Red blood cell folate concentrations in mothers/infants in pregnancy: dolutegavir vs efavirenz

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IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

BACKGROUND

The Botswana Tsepamo Surveillance study found a possible association between the antiretroviral (ART) treatment with dolutegravir (DTG) at conception and increased risk of neural tube defects. The signal was no longer evident in a subsequent analysis that expanded the surveillance period. To explore mechanisms of this early finding, we studied folate concentrations in pregnant women and their infant enrolled in the Virologic Efficacy and Safety of ART Combinations (VESTED) trial (IMPAACT 2010), which compared 3 ART regimens started in pregnancy. **We hypothesized that DTG may block cellular uptake of folate.**

Study objectives:

- To **describe** the distribution of maternal red blood cell (RBC) folate concentrations at study entry and delivery, infant folate at the birth visit, and infant:maternal ratio at birth by treatment arms.
- To **compare** the average trajectory over time in maternal RBC folate concentrations from study entry to delivery, infant RBC folate and infant:maternal delivery ratio between each of the three study arms.

METHODS

Study population

IMPAACT 2010: Multicenter, open-label, randomized controlled phase 3 clinical trial (9 countries)

- Assigned pregnant women with HIV between 14-28 weeks of gestational age to initiate one of three ART regimens: Dolutegravir (DTG) + emtricitabine (FTC)/tenofovir alafenamide (TAF)
  DTG+FTC/tenofovir distoproxil fumarate (TDF)
  Efavirenz (EFV)/FTC/TDF.
- **Six months after IMPAACT 2010 began enrollment, Letter of Amendment (LOA)** approved to measure RBC folate in mothers and infants. Dataset and samples are from June 2018 to August 2019.

Data

- Blood sample: At study entry and delivery from the mother and at the birth visit from the infant.
- Use of folic acid antagonists, folic acid and other vitamin/micronutrient supplementation use: within 28 days prior to study entry and throughout the study was recorded.
- Red blood cell (RBC) folate: Measured at the US Centers for Disease Control and Prevention (CDC) by use of a microbiologic assay calibrated with 5-methyltetrahydrofolate.[1]

$$\textbf{RBC folate concentration (nmol/L) calculated as } = \frac{(\textbf{whole blood folate in nmol/L})}{(\textbf{Hematocrit as \%})/100}$$

Analysis

- Study Outcomes 1) Maternal RBC folate at entry and delivery (and trajectory from entry to delivery)
  2) Infant RBC folate
  3) Ratio of infant-to-maternal RBC folate at birth/delivery
- Models: Generalized estimating equation models for the $\log_e$ of folate outcomes were fit to estimate the geometric mean ratio (GMR) and 95% confidence intervals (CIs) of each arm comparison, unadjusted and adjusted for precision variables. The estimated GMR trajectory of maternal RBC folate was compared between arms with a ratio ((GMRT/C).
  - ***Maternal folate trajectories model*** *includes treatment arm, time from entry to delivery (weeks) treatment arm*weeks. Adjusted model also includes precision variables*
  - ***Infant RBC folate at birth*** *and* ***infant-to-maternal RBC folate ratio*** *- includes treatment arm. Adjusted model also includes precision variables*
  - ***Precision variables included in adjusted models****: country, use of folic acid supplements, use of folate antagonists, mandatory folic acid fortification in country, season folate sample collected.*

The distribution of maternal folate concentrations was similar by treatment arm at entry and delivery, and in infants at birth.

Results are consistent with no clinically meaningful differences between treatment arms in maternal RBC folate trajectory during pregnancy, infant RBC folate at birth, or infant-to-maternal RBC folate ratio at birth/delivery.

RESULTS

Entry characteristics (Table 1):

- 340 mothers and 310 infants had at least one RBC folate measurement available (**Table 1**). Among participants enrolled in IMPAACT after the date of the LOA implementation, a folate result was obtained at entry on 319/415 (78%), at delivery on 323/435 (74%) and in 310/420 (73%) of infants.
- Most (78%) women enrolled in Africa, with median (IQR) age 25 (22,30) years, gestational age 22 (17, 25) weeks, and CD4 count 482 (326, 644) cells/mm^3.

Factors that may affect folate levels, by treatment arm:

- Randomization balanced the baseline distributions of factors that could affect folate levels among the treatment arms, including use and timing of folic acid supplementation, folate antagonist use, mandatory folic acid fortification in country, and time of year of folate measurements.
- 90% of mothers received folic acid supplements and 90% lived in countries with folic acid fortification of food.

RBC folate concentrations:

- RBC folate was low (<305 nmol/L) in 6% and 5% mothers at entry and delivery, respectively.[2]
- Distribution of RBC folate was similar by treatment arm at maternal entry, at delivery and in the infant **(Figure 1**).

Adjusted differences in folate outcomes by treatment arm (**Table 2**)**:**

- The estimated geometric mean trajectory of maternal folate was only 3% higher in the DTG+FTC/TAF arm than the EFV/FTC/TDF arm (aGMRT/C: 1.03, 95%CI 1.00, 1.06) (**Table 2**).
- The DTG+FTC/TAF arm had only an estimated 8% lower infant-maternal folate ratio (aGMR 0.92, 95%CI 0.78, 1.09) compared to the EFV/FTC/TDF arm.

STRENGTHS AND LIMITATIONS

A major strength of this study is that it was conducted within a randomized controlled clinical trial, balancing the distribution of baseline factors at the time of randomization across treatment arms.

The study has some limitations. Measurement of folate began mid-study. There were varying lengths of time between entry gestational age and delivery. Maternal folate trajectories may not be linear; folate was only measured at entry and delivery. Finally, we do not have folate measurements at conception to evaluate the effect of folate on neural tube defects.

CONCLUSIONS

We initially hypothesized that DTG may block cellular uptake of folate during pregnancy. However, our findings suggest that cellular uptake of folate and transport of folate to the infant do not differ in pregnant persons starting DTG- vs. EFV-based ART (nor TAF vs. TDF).

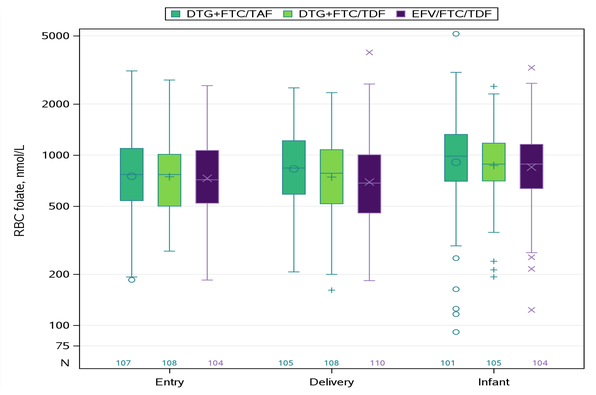

FIGURE 1. **Box plot of maternal RBC folate at entry and delivery and infant folate at delivery, by treatment arm**

