Women Living with HIV (WLWH) Lose IFNγ Responses Diagnostic of Latent TB Infection (LTBI) during Pregnancy and after INH Prophylactic Treatment (IPT)

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IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Introduction

Tuberculosis (TB) is the most common opportunistic infection and the most important cause of morbidity and mortality among people with HIV in low-income settings. The diagnosis of TB infection, particularly of latent infection (LTBI), has relied on tuberculin skin test (TST) and IFNγ release assay (IGRA) results.

We hypothesized that pregnancy decreased the sensitivity of IGRA and TST due to maternal immune suppression. Moreover, since IFNγ responses are primarily effector responses, we also hypothesized that isoniazid preventive therapy (IPT) may decrease the sensitivity of IGRA by reducing the exposure of the immune system to TB antigens.

The main objectives of this sub-study of P1078 were:
1) to determine the effect of pregnancy and IPT on IGRA and TST;
2) to compare the results of IGRA with TST at delivery and postpartum;
3) to identify factors associated with the diagnosis of LTBI in pregnancy in women with HIV infection.

Methods

Study Design:

- P1078 was a phase IV, prospective, double-blinded, placebo-controlled trial.
- Participants were randomized to initiate IPT antepartum (AP; immediate arm) or 12 weeks postpartum (PP; deferred arm).
- Eligible participants were pregnant women with HIV, ≥18 years of age, ≥14 and ≤34 weeks gestational age. Exclusion criteria were suspected TB, recent known TB exposure, treated for TB >30 days in the previous year, evidence of recent acute hepatitis, liver enzymes >1.25 upper limit of normal; or grade ≥1 peripheral neuropathy.

IGRA used was the QuantiFERON Gold in-tube (QGIT) performed at entry, delivery, and at 44 weeks postpartum at National Institutes of Health Division of AIDS-certified local laboratories using kits provided by the study. The test was performed and interpreted as per manufacturer's instructions; positive results were IFNγ -nil ≥0.35 U/ml, provided all other result acceptability criteria were also met.

TST used locally available product. TST was placed by trained research nurses at delivery and 44 weeks postpartum and read at 48 to 72 h after placement. Positive results were defined by an induration ≥5 mm in diameter at the site of inoculation.

Statistical Analysis:

- Generalized estimating equation models were fit to assess the trend over time in diagnosis of LTBI using QGIT at entry, delivery, and week 44 postpartum. Indeterminate QGIT results were considered negative. Linear mixed modeling was performed on the corresponding quantitative values of Nil, TB antigen, and PHA mitogen.
- All multivariable models included study arm and factors that had p-value less than or equal to 0.15 in univariate analysis.
- Concordance between QGIT and TST results at delivery and at week 44 postpartum was assessed using the Kappa measure of agreement and conditional logistic regression.

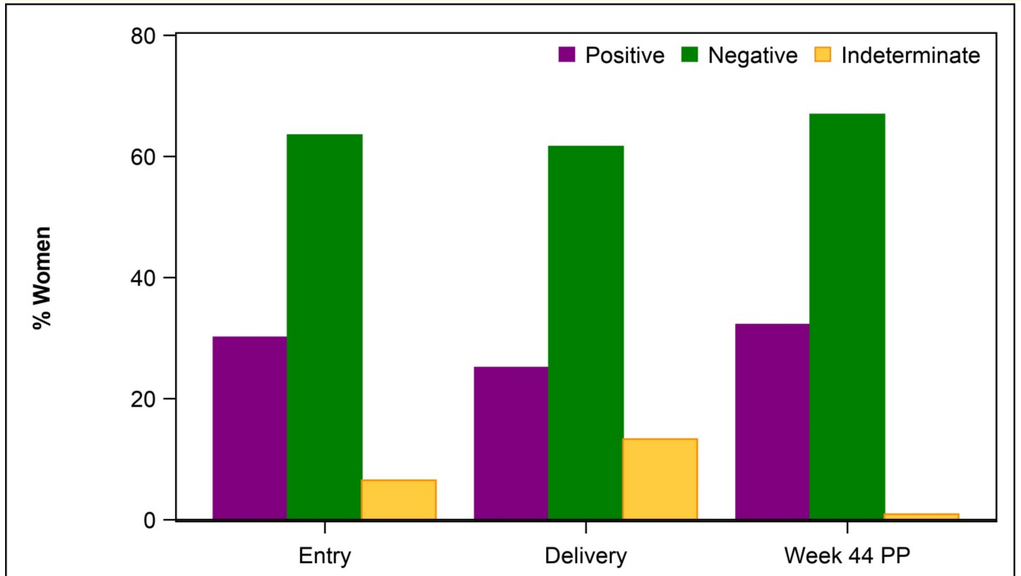
Study Population

Table 1: Demographic and HIV Disease Characteristics of the Study Population at Study Entry

Characteristics	Immediate INH (N=471)	Deferred INH (N=471)	Overall (N=944)
Age in years, median (IQR)	29 (25 – 33)	29 (24 – 33)	29 (24 – 33)
Country, N (%)			
Botswana	59 (12.5)	60 (12.7)	119 (12.6)
Haiti	5 (1.1)	10 (2.1)	15 (1.6)
India	17 (3.6)	15 (3.2)	32 (3.4)
South Africa	90 (19.1)	91 (19.2)	181 (19.2)
Tanzania	41 (8.7)	39 (8.2)	80 (8.5)
Thailand	15 (3.2)	18 (3.8)	33 (3.5)
Uganda	82 (17.4)	83 (17.5)	165 (17.5)
Zimbabwe	162 (34.4)	157 (33.2)	319 (33.8)
Gestational age in weeks, N(%)			
14 - <24	159 (33.8)	157 (33.2)	316 (33.5)
24 – 34	312 (66.2)	316 (66.8)	628 (66.5)
CD4 Count in cells/mm^3, median (IQR)	491 (351 – 668)	498 (351 – 676)	493 (351 – 670)
HIV RNA < Lower Limit of Quantification, N(%)	299/470 (63.6)	295/472 (62.5)	594/942 (63.1)
Time on Current ARV Regimen in months, median (IQR)	3 (1 – 14)	3 (1 – 17)	3 (1 – 15)
Maximum BMI during pregnancy in kg/m^2, median (IQR)	28 (25 – 31)	28 (24 – 31)	28 (25 – 31)

Results

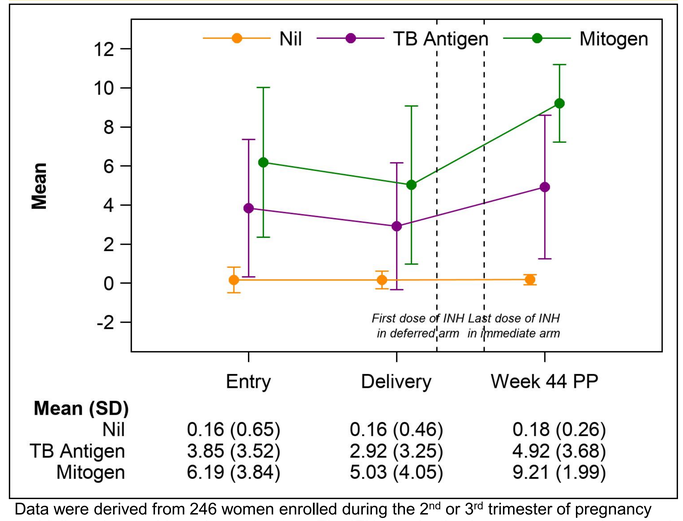
Figure 1. Changes in the Proportions of QGIT Positive, Negative and Indeterminate Results During Pregnancy and Postpartum in Women with HIV



N/Total N (%)	Entry	Delivery	Week 44 PP
Positive	284/944 (30.1)	216/862 (25.1)	246/764 (32.2)
Negative	599/944 (63.5)	531/862 (61.6)	511/764 (66.9)
Indeterminate	61/944 (6.5)	115/862 (13.3)	7/764 (0.9)

Data were derived from 944 women enrolled during the 2nd or 3rd trimester of pregnancy and longitudinally followed up. The proportion of women with positive results was significantly lower at delivery compared with entry (p<0.001) and higher postpartum compared with entry (p=0.04).

Figure 2. Changes in IFNγ Production Measured by QGIT in Women with Positive QGIT Results Postpartum



Mean (SD)	Entry	Delivery	Week 44 PP
Nil	0.16 (0.65)	0.16 (0.46)	0.18 (0.26)
TB Antigen	3.85 (3.52)	2.92 (3.25)	4.92 (3.68)
Mitogen	6.19 (3.84)	5.03 (4.05)	9.21 (1.99)

Data were derived from 246 women enrolled during the 2nd or 3rd trimester of pregnancy and followed up to 44 weeks postpartum. The IFNγ production in response to antigens and mitogen significantly increased postpartum compared with entry and/or delivery (p<0.001).

Table 2a: Agreement between QuantiFERON and Tuberculin Skin Test Results at Delivery

		TST Result		
		Positive	Negative	Total
QGIT Result	Positive	85	121	206
	Negative	28	480	508
Total		113	601	714

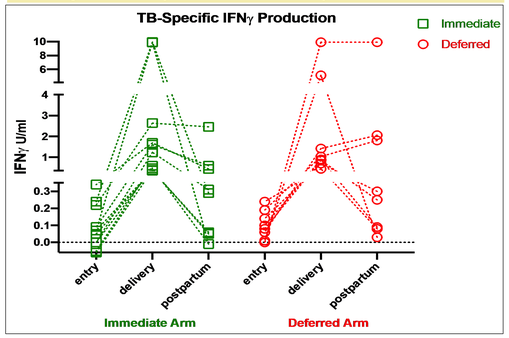
Kappa coefficient (95% CI) = 0.41 (0.34 – 0.49); QGIT result was 4.3 times more likely to be positive than TST at delivery (CI: 2.8 - 6.8).

Table 2b: Agreement between QuantiFERON and Tuberculin Skin Test Results Postpartum

		TST Result		
		Positive	Negative	Total
QGIT Result	Positive	102	127	229
	Negative	20	465	485
Total		122	592	714

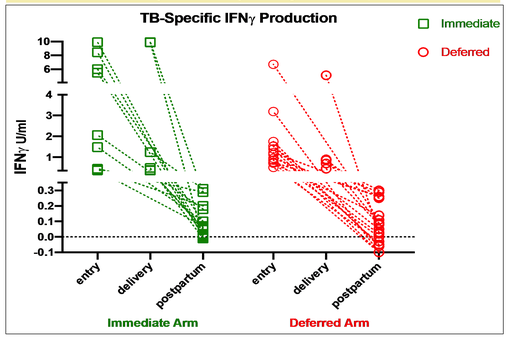
Kappa coefficient (95% CI) = 0.46 (0.39 – 0.53); QGIT result was 6.4 times more likely to be positive than TST postpartum (CI: 3.9 - 10.7).

Figure 3. Quantitative TB Antigen Responses in QGIT Converters from Negative at Entry to Positive at Delivery



Data were derived from 19 participants, including 11 in the immediate and 8 in the deferred IPT arms. Each point represents TB-nil responses at the designated visits. The lines connect data obtained from the same participant. The ordinate was organized in segments separating QGIT negative results <0.35 IFNγ U/ml from positive results; and positive results below and higher the 4 U/ml threshold previously proposed by others as an indicator of sustained conversion and predictor of development of TB disease. Three participants in each arm maintained QGIT positivity postpartum, including 2 in each arm with TB-specific IFNγ responses at delivery <4 U/ml and 1 in each arm with delivery responses >4 U/ml; 6 participants in the immediate arm and 5 in the deferred arm reverted to QGIT negative postpartum, including 1 in each arm with responses >4 U/ml at delivery. Two participants in the immediate arm lacked postpartum data.

Figure 4: Quantitative TB Antigen Responses in QGIT Reverters from Positive at Entry or Delivery to Negative Postpartum



Data were derived from 15 participants in the immediate IPT arm, including 9 who reverted from entry to postpartum and 6 additional participants who reverted from delivery to postpartum; and from 19 participants in the deferred IPT arm, including 14 who reverted from entry and 5 from delivery to postpartum. Each participant contributed a single set of data. In participants who were QGIT positive both at entry and delivery, only the entry and postpartum data were included. The points represent TB-nil responses at the designated visit. The lines connect data from individual participants. The ordinate was organized in segments separating QGIT negative results <0.35 IFNγ U/ml from positive results; and positive results below and higher the 4 U/ml threshold previously proposed by others as an indicator of sustained QGIT positivity and predictor of TB disease

Conclusions

- The sensitivity of QGIT was lower AP and at delivery compared with PP regardless of treatment arm. This was due to decreased IFNγ responses to TB antigen and/or PHA mitogen AP compared with PP. IFNγ production and QGIT rate of positive results were lowest at delivery.
- TST was less sensitive than QGIT for the diagnosis of LTBI at all time points.
- Decreased IFNγ responses in pregnancy were NOT associated with increased incidence of active TB infection.
- The frequency of conversions from QGIT negative at study entry to positive at delivery did not differ between treatment arms, suggesting that IPT administered AP did not prevent acquisition of new TB infections.
- 34 (14%) participants reverted from QGIT positive AP and/or at delivery to QGIT negative PP. All reversions occurred after completing the course of IPT, suggesting that IPT might decrease IFNγ responses to TB.

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