EARLY PREGNANCY INSULIN DYNAMICS IN SOUTH AFRICAN WOMEN WITH HIV ON DOLUTEGRAVIR: THE ORCHID STUDY

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Julia H. Goedecke[1,2], Georgia Roussos[3], Kristina Utzschneider[4], Elton Mukonda[3], Justine Legbedze[5], Allison Zerbe[6], Landon Myer[3], Elaine Abrams[6], Hlengi Madlala[3], Sandisiwe Matyeseni[3], Jody Rusch[7], Jami Josefson[8], Patrick Catalano[9], **Jennifer Jao[8]**

[1] South African Medical Research Council, Biomedical Research and Innovation Platform, Cape Town, South Africa; [2] University of Cape Town, Department of Human Biology[3], Division of Epidemiology and Biostatistics[4], Cape Town, South Africa; [4] VA Puget Sound Health Care System and University of Washington, Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, Seattle, USA; [5] Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [6]ICAP at Columbia, Mailman School of Public Health and Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA; [7] University of Cape Town, Division of Chemical Pathology; National Health Laboratory Service, Groote Schuur Hospital, Cape Town, South Africa; [8] Northwestern University Feinberg School of Medicine, Department of Pediatrics, Chicago, IL, USA; [9]Massachusetts General Hospital, Department of Obstetrics and Gynecology, Boston, MA, USA

BACKGROUND

- Little is known about glucose regulation by insulin in early pregnancy in women with HIV (WWH) receiving tenofovir/lamivudine/dolutegravir (TLD).
- We assessed differences in insulin dynamics in early pregnancy in WWH receiving TLD.

METHODS

Study population

- The Obesogenic oRigins of maternal and Child metabolic Health Involving Dolutegravir (ORCHID) enrolled pregnant WWH initiating/receiving TLD and HIV-seronegative pregnant women in Cape Town, South Africa
- Inclusion:
  - ≥16 years
  - ≤18 weeks gestational age (GA)
- Exclusion:
  - Diabetes
  - Hypertension
- For this analysis we included only participants enrolled ≤14 weeks GA

Primary outcome

- Insulin sensitivity (Matsuda index), 1st phase insulin response (Stumvoll equation), beta-cell function (oral disposition index, DIo, calculated as: Stumvoll X Matsuda), and Mari model-derived measures of beta-cell function (glucose sensitivity), insulin secretion rate, and postprandial insulin clearance assessed by 75g Oral Glucose Tolerance Test (OGTT) at enrollment

Exposure of interest

- HIV status
- Duration of TLD prior to enrollment:
  - ≤15 days (TLD_{15})
  - 15-90 days ($TLD_{15\text{-}90}$)
  - >90 days ($TLD_{>90}$)

Statistical analysis

- Quantile regression models were used to assess the association of measures of insulin dynamics with the following, adjusting for confounders:
  1) HIV status
  2) duration of TLD

We thank the ORCHID study participants and study staff without whom this study would not be possible. This study was funded by R01HD104599.

WWH receiving TLD have better insulin sensitivity and beta-cell function than HIV-seronegative women, with longer TLD use associated with enhanced beta-cell function in early pregnancy.

Table 1: Characteristics of pregnant women by maternal HIV status at enrollment

Characteristic	HIV-seronegative, N = 537	WWH, N = 357	p-value
Age (years)	26 (22, 31)	29 (25, 34)	<0.001
SES score	24.8 (20.0, 30.0)	23.0 (19.0, 28.8)	0.023
Gestational Age (weeks)	10.9 (9.0, 12.9)	10.9 (9.3, 12.6)	>0.9
Multiparous	107 (20%)	109 (31%)	<0.001
BMI (kg/m^2)	30.0 (25.5, 35.6)	29.6 (24.6, 34.3)	0.063
Fat mass index (kg/m^2)	12.7 (9.4, 17.0)	12.1 (8.7, 16.1)	0.10
Body fat (%)	42.9 (36.1, 48.4)	41.0 (34.3, 48.9	0.6
Glycemic status:			0.667
Normal glucose tolerance	503 (94%)	340 (95%)	
Gestational diabetes	30 (5.6%)	15 (4.2%)	
Frank diabetes	4 (0.7%)	2 (0.6%)	
CD4 <200 cells/mm^3	--	25 (7%)	--
HIV RNA >50 copies/mL	--	89 (25%)	--

Values are expressed as median (IQR) for continuous and n (%) for categorical variables.