TABLE 1. Maternal baseline characteristics by treatment arm

		DTG+FTC/TAF (N=114)	DTG+FTC/TDF (N=114)	EFV/FTC/TDF (N=112)
		Median (Q1, Q3) or N (%)		
Race	Asian	6 (5%)	5 (4%)	6 (5%)
	Black Or African American	93 (82%)	96 (84%)	95 (85%)
	White	5 (4%)	6 (5%)	7 (6%)
	Other	10 (9%)	6 (5%)	4 (4%)
	Unknown	0 (0%)	1 (1%)	0 (0%)
Ethnicity	Hispanic Or Latino	21 (18%)	19 (17%)	17 (15%)
	Not Hispanic Or Latino	91 (80%)	94 (82%)	95 (85%)
	Unknown	2 (2%)	1 (1%)	0 (0%)
Country	Brazil	21 (18%)	19 (17%)	17 (15%)
	Botswana	4 (4%)	6 (5%)	7 (6%)
	India	2 (2%)	1 (1%)	0 (0%)
	Thailand	4 (4%)	4 (4%)	6 (5%)
	Tanzania	7 (6%)	5 (4%)	8 (7%)
	Uganda	34 (30%)	32 (28%)	32 (29%)
	United States	1 (1%)	1 (1%)	0 (0%)
	South Africa	0 (0%)	3 (3%)	0 (0%)
	Zimbabwe	41 (36%)	43 (38%)	42 (38%)
At Study entry				
Age (years)		26 (22, 30)	25 (21, 29)	25 (22, 30)
BMI (kg/m²)		24 (22, 28)	24 (22, 27)	23 (21, 26)
Gestational age (weeks)		22 (17, 25)	21 (18, 25)	22 (18, 26)
CD4 (cells/mm³)		483 (334, 632)	480 (349, 622)	482 (306, 673)
HIV RNA ($\log_{10}$ copies/mL)		3 (2, 4)	3 (2, 4)	3 (2, 4)

TABLE 2. Geometric Means of Each RBC Folate Outcome by Treatment Arm and Comparisons of Maternal/Infant RBC Folate Outcomes Between Arms

RBC Folate Measurement	Treatment Arm	RBC Folate (nmol/L) Geometric mean (geometric SD)[1]	Model Estimates of the Geometric Mean Ratio (95%CI) of Each Arm Comparison for Each RBC Folate Outcome			
			RBC Folate Outcome	Treatment Arm Comparison	Estimate (95%CI), P-value[2,3] Unadjusted	Adjusted
Maternal Entry / Delivery	DTG+FTC/TAF	751 (1.76) / 830 (1.68)	**Maternal RBC folate trajectory**	DTG+FTC/TAF vs. DTG+FTC/TDF	1.02 (0.98, 1.06) P=0.34	1.02 (0.99, 1.05) P=0.22
	DTG+FTC/TDF	746 (1.62) / 743 (1.67)		DTG+FTC/TAF vs. EFV/FTC/TDF	1.02 (0.98, 1.06) P=0.22	1.03 (1.00, 1.06) P=0.094
	EFV/FTC/TDF	731 (1.67) / 694 (1.78)		DTG+FTC/TDF vs. EFV/FTC/TDF	1.01 (0.97, 1.05) P=0.69	1.01 (0.98, 1.04) P=0.62
Infant at birth	DTG+FTC/TAF	907 (1.96)	**Infant RBC folate at birth (nmol/L)**	DTG+FTC/TAF vs. DTG+FTC/TDF	1.04 (0.90, 1.22) P=0.59	1.02 (0.88. 1.17) P=0.81
	DTG+FTC/TDF	869 (1.57)		DTG+FTC/TAF vs. EFV/FTC/TDF	1.07 (0.92, 1.24) P=0.44	1.08 (0.93, 1.24) P=0.36
	EFV/FTC/TDF	850 (1.70)		DTG+FTC/TDF vs. EFV/FTC/TDF	1.02 (0.88, 1.19) P=0.74	1.06 (0.92, 1.22) P=0.41
Infant-to-maternal ratio	DTG+FTC/TAF	1.16 (2.15)	**Infant-to-maternal ratio**	DTG+FTC/TAF vs. DTG+FTC/TDF	0.97 (0.81, 1.17) P=0.79	0.96 (0.82, 1.14) P=0.69
	DTG+FTC/TDF	1.19 (1.86)		DTG+FTC/TAF vs. EFV/FTC/TDF	0.95 (0.79, 1.14) P=0.62	0.92 (0.78, 1.09) P=0.36
	EFV/FTC/TDF	1.21 (1.76)		DTG+FTC/TDF vs. EFV/FTC/TDF	0.98 (0.82, 1.17) P=0.80	0.96 (0.81, 1.13) P=0.57

[1]The geometric standard deviations are on the multiplicative scale not the additive scale. [2] This was a complete case analysis.

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