Dolutegravir exposure and congenital anomalies in sub-Saharan Africa

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The MANGO Study

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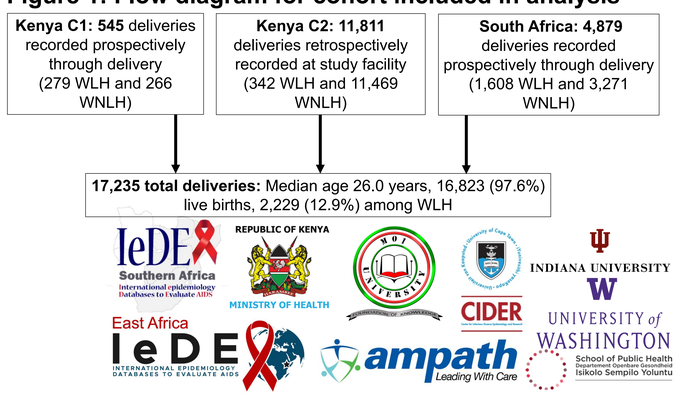
BACKGROUND

- Limited regional data eliciting associations between antiretroviral therapy (ART) use and adverse maternal and newborn outcomes, including congenital anomalies (CAs)
- Measuring Adverse Pregnancy and Newborn Congenital Outcomes (MANGO) is a collaboration between IeDEA-supported sites in Kenya and South Africa
- We explored associations between periconception dolutegravir (DTG) exposure and risk of major CAs

METHODS

- Delivery outcomes were ascertained among pregnant women living with HIV (WLH) and not living with HIV (WNLH)
  - Sites: Eldoret, Kenya and Cape Town, South Africa
  - Kenyan cohort (**Figure 1**)
    - Prospective C1: women followed during pregnancy and through delivery in Kenya
    - Retrospective C2: all women delivering at the tertiary care facility) components in Kenya
    - Prospective: women followed during pregnancy at a primary care facility delivering at the enrollment facility or at two referral facilities in South Africa
- Deliveries September 2020 to August 2022
  - Stratified by HIV status and ART exposure periconception (+/- 60 days from estimated date of conception)
- Used log-linear regression models for factors associated with risk of major CAs detected at a birth surface exam

Figure 1: Flow diagram for cohort included in analysis



Early analysis: ***no significant differences*** in risk of **major congenital anomalies** by 1) **HIV status** or 2) periconception **dolutegravir vs. non-dolutegravir ART** exposure

RESULTS

- Among 17,235 deliveries, 309 (29.0%) of 1,064 with known periconception ART were on DTG-containing ART
- Any CA were detected in 226 births (23.4% polydactyly [**Figure 2**]), and major CAs in 123 births:
  - 111 (7.40/1000 births) among WNLH, 12 (5.38/1000 births) among all WLH regardless of ART exposure, 2 (6.47/1000 births; 1 encephalocele and 1 Down syndrome) among WLH on periconception DTG, 4 (5.30/1000 births; 2 congenital cytomegalovirus infections, 1 Down syndrome, and 1 chromosomal abnormality) among WLH on periconception non-DTG ART, and 6 (5.15/1000 births) among WLH with unknown ART
  - 1 (1.83/1000 births), 102 (8.64/1000 births), and 20 (4.10/1000 births) among the prospective Kenyan, retrospective Kenyan, and prospective South African cohorts, respectively
- Neither HIV status (aRR 1.0, 95% CI 0.53, 1.90) nor DTG exposure (aRR 1.46, 95% CI 0.24, 8.73) were associated with CAs, though Kenya was (aRR 2.05, 95% CI 1.23, 3.42 [**Table 1**])

Table 1: Factors associated with any major congenital anomaly detected by a birth surface exam, stratified by HIV status and dolutegravir exposure, from the IeDEA Multiregional MANGO Collaboration, September 2020 to August 2022

Variable	All women regardless of HIV status (n=17,235)		All WLH with known ART (n=1,064)	
	uRR (95% CI)	aRR[1] (95% CI)	uRR (95% CI)	aRR[2] (95% CI)
Maternal age at delivery outcome (per year)	1.003 (0.974-1.032)	1.007 (0.978-1.037)	1.031 (0.901-1.179)	1.030 (0.899-1.180)
Country (Kenya vs. South Africa)	2.033 (1.261-3.279)	**2.053 (1.231-3.421)**	0.631 (0.074-5.378)	
HIV status at delivery (positive vs. negative)	0.728 (0.402-1.318)	0.999 (0.525-1.902)	n/a	n/a
Periconception DTG exposure (vs. non-DTG)	n/a	n/a	1.222 (0.225-6.636)	1.460 (0.244-8.732)

uRR=unadjusted risk ratio; aRR=adjusted risk ratio; ART=antiretroviral therapy; CI=confidence interval; DTG=dolutegravir; WLH= women living with HIV; WNLH=women not living with HIV
[1] Calculated with a log-link regression model with a log link among the cohort of WLH (regardless of ART exposure) and WNLH, adjusting for the other variables, as applicable, in the table.
[2] Calculated with a log-link regression model with a log link among the cohort of WLH on DTG and WLH on non-DTG ART, adjusting for the other variables, as applicable, in the table.

CONCLUSIONS

- Our early analysis did not find any significant differences in risk of major CAs detected by birth surface exam based on HIV status or periconception DTG vs. non-DTG ART exposure
  - Longer follow up will yield larger sample sizes
- Risk of major CAs was higher in Kenya, driven by the higher rate of CAs detected among the retrospective Kenyan cohort (C2), likely due to the referral facility receiving women for delivery with known complications (data not shown)

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Figure 2. Example congenital abnormalities recorded in the MANGO study

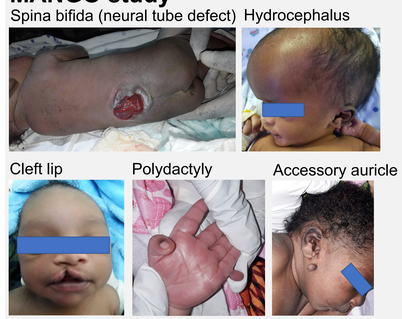

Photo credits: MANGO Kenya