RESULTS

- 894 women (357 WWH and 537 HIV-seronegative) were included (Table 1); among WWH, 109 (31%) were $TLD_{<15}$, 34 (9.5%) $TLD_{15\text{-}90}$, and 214 (60.0%) $TLD_{>90}$.
- Rates of gestational diabetes or frank diabetes measured by OGTT did not differ by HIV status (p=0.667), or by duration of TLD in WWH (p=0.510).
- 25% HIV RNA >50 copies/mL at enrollment.
- While fasting glucose did not differ by HIV status, fasting insulin, HOMA-IR, and 1st phase insulin secretion were lower, and Matsuda, DIo, and postprandial insulin clearance were higher in WWH than HIV-seronegative women in univariate analyses (Table 2).

Table 2: Insulin dynamics of pregnant women by HIV status

Characteristic	HIV-seronegative, N = 537	WWH, N = 357	p-value
Fasting glucose (mmol/L)	4.2 (3.9, 4.4)	4.2 (3.9, 4.4)	0.8
Fasting insulin (mIU/L)	8.6 (5.4, 12.9)	7.5 (4.9, 11.5)	0.003
HOMA-IR	1.60 (0.98, 2.43)	1.38 (0.85, 2.2)	0.005
Matsuda index	6.27 (4.24, 9.17)	7.48 (4.96, 10.26)	<0.001
Stumvoll 1st phase insulin secretion (pmol/L)	1640 (1249, 2157)	1507 (1188, 1963)	0.008
DIo	3054 (2199, 4640)	3569 (2499, 5433)	<0.001
Glucose Sensitivity (pmol min-1m-2mmol-1L)	112.6 (80.5, 160.7)	117.7 (79.0, 176.7)	0.4
Total insulin secretion rate (nmol m^{-2})	40.2 (30.1, 50.9)	38.4 (29.1, 47.6)	0.049
Postprandial insulin clearance (L min^{-1}m^{-2})	5.6 (4.4, 6.9)	6.4 (5.7, 8.0)	<0.001

Values are Median (IQR), HOMA-IR, homeostatic model of insulin resistance; DIo, oral disposition index.

RESULTS CONTINUED

- After adjusting for age, socioeconomic status and fat mass index, WWH had higher insulin sensitivity, beta-cell function (estimated using the DIo and Mari-derived glucose sensitivity index), and postprandial insulin clearance (Table 3).
- Compared to HIV-seronegative women, $TLD_{<15}$ and $TLD_{>90}$ were associated with higher insulin sensitivity and postprandial insulin clearance, whereas only $TLD_{>90}$ was associated with higher beta-cell function (DIo and glucose sensitivity).

Table 3. Adjusted median differences in insulin dynamics outcomes in early pregnancy by HIV infection status and duration of tenofovir/lamivudine/dolutegravir use

	Model Outcome				
Exposure of Interest	Matsuda	Stumvoll 1st phase insulin secretion	DIo	Glucose Sensitivity	Postprandial Insulin Clearance
HIV-seronegative	Ref	Ref	Ref	Ref	Ref
WWH	1.13 (*p*=0.003)	-90.74 (*p*=0.050)	571 (*p*=0.004)	10.40 (*p*=0.046)	0.785 (*p*<0.001)
HIV-seronegative	Ref	Ref	Ref	Ref	Ref
TLD_{15}	1.025 (*p*=0.021)	-168.55 (*p=0.025*)	542 (*p*=0.055)	-2.64 (*p*=0.722)	0.793 (*p*<0.001)
$TLD_{15\text{-}90}$	1.40 (*p*=0.120)	-62.60 (*p*=0.617)	405 (*p*=0.389)	12.25 (*p*=0.319)	0.161 (*p*=0.675)
TLD_{90}	0.82 (*p*=0.062)	-75.27 (*p*=0.221)	702 (*p*=0.002)	15.62 (*p*=0.010)	0.870 (*p*<0.001)

Values are expressed as coefficients and p values. Models adjusted for age, socioeconomic status, and fat mass index. DIo=oral disposition index, TLD=tenofovir/lamivudine/dolutegravir

CONCLUSIONS

- WWH receiving TLD have better insulin sensitivity and beta-cell function than HIV-seronegative women, with longer TLD use associated with enhanced beta-cell function in early pregnancy..
- Longitudinal studies in pregnant WWH will be useful to understand whether this favorable profile persists throughout pregnancy and post-partum.