#219: A Randomized, Double-Masked, Placebo-Controlled Phase IIB Trial of Azithromycin and Trimethoprim-Sulfamethoxazole as Bacterial STI Prophylaxis in Pregnant Women with HIV (PREMISE Trial)

UAB MEDICINE

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BACKGROUND

- This phase IIB randomized clinical trial was designed to test the efficacy of a novel regimen to prevent bacterial sexually transmitted infections and malaria in pregnant women living with HIV in Cameroon.
- Daily TMPS prophylaxis is recommended for all pregnant women living with HIV in Cameroon to prevent malaria in an endemic region. Findings presented here focus on STI outcomes.
- In Cameroon, HIV prevalence among pregnant women is 5.7% and bacterial STI prevalence ranges from 2-10%.

STUDY GOAL

To assess the efficacy of adding azithromycin prophylaxis (1 gram daily x 3 days) to the standard daily trimethoprim-sulfamethoxazole (TMPS) prophylaxis regimen on a composite STI measure at the time of delivery (incident syphilis/chlamydia/gonorrhea).

STUDY DESIGN

- **Design:** phase IIB, double masked, placebo-controlled randomized clinical trial
- Randomized to a novel regimen of monthly AZ 1 gram daily for 3 days and daily trimethoprim-sulfamethoxazole (TMPS) or the standard regimen of daily TMPS alone with monthly placebo AZ for 3 days
- Medication was administered as directly observed therapy at baseline and provided at monthly follow up visits until delivery.
- **Inclusion Criteria:**
  - Pregnant women in prenatal care at 3 study facilities in Yaounde, Douala and Mutengene, Cameroon.
  - Confirmed HIV infection
  - Gestational age < 28 weeks
  - Singleton Pregnancy
  - No known fetal anomaly at time of enrollment
- **STI Testing:**
  - Nucleic acid amplification testing (NAAT) for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) was performed on provider-collected vaginal swabs.
  - Syphilis was defined serologically with a newly positive treponemal screening test or 4-fold increase in RPR or VDRL titer compared to baseline.
- **Statistical Analysis**
  - Proportions compared by relative risk with 95% confidence intervals and a significant p value defined as <0.05.

Table 1: Baseline Characteristics of Study Participants (n=308)

Characteristic	Active (TMPS - AZ) n=155 n (%)	Standard of Care (TMPS) n=153 n (%)	Total n=308 n (%)	p-value
Median age in years (IQR)	32 (28-36)	32 (28-36)	32 (28-36)	0.95
Region of Residence				1.00
Douala (urban)	100 (64.5)	98 (64.1)	198 (64.3)	
Yaounde (urban)	18 (11.6)	18 (11.8)	36 (11.7)	
Mutengene (suburban)	37 (23.9)	37 (24.2)	74 (24.0)	
Education				0.16
None/Primary	48 (31.0)	41 (26.8)	89 (28.9)	
Secondary/High School	72 (46.5)	84 (54.9)	156 (50.6)	
University	35 (22.6)	28 (18.3)	63 (20.5)	
Marital Status				0.31
Married	91 (58.7)	88 (57.5)	179 (58.1)	
Living with Partner	34 (21.9)	24 (15.7)	58 (18.8)	
Single	30 (19.4)	41 (26.8)	71 (23.1)	
Gestational Age (completed weeks)				0.12
<14 weeks	0 (0)	4 (2.6)	4 (1.3)	
14-20 weeks	48 (31.0)	48 (31.4)	96 (31.2)	
21-28 weeks	107 (69.0)	101 (66.0)	208 (67.5)	
Weight - kg	72	74	73	0.05
Median WBC Count/mm³ (IQR)	6.1 (4.7-7.3)	5.8 (4.8 - 7.0)	5.9 (4.7- 7.1)	0.39
Most Recent CD4 count/mm³ (IQR)	477 (308-664)	496 (360-655)	493 (326-663	0.65
Median Hemoglobin (g/dL)	10.7	10.8	10.8	0.11
Median Years since HIV Diagnosis	3	3	3	0.37
HIV Status of Partner				0.95
Positive	46 (29.7)	43 (28.1)	89 (28.9)	
Negative	81 (52.3)	82 (53.6)	163 (52.9)	
Unknown	28 (18.1)	28 (18.3)	56 (18.2)	
Currently Taking ART	155 (100%)	153 (100%)	308 (100%)	
Excellent Reported ART Adherence	150 (96.8)	139 (90.8)	289 (93.8)	0.03
Peripheral Malaria by microscopy	5 (3.2)	5 (3.3)	10 (3.2)	0.98

