Predictