.0% (9.0 PHIV vs 3.0% without HIV). In multivariable analyses, PHIV were at higher risk of GDM (RR 3.9 95% CI 1.4, 10.7) after adjustment for pre-pregnancy BMI and other confounders. GDM risk did not differ by ART regimen (unadjusted prevalence 8.1% DTG vs 5.6% EFV, adjusted RR 1.1, 95% CI 0.2, 6.6). Few participants had diabetes, impaired glucose tolerance, or impaired fasting glucose postpartum (n=13, 6%) with no differences by HIV or ART status.

Conclusions: In a setting of universal GDM testing, PHIV had an increased risk of impaired glucose metabolism during pregnancy but not postpartum. Among PHIV, GDM risk was similar regardless of EFV or DTG use. Given concerns about DTG and weight gain, diabetes risk should continue to be monitored.

Keywords

HIV; gestational diabetes; diabetes; antiretroviral therapy; glucose metabolism; adverse birth outcome; dolutegravir

Introduction

Gestational diabetes (GDM) is characterized by hyperglycemia first detected or diagnosed during pregnancy.[1] GDM complicates an estimated 10-14% of pregnancies globally[2] and is associated with an increased risk of adverse birth outcomes, including large-for-gestational age (LGA) infants and cesarean delivery, as well as an increased risk of progressing to type 2 diabetes mellitus (DM) postpartum.[3-6] Pregnant persons with HIV (PHIV) may be particularly at high risk for GDM or DM due to persistent HIV-associated inflammation and antiretroviral therapy (ART)-specific effects which influence insulin sensitivity and glucose homeostasis.[7, 8] However, little data on GDM or postpartum DM risk are available for PHIV in low- and middle-income countries (LIMCs), where the burden of HIV is highest.[2]

For PHIV, an increased risk of GDM has most commonly been associated with protease-inhibitor (PI)-based ART.[9-12] However recommendations for first line ART have shifted away from PI-based and non-nucleoside reverse-transcriptase inhibitor(NNRTI)- based ART, in favor of integrase strand-inhibitors (INSTIs). In 2019 the WHO recommended dolutegravir (DTG), an INSTI, as first line therapy for all PHIV.[13] Following this recommendation, South Africa began initiating or switching pregnant PHIV from efavirenz(EFV)-based ART to DTG-based ART. DTG has been associated with weight gain, including in pregnancy, and reports of hyperglycemia in non-pregnant adults.[14-16] Currently, there are no data on HIV, ART and GDM risk in pregnancy or postpartum DM risk among pregnant PHIV in South Africa following the rollout of DTG.

To address this gap, we conducted a prospective cohort study among pregnant PHIV and without HIV in Cape Town, South Africa. The study took place during the roll out of DTG in South Africa, and therefore included participants on both EFV and DTG. We evaluated differences in GDM risk in pregnancy and glucose metabolism postpartum by HIV

status and ART regimen, and report on associations of GDM with the risk of adverse birth outcomes.

Methods

Study setting and design

Data come from the Cardiometabolic Health in Pregnancy (CAMP) study, a prospective cohort study which enrolled consecutive pregnant persons with and without HIV, who were ≥18 years of age and presented for antenatal care (ANC) in Gugulethu, Cape Town between November 2019 and June 2022. Participants were enrolled at 24-28 weeks gestation (baseline) and completed a follow-up postpartum visit, planned at 6 months postpartum. Due to COVID-19 pandemic disruptions, postpartum visits took place between 6-32 months postpartum (median 9.6 months, IQR 6.8-12.3 months). We enrolled equal numbers of persons without HIV and PHIV, with no restriction on timing of ART initiation for PHIV. All participants were tested for GDM at 24-28 weeks gestation and for impaired glucose metabolism postpartum using a 75 g 2-hour oral glucose tolerance test (OGTT) after an overnight fast. Information on birth outcomes was abstracted from medical records.[17-19] Ethics approval for the CAMP study was provided by the University of Cape Town's Human Research Ethics Committee (protocols 486 and 505).

Gugulethu is a peri-urban community in Cape Town with a population of approximately 300,000, characterized by high levels of poverty and HIV among pregnant persons.[19-21] Access to antenatal care is nearly universal (95%) and same-day initiation of ART is provided at no cost as a part of routine antenatal care at all public-sector clinics.[20, 22] In June 2019, South Africa transitioned from initiating PHIV on EFV-based ART (tenofovir 300 mg + emtricitabine 200 mg/lamivudine 300 mg + efavirenz 600 mg) to DTG-based ART (tenofovir 300mg + lamivudine 300mg/emtricitabine 200mg + dolutegravir 50mg (TLD)).[23, 24] Both regimens are available as a fixed-dose combination pill taken once daily.[23]

Study population

Participants with frank diabetes at baseline, based on the 2h OGTT and WHO criteria[25] (n=3), were excluded from all analyses. We included all PHIV and without HIV in the analysis of GDM (n=397) and all participants who completed a postpartum study visit and did not seroconvert to HIV (n=1) in the analysis of postpartum glucose impairment (n=292, 74%). To understand the effect of initiating DTG or EFV on glucose metabolism, primary comparisons by ART regimen were restricted to PHIV on post-conception EFV or DTG. We included all PHIV on EFV- or DTG-based ART in a sensitivity analysis. Participants with an unknown pregnancy outcome (n= 13) or stillbirth (n=2) were excluded from the analysis of birth outcomes (n=385 live births).

Exposures and Outcomes

The exposures of interest were HIV status and ART regimen, collected via self-report at baseline and confirmed via medical records. Outcomes included GDM, diagnosed according to WHO criteria as one or more of the following: fasting plasma glucose ≥5.1-6.9 mmol/l [92-125 mg/dL], 1-hour (h) plasma glucose ≥10.0 mmol/l [180 mg/dL], or 2h plasma

glucose ≥8.5-11.0 mmol/l [153-199 mg/dL].[25] Plasma glucose levels at fasting, 1h, and 2hs were also assessed. Postpartum impaired glucose metabolism was categorized as: impaired fasting glucose (IFG; fasting glucose 6.1-6.9mmol/l [110-125 mg/dL] and 2h glucose <7.8mmol/l [140 mg/dL]), impaired glucose tolerance (IGT; fasting glucose <7.0mmol/l [126 mg/dL] and 2h glucose ≥7.8- <11.1 mmol/l [140-200 mg/dL]) or DM (fasting glucose ≥7.0mmol/l [126 mg/dL] or 2h glucose ≥11.1mmol/l [200 mg/dL]) according to WHO criteria.[26] Due to few postpartum events, IFG, IGT, and DM were collapsed into a binary measure of 'any impaired glucose metabolism' versus 'none'. Insulin resistance (evaluated as Homeostatic Model Assessment for Insulin resistance (HOMA-IR)[27] and sensitivity (Matsuda Index)[28] were considered as additional outcomes.

We evaluated associations between GDM and several birth outcomes, including cesarean delivery (as indicated in medical records), infant birthweight (g), low birthweight (<2500 grams), high birthweight (>4000 grams), preterm birth (<37 completed weeks' gestation), small for gestational age (SGA, birthweight <10th percentile for gestational age) and large for gestational age (LGA, birthweight >90th percentile for gestational age).[29] Gestational age at enrollment was determined primarily by ultrasound (360/400, 90%) at entry into antenatal care (mean gestational age 16 weeks' (SD 5.7). In some cases last menstrual period and symphysis fundal height were used for women presenting later in pregnancy when ultrasound is less reliable.[30, 31] Gestational birth weight percentiles were defined using the INTERGROWTH-21 standards.[32, 33]

Covariates

At baseline, information on clinical, behavioral, and HIV disease (if applicable) characteristics was collected. We developed a composite socio-economic status (SES) score, based on current employment, education, housing type, and access to household assets, that was used to categorize participants into tertiles of 'highest, 'moderate' or 'lowest SES.[34] Alcohol use was measured using the 3-item Alcohol Use Disorders Identification Test-Consumption (AUDIT-C; range 0-12) and a score of ≥3 indicates hazardous drinking for women in the previous 12 months.[35] Pre-pregnancy body mass (BMI, kg/m^2) was calculated based on self-reported pre-pregnancy weight[36] and categorized as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obese (≥30 kg/m^2). Physical activity was evaluated as the number of times and intensity of physical activity in a week. Household food security was assessed using adapted measures of the Household Food Insecurity Access Scale, Food and Nutrition Technical Assistance Project, and the Community Childhood Hunger Identification Project Index.[37] Tuberculosis status (defined as no previous, previous, or current tuberculosis treatment) was defined based on medical records. Blood pressure was evaluated by trained research assistants on seated participants using an Edan M3A Vital Signs Monitor. Four measures, at least 30 minutes apart, were taken and averaged for analyses. Lipid levels (total cholesterol, high- and low-density cholesterol, triglycerides) were evaluated using fasted blood samples.

Among PHIV, CD4 cell count and viral load information within 6 months of study enrollment (mean 2 months, SD 1.3) was abstracted from medical records. Timing of

HIV diagnosis (during the current pregnancy or previously), ART regimen, and pre- or post-conception initiation of ART were assessed at baseline and confirmed in medical records.

Statistical Analysis

The goals of the analysis were to estimate the prevalence of GDM, to determine associations of HIV status with GDM and impaired glucose metabolism postpartum, and associations of GDM with adverse birth outcomes. Subgroup analyses among PHIV assessed associations of ART (DTG versus EFV) with GDM and postpartum glucose metabolism.

PHIV were overrepresented in our study population relative to the general population (50% versus 24%) in South Africa.[21] Thus, we estimated the prevalence of GDM in the study population and weighted to represent the general population. We estimated associations between HIV status and ART regimen using Poisson models with robust variance estimators for binary outcomes (e.g. GDM) and linear regression for continuous outcomes (e.g. plasma glucose). Associations between GDM and birth outcomes were estimated using similar methods. All models were adjusted for a minimally sufficient adjustment set of confounders identified using directed acyclic graphs (Figure S1). Collinearity among potential confounders was evaluated and the covariate that predicted the outcome most strongly was selected (e.g. pre-pregnancy BMI and parity over age). Limited sample size precluded examining HIV as a potential effect measure modifier of GDM and adverse birth outcomes. However, we graphically examined differences in the risk of adverse birth outcomes by GDM and HIV status. Except for viral load (56%) and CD4 count (21%) which were available from medical records, missing data was limited (≤3%) and therefore all analyses were complete case. Statistical analyses were conducted in Stata version 15 (StataCorp, College Station, TX).

Results

We enrolled 397 participants (n=198 without HIV, n=199 PHIV) during pregnancy (median gestational age 26 weeks; IQR 24, 27). PHIV were slightly older (median age 31 versus 27 years) and had higher parity (median 3 versus 2), compared to those without HIV (Table 1). Over half of the cohort (52%) reported living with obesity pre-pregnancy and 17% reported food insecurity. PHIV were less likely to be living with obesity pre-pregnancy (48% versus 55%), but more likely to experience food insecurity (20% versus 14%) and to have low SES (40% versus 15%), compared to participants without HIV. PHIV were also more likely to have a family history of diabetes (13% versus 7%) and to report tuberculosis treatment (16% versus 5%). Blood pressure and lipid levels at enrollment were similar by HIV status.

Among PHIV, ART 44% initiated ART pre-conception (n=88; n=71 EFV, n=11 DTG, n=6 other) and 56% post-conception (n=111; n=36 EFV, n=74 DTG, n=1 other). Post-conception initiators were on ART an average of 6.7 weeks (SD 5.1) at baseline. Pre-pregnancy BMI was similar between those initiating DTV versus EFV (31 versus 29 kg/m^2). About a third of PHIV with measures available had a CD4 count ≤350 cells/mm3 or a detectable viral load (≥50 copies/ml) at enrollment.

The unadjusted prevalence of GDM in the study population was 6.0% (9.0% PHIV vs 3.0% without HIV, Table 2) and 4.5% when weighted reflect the general population (Table S1). In multivariable analyses, PHIV were at higher risk of GDM (RR 3.9 95% CI 1.4, 10.7) after adjustment for pre-pregnancy BMI, family history of diabetes, and other confounders. This translates to a 6.1% (95% CI 1.1%, 11.1%) higher absolute risk of GDM for PHIV, relative to participants without HIV. The association between HIV status and GDM was similar when restricted to PHIV initiating post-conception ART only (unadjusted prevalence 7.2% PHIV vs 3.0% without HIV: adjusted RR 3.7, 95% CI 1.2, 11.6). Among the 18 PHIV who developed GDM, 9 (50%) were on pre-conception EFV, 2 on post-conception EFV (11%), 6 were on post-conception DTG (33%), and 1 was on an alternative pre-conception regimen (6%).

When considering plasma glucose levels, PHIV had higher fasting plasma glucose (unadjusted mean 4.3 versus 4.1 mmol/l, adjusted mean difference (MD) 0.2 95% CI 0.1, 0.3), but no differences in 1- and 2-hour glucose levels (Table 2; Figure S2). Among the 24 participants with GDM, GDM was diagnosed primarily based solely on elevated fasting plasma glucose (19/24 79%, mean 5.5 (SD 0.6), rather than 1-hour (mean 7.4, SD 2.7) or 2-hour (mean 6.8, SD 1.8) plasma glucose.

Among participants on post-conception ART, the risk of GDM was similar (unadjusted prevalence 8.1% DTG versus 5.6% EFV, adjusted RR 1.1, 95% CI 0.2, 6.6). However, those initiating EFV tended to have slightly higher plasma glucose levels, with the largest difference at 2h post-glucose load (5.6 versus 5.1 mmol/l) (Table 2; Figure S2). In a sensitivity analysis including pre- and post-conception ART initiators, 10.1% of EFV users developed GDM compared to 7.1% of DTG users (adjusted RR 0.6, 95% CI 0.2, 1.6).

Of the 24 participants who developed GDM, 15 (65%) were living with obesity pre-pregnancy (Table 3). Pre-pregnancy obesity was not associated with GDM overall or when stratified by HIV status; however, confidence intervals were wide due to the small number of events. For both PHIV and without HIV, the highest proportion of GDM diagnoses occurred among participants who were living with obesity pre-pregnancy.

Among 385 live births, 16% of infants were preterm, 13% low birthweight, 4% high birthweight, 8% were SGA, 15% LGA and 20% of deliveries were by emergency cesarean section (Table 4). After adjustment for confounders, participants with GDM delivered at slightly earlier gestation age (MD −1.0 week, 95% CI −2.0, −0.0). Participants with GDM were more likely to have a LGA (RR 2.40, 95 %CI 1.23, 4.66), preterm birth (RR 2.44, 95% CI 1.24, 4.81), and an emergency cesarean (RR 2.37, 95% CI 1.26, 4.46). In exploratory analyses among participants with GDM, there was little difference in LGA or preterm birth risk by HIV status (Figure 1). The risk of an emergency cesarean section was higher among participants with GDM and HIV, compared to those with GDM but without HIV.

In the postpartum period, only 5% (n=15) of participants had any form of impaired glucose metabolism (Table 2). Of the 24 participants with GDM, 17 (71%) had a postpartum visit and 3 (18%) had DM; none had IFG or IGT. Of the 4 cases of DM postpartum, 3 (75%)

were among participants with GDM. Postpartum, there were no differences in impaired glucose metabolism, insulin resistance or insulin sensitivity by HIV status or ART regimen.

Discussion

In a cohort of pregnant persons with and without HIV, 6.0% were diagnosed with GDM. Compared to those without HIV, PHIV were at an increased risk of GDM, after accounting for pre-pregnancy BMI and other important confounders. Among post-conception ART initiators, the risk of GDM was similar regardless of EFV or DTG use. Participants with GDM were at an increased risk of an emergency cesarean and a LGA or preterm infant. In exploratory analyses, the risk of LGA and preterm birth did not meaningfully differ by HIV status among participants with GDM, but the risk of an emergency cesarean was highest for participants with GDM and HIV. The risk of postpartum impaired glucose metabolism did not differ by HIV or ART status.

Estimates of GDM vary widely globally, in part due to differences in screening guidelines and diagnostic criteria.[1, 25, 38-40] Across much of sub-Saharan Africa, GDM screening is risk-based and screening for diabetes outside of pregnancy varies, making it challenging to estimate GDM prevalence and distinguish GDM from pre-existing DM.[41] Our observed GDM prevalence of 6.0% in the cohort (4.5% general population) was lower than estimates from several meta-analyses in Africa (range 9%-14%)[42-44] and in South Africa (9.1%).[45] Among PHIV, 9% developed GDM, the same as a recent study in Botswana[46], but higher than GDM estimates among PHIV in Rwanda, Kenya, and a recent meta-analysis of PHIV in Africa (3.2%).[47-49] These differences may reflect differences in study population, GDM screening and diagnosis, or the increasing prevalence of GDM among pregnant persons.[3]

Our study is among the first to identify a higher risk of GDM among PHIV in a setting of universal GDM screening and ART. A recent study in India found an increased risk of GDM among PHIV (13.9% vs 6.5% HIV-uninfected participants) primarily on NNRTI-based ART.[50] In our study, PHIV were nearly 4 times as likely to develop GDM, compared to participants without HIV, controlling for important risk factors including pre-pregnancy BMI and family history of diabetes. No evidence of an association between HIV and GDM has been reported in several other studies.[10, 12, 48, 51, 52] A recent study in Botswana, which used the same GDM screening and diagnostic criteria and had a similar study population, did not observe an association between HIV and GDM (adjusted OR 0.83, 95% CI 0.37, 1.85).[46] These differing results may be driven by the lower prevalence of GDM among participants without HIV in our study (3.0% versus 7.4% in the Botswana study), rather than PHIV (9.0% in both studies).

We found a similar risk of GDM among women initiating EFV- versus DTG-based ART. To our knowledge, only one other study has examined associations of EFV versus DTG in pregnancy with GDM and found a lower risk of GDM among women on DTG (6.1% versus 13.5% EFV; adjusted OR 0.40 95% CI 0.18, 0.92). We did not observe evidence of a protective association between DTG and GDM, possibly due to limited sample size. However, we did observe higher levels of plasma glucose in participants initiating EFV, particularly at 2h post-glucose load, and a higher risk of GDM among EFV users (10.1%

vs 7.1% on DTG), when all ART users were included. GDM has most commonly been associated with PI-based, rather than NNRTI-based, ART.[9-12] However, NNRTIs, including EFV, are associated with mitochondrial toxicity which may contribute to abnormalities in adipose tissue and inflammatory pathways linked to GDM and diabetes risk.[53, 54] The relationship between DTG and glucose metabolism is less clear. In treatment experienced non-pregnant PHIV, switching to DTG, particularly from a PI-boosted regimen, has been associated with no change[55, 56] improvements in insulin sensitivity,[57, 58] an increased risk of hyperglycemia[14, 15] and diabetes in PHIV initiating ART.[16] DTG has been linked to weight gain in and outside of pregnancy,[59-61] which over time, could influence GDM or diabetes risk.[62, 63] As DTG use expands, ongoing studies of ART regimen, GDM, and progression to postpartum DM are needed.

As previously reported in South Africa, GDM was diagnosed in this study primarily due to higher fasting plasma glucose.[45] While the OGTT is the gold standard of GDM screening, universal OGTT screening presents operational challenges.[64, 65] Fasting plasma glucose is not as accurate as an OGTT in diagnosing GDM,[66-68] but is operationally more efficient than an OGTT and predicts adverse birth outcomes,[69] although not as well as in conjunction with 1h and 2h hyperglycemia.[70] If the finding of higher fasting plasma glucose leading to GDM is replicated in larger cohorts in LMICs, additional research may consider whether fasting plasma glucose could be part of a GDM screening algorithm in LMICs to improve GDM screening coverage.

In this cohort, postpartum impaired glucose metabolism was uncommon (5%), with the risk of postpartum DM highest among with GDM in pregnancy.[71, 72] The risk of any impaired glucose metabolism postpartum in this cohort did not differ by HIV or ART status. The low prevalence of postpartum glucose impairment in the presence of high levels of pre-pregnancy obesity but may reflect a different diabetes phenotype in persons of African ancestry.[73] Persons with GDM are at increased risk of progressing to impaired glucose metabolism or DM postpartum. However, to date no data is available on how HIV or ART may affect the risk of progression to postpartum DM for PHIV.[74] If HIV or ART are confirmed to influence GDM risk in larger cohorts, efforts to improve postpartum glucose mentalism screening will be important to prevent progression to DM for PHIV.

Our study has several strengths and limitations. Major strengths include universal GDM testing using WHO diagnostic criteria, robust control of confounders and risk factors for GDM, and the ability to evaluate associations between EFV and DTG and GDM. Limitations include the relatively small sample size of PHIV initiating ART, which may have resulted in limited power to detect differences between EFV and DTG users, the imprecision of associations of pre-pregnancy BMI with GDM due to limited GDM cases, postpartum loss to follow-up, and the large timespan among postpartum visits (6-32 months). Most pregnant persons with GDM return to euglycemia by 6-12 weeks postpartum, indicating that assessment after that time point is a reasonable indication of postpartum glucose metabolism. In addition, there were no important differences in sociodemographic characteristics between the full cohort and those with a postpartum visit (Table S2). Our study took place during the COVID-19 pandemic, but we did not have data on COVID-19 exposure or treatment. SARS-CoV-2 seroprevalence among pregnant women in South Africa

is estimated at >60% and is typically asymptomatic but may increase the risk of low birthweight.[75-77]

Conclusion

In a setting of universal GDM screening, we observed a higher risk of GDM among PHIV, but no difference in GDM risk among participants initiating EFV- versus DTG-based ART or in postpartum glucose metabolism by HIV or ART status. GDM increased the risk of LGA, preterm birth and emergency cesarean section, with no appreciable difference in LGA or preterm birth risk by HIV status among participants with GDM. Improved screening for hyperglycemia in pregnancy in LMICs, and in particular among PHIV, is needed to improve clinical outcomes and monitor GDM risk over time. Given concerns about weight gain associated with DTG, glucose metabolism and GDM risk in pregnancy and progression to postpartum DM should continue to be monitored among pregnant PHIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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AMB and LM received funding for the study; AMB, HM, and LM were involved in data collection; AMB conducted the statistical analysis with input from HM and LM and drafted the paper. All authors assisted with the interpretation of the study findings and critically reviewed the manuscript.

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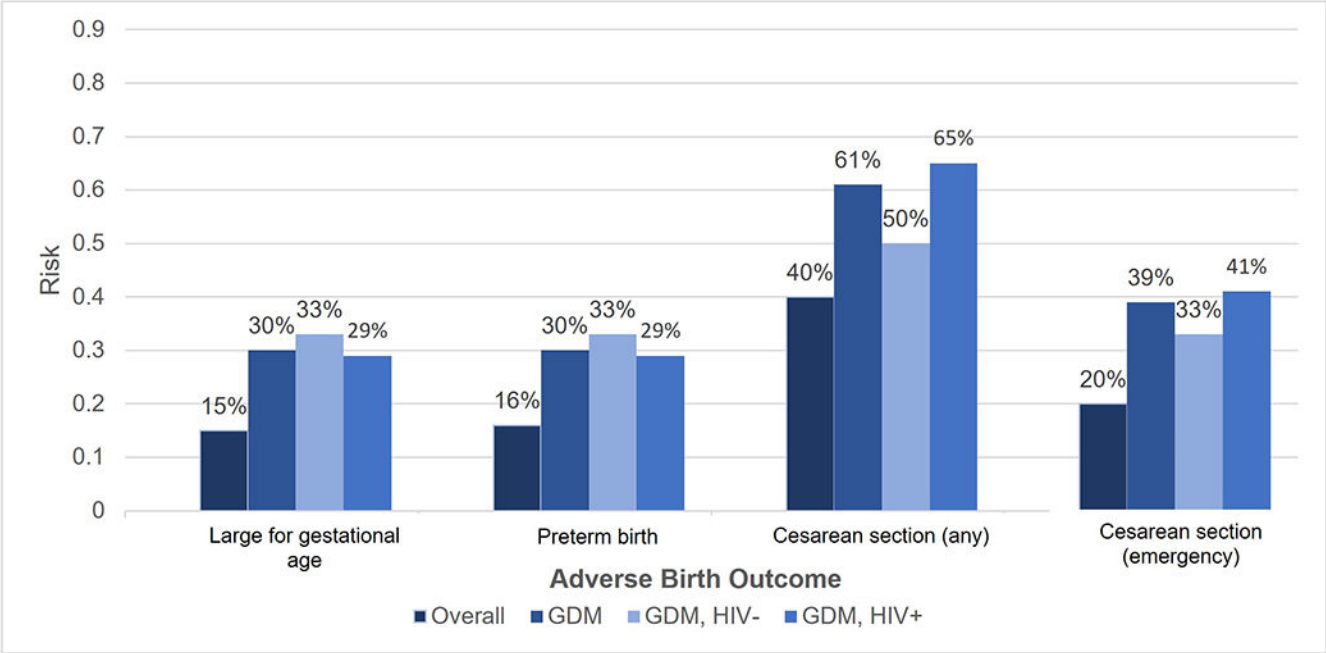

Figure 1.

Risk of an adverse birth outcomes overall, among women with gestational diabetes (GDM) and among participants with GDM by HIV status

Table 1.

Characteristics at 24-28 weeks gestation among 397 pregnant persons in Cape Town, South Africa, overall and by HIV status

	Without HIV- (n=198)	With HIV (n=199)	Total (n=397)
	Median, IQR		
Age	27 (24, 31)	31 (27, 36)	30 (25, 34)
Gestational age	26 (24, 27)	26 (24, 27)	26 (24, 27)
Parity	2 (1, 3)	3 (2, 4)	2 (2, 3)
Blood pressure, mm/Hg			
Systolic	113.5 (105.5, 120.8)	111.5 (103.8, 119.8)	112.3 (104.7, 120.1)
Diastolic	67.0 (62.5, 71.3)	66.8 (62.8, 73.0)	67.0 (62.5, 72.1)
Lipids, mmol/l			
Total cholesterol	4.8 (4.2, 5.4)	4.5 (3.9, 5.1)	4.6 (4.0, 5.3)
LDL cholesterol	2.4 (1.8, 2.9)	2.1 (1.6, 2.6)	2.3 (1.7, 2.8)
HDL cholesterol	1.7 (1.4, 1.9)	1.6 (1.4, 1.9)	1.6 (1.4, 1.9)
Triglycerides	1.5 (1.2, 1.8)	1.6 (1.3, 2.0)	1.5 (1.2, 1.9)
	N(%)		
Pre-pregnancy BMI category (m/kg^2)[1]			
Underweight (<18.5)	0 (0.0)	0 (0.0)	0 (0.0)
Normal weight (18.5 - <25.0)	37 (18.8)	42 (21.0)	79 (19.9)
Overweight (25.0 - <30.0)	51 (25.9)	61 (30.6)	112 (28.3)
Obese (≥ 30.0)	109 (55.3)	96 (48.2)	205 (51.8)
SES Category			
Lowest	50 (25.3)	77 (39.7)	127 (32.0)
Moderate	58 (29.3)	51 (25.6)	109 (27.5)
Highest	90 (45.4)	71 (35.7)	161 (40.5)
Marital status			
Not married/cohabitating	114 (57.6)	112 (56.3)	226 (56.9)
Married/cohabitating	84 (42.4)	87 (43.7)	171 (43.1)
Primigravida			
No	147 (74.2)	176 (88.4)	323 (81.4)
Yes	51 (25.8)	23 (11.6)	74 (18.6)
Alcohol use[2]			
Below threshold	186 (93.9)	187 (94.0)	373 (94.0)
Hazardous drinking	12 (6.1)	12 (6.0)	24 (6.0)
Food security[3]			
No perceived food insecurity	170 (85.9)	160 (80.4)	330 (83.1)
Perceived food insecurity	28 (14.1)	39 (19.6)	67 (16.9)
Physical activity			

	Without HIV- (n=198)	With HIV (n=199)	Total (n=397)
	Median, IQR		
None	103 (52.0)	77 (38.7)	180 (45.3)
1-2 times/week	51 (2.5.8)	48 (24.1)	99 (24.9)
3-4 times/week	35 (17.7)	57 (28.6)	92 (23.2)
>4 times/week	9 (4.5)	17 (8.5)	26 (6.6)
Physical activity intensity (*among women who engage in physical activity n=219*)			
Light	80 (84.2)	112 (91.8)	192 (88.5)
Moderate	10 (10.5)	9 (7.4)	19 (8.8)
Vigorous	5 (5.3)	1 (0.8)	6 (2.8)
Family history of diabetes			
No	181 (92.8)	169 (87.1)	350 (90.0)
Yes	14 (7.2)	25 (12.9)	39 (10.0)
Tuberculosis			
No tuberculosis	188 (95.0)	170 (85.4)	358 (90.2)
Previous tuberculosis	10 (5.0)	28 (14.1)	38 (9.6)
Current tuberculosis	0 (0.0)	1 (0.5)	1 (0.2)
Maternal HIV characteristics (N=199)			
	Preconception ART N=88	**Postconception ART N=111**	**Participants with HIV N=199**
HIV diagnosis	N (%)		
Before this pregnancy, but during another pregnancy	47 (53.4)	18 (16.2)	65 (32.7)
Before this pregnancy, but not during another pregnancy	41 (46.6)	27 (24.3)	68 (34.2)
During this pregnancy	0 (0.0)	65 (58.6)	65 (32.7)
Perinatally infected	0 (0.0)	1 (0.9)	1 (0.5)
ART regimen			
Efavirenz based	71 (80.6)	36 (32.4)	107 (53.8)
Dolutegravir based	11 (12.5)	74 (66.7)	85 (42.7)
Other	6 (6.8)	1 (0.9)	7 (3.5)
Viral load			
Undetectable (<50 copies/ml)	60 (84.5)	2 (11.1)	62 (69.7)
Detectable (≥50 copies/ml)	11 (15.5)	16 (88.9)	27 (30.3)
CD4 count, cells/mm^3			
≤350	9 (12.0)	38 (45.8)	47 (29.8)
351 - ≤500	23 (30.7)	19 (22.9)	42 (26.6)
>500	43 (57.3)	26 (31.3)	69 (43.7)

BMI = body mass index; ART = antiretroviral therapy, GA= gestational age.

[1]Based on WHO categories and self-reported pre-pregnancy weight.

[2]Based on the AUDIT-C (range 0-12); a score of ≥3 indicates hazardous drinking.

[3]Household food security was assessed using adapted measures of the Household Food Insecurity Access Scale, Food and Nutrition Technical Assistance Project, and the Community Childhood Hunger Identification Project Index'. Missing data: pre-pregnancy BMI n=1 (03%); family history of diabetes n=8 (2.0%); CD4 cell count n=41 (21%); viral load n=110 (55%).

Table 2.

Glucose metabolism at 24-28 weeks gestation and up to 32 months postpartum, by HIV status and ART regimen among post-conception ART new

	Without HIV	With HIV	Full Cohort		Efavirenz	Dolutegravir	Post-conception ART
	Pregnancy				Pregnancy		
	n=198	n=199	N=397		n=36	n=74	N=110*
	Mean (SD)		Mean difference (95% CI)[1]		Mean (SD)		Mean difference (95% CI)[1]
Plasma Glucose, mmol/l							
Fasting	4.1 (0.4)	4.3 (0.5)	0.2 (0.1, 0.3)		4.4 (0.5)	4.2 (0.6)	−0.2 (−0.4, 0.1)
1-hour	5.9 (1.4)	5.9 (1.4)	−0.1 (−0.4, 0.2)		5.7 (1.1)	5.5 (1.3)	−0.4 (−0.9, 0.1)
2-hours	5.5 (1.1)	5.5 (1.2)	−0.1 (−0.3, 0.2)		5.6 (1.0)	5.1 (1.0)	−0.5 (−1.0, −0.1)
	N (%)		Risk Ratio (95% CI)		N (%)		Risk Ratio (95% CI)
Gestational Diabetes							
No	191 (97.0)	181 (91.0)	1.00		34 (94.4)	68 (91.9)	1.00
Yes	6 (3.0)	18 (9.0)	3.9 (1.4, 10.7)		2 (5.6)	6 (8.1)	1.1 (0.2, 6.6)[2]
	Postpartum				Postpartum		
	n=142	n=150	N=292		n=22	n=60	N=82
	Mean (SD)		Mean difference (95% CI)[1]		Mean (SD)		Mean difference (95% CI)[1]
Plasma Glucose, mmol/l							
Fasting	4.7 (0.6)	4.7 (0.5)	0.0 (−0.1, 0.2)		4.7 (0.6)	4.6 (0.5)	−0.1 (−0.4, 0.2)
1-hour	5.8 (1.3)	5.5 (1.7)	−0.4 (−0.8, 0.0)		5.6 (1.7)	5.6 (1.6)	0.0 (−0.9, 0.9)
2-hours	5.5 (1.2)	5.3 (1.2)	−0.2 (−0.5, 0.1)		5.3 (0.9)	5.3 (1.1)	0.1 (−0.4, 0.7)
HOMA-IR	2.9 (2.2)	2.5 (2.1)	0.0 (−0.6, 0.4)		2.5 (2.4)	2.4 (1.8)	−0.2 (−1.2, 0.8)
Matsuda Index	6.5 (4.6)	8.0 (6.1)	0.9 (−0.5, 2.3)		8.4 (5.4)	8.1 (6.8)	−1.2 (−4.7, 2.3)
	N (%)		Risk Ratio (95% CI)[1]		N (%)		Risk Ratio (95% CI)1
Glucose Metabolism							
Normal	124 (93.2)	137 (95.8)	1.00		21(100.0)	56 (96.6)	1.00
Any glucose metabolism impairment (combined)	9 (6.8)	6 (4.2)	0.5 (0.2, 1.2)		0 (0.0)	2 (3.5)	--[3]
Impaired fasting glucose	1 (0.8)	2 (1.4)	--		0 (0.0)	1 (1.7)	--
Impaired glucose tolerance	6 (4.5)	2 (1.4)			0 (0.0)	1 (1.7)	