Table 2: Efficacy Outcomes at Delivery by Arm - Intention to Treat Analysis (n= 278)

Outcome	Active TMPS-AZ	Standard of Care TMPS	Relative Risk (95% CI)	p-value
Infection at Delivery				
C trachomatis positive NAAT	2 (1.4%)	2 (1.5%)	0.95 (0.14 - 6.65)	0.96
N gonorrhoeae positive NAAT	1 (0.7%)	0 (0%)	NA	
Incident Syphilis during pregnancy	2 (1.4%)	3 (2.0%)	0.65 (0.11 - 3.82)	0.63
Composite STI Outcome (CT/NG/Syph)	5 (3.2 %)	5 (3.3%)	0.78 (0.21 - 2.84)	0.70
Malaria - peripheral blood PCR	9 (6.4%)	6 (4.4%)	1.45 (0.53-3.95)	0.47
Birth Outcomes				
Stillbirth (>28 weeks)	1 (0.6%)	2 (1.3%)	0.49 (0.05 - 5.39)	0.56
Low birthweight (<2500 grams)	4 (2.8%)	7 (5.1%)	0.56 (0.17 - 1.85)	0.34
Preterm delivery (<37 weeks)	7 (5.0%)	14 (10.3%)	0.48 (0.20-1.16)	0.10
Congenital anomaly	2 (1.4%)	3 (2.2%)	1.32 (0.3 - 5.79)	0.71
Neonatal Death (<28 days old)	4 (3.1%)	3 (2.4%)	0.66 (0.11-3.87)	0.64
Composite Adverse Outcome	13 (8.4%)	20 (13.1%)	0.64 (0.33 - 1.24)	0.19

RESULTS

- A total of 308 pregnant women were enrolled at three hospital facilities in Cameroon between March 2018 and August 2020.
- 155 women were randomized to the AZ/TMPS intervention arm and 153 women were randomized to the TMPS standard care arm. A total of 278 women (90%) had delivery samples collected.
- Both groups were similar at baseline with median age 32 years, maternal education (71% secondary school or university), HIV diagnosis 3 years prior.
- More women in the active arm reported excellent adherence to antiretroviral therapy (97% vs 91%; p=0.03).
- Median CD4 count was 473 cells/mm3 (IQR 326-663).
- There was no difference in the proportion of women with the composite STI measure at delivery (3.2% in the AZ/TMPS arm and 3.3% in the TMPS arm; RR 0.78 (95% CI 0.21 - 2.84); p=0.70).
- Adverse birth outcomes were lower in the active AZ arm, but the difference was not significant (preterm delivery 5% vs 10.3% [p=0.1], low birthweight 2.8% vs 5.1% [p=0.34], composite adverse birth outcome 8.4% vs 13.1% [p=0.19].

CONCLUSIONS

- Contrary to our hypothesis, the addition of monthly azithromycin to standard daily TMPS prophylaxis among pregnant women living with HIV in Cameroon and mostly enrolled in the 2nd trimester did not reduce the rate of bacterial STI at delivery.
- The study was underpowered for this outcome due to lower than anticipated rates of incident and prevalent bacterial STI. Reasons for this are unclear.
- Women reported excellent ART adherence and rates of STI, malaria, and adverse birth outcome were low.

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