	Without HIV	With HIV	Full Cohort		Efavirenz	Dolutegravir	Post-conception ART
	Pregnancy				Pregnancy		
	n=198	n=199	N=397		n=36	n=74	N=110*
	Mean (SD)		Mean difference (95% CI)[1]		Mean (SD)		Mean difference (95% CI)[1]
Diabetes mellitus	2 (1.5)	2 (1.4)			0 (0.0)	0 (0.0)	

[1]Adjusted for: pre-pregnancy BMI, food insecurity status, family history of diabetes, tuberculosis status, physical activity frequency, parity, socioeconomic status.

[2]Adjusted for: pre-pregnancy BMI, family history of diabetes, physical activity frequency, parity, socioeconomic status due to model convergence issues.

[3]Cannot be estimated. Missing data: Pregnancy fasting glucose n=2, 1-hour glucose n=3, 2-hour glucose n=2; Postpartum: fasting glucose n=17, 1-hour glucose n=19, 2-hour glucose n=18, HOMA-IR n=17, Matsuda index n=22.

Table 3.

Associations between pre-pregnancy BMI category and gestational diabetes (GDM), overall and by HIV status.

	Without HIV N=198			With HIV N=199			Full Cohort N=397		
	No GDM N=191	GDM N=6	Risk Ratio	No GDM N=181	GDM N=18	Risk Ratio	No GDM N=372	GDM N=24*	Risk Ratio
	N (%)		(95% CI)	N (%)		(95% CI)	N (%)		(95% CI)
Pre-pregnancy BMI (m/kg^2)									
Underweight (<18.5)	0 (0.0)	0 (0.0)	--	0 (0.0)	0 (0.0)	--	0 (0.0)	0 (0.0)	--
Normal weight (18.5 - <25.0)	36 (97.3)	1 (2.7)	1.00	39 (92.9)	3 (7.1)	1.00	75 (94.9)	4 (5.0)	1.00
Overweight (25.0 - <30.0)	49 (98.0)	1 (2.0)	0.74 (0.05, 11.53)	58 (95.1)	3 (4.9)	0.69 (0.15, 3.26)	107 (96.4)	4 (3.6)	0.71 (0.18, 2.77)
Obese (≥ 30.0)	106 (97.2)	3 (2.8)	1.01 (0.11, 9.54)	84 (87.5)	12 (12.5)	1.75 (0.52, 5.89)	190 (92.7)	15 (7.3)	1.45 (0.49, 4.23)

*1 person with without HIV, but with GDM was missing pre-pregnancy BMI.

Table 4.

Associations between gestational diabetes in pregnancy and birth outcomes among 385 live births.

	Overall		Gestational Diabetes (GDM)		
	Median (IQR)		Without GDM n=385 (94%)	With GDM n=24 (6%)	Mean Difference (95% CI)[1]
Birthweight (grams)	3160 (2800, 3520)		3160 (2800, 3520)	3250 (2880, 3550)	8.0 (−1245.3, 261.3)
Gestational age	39 (37, 39)		39 (37, 40)	38 (36, 39)	−1.0 (−2.0, −0.0)
	N (%)				RR 95% CI[1]
Preterm Birth	63 (16.4)		55 (15.4)	7 (30.4)	2.44 (1.24, 4.81)
Low birthweight	49 (12.7)		44 (12.3)	4 (17.4)	1.70 (0.68, 4.23)
High birthweight	16 (4.2)		14 (3.9)	2 (8.7)	3.38 (0.76, 14.95)
Small for gestational age	30 (7.8)		27 (7.6)	2 (8.7)	1.22 (0.29, 5.12)
Large for gestational age	58 (15.1)		51 (14.3)	7 (30.4)	2.40 (1.23, 4.66)
Emergency Cesarean	74 (19.9)		64 (18.6)	9 (39.1)	2.37 (1.26, 4.46)

Preterm birth: birth <37 weeks' gestation. Low birthweight: <2500 grams. Small for gestational age: birthweight <10th percentile for gestational age. Large for gestational age: birthweight> 90th percentile for gestational age. Missing Data: 3 people missing GDM; 1 person missing BP; 1 missing birthweight; 8 missing emergency c-section outcome. RRs estimated using Poisson models with robust variance estimators.

[1] Adjusted for: pre-pregnancy BMI, food insecurity status, family history of diabetes, tuberculosis status, physical activity frequency, parity, socioeconomic status.

[2] Adjusted for: pre-pregnancy BMI, food insecurity status, tuberculosis status, physical activity frequency, parity, socioeconomic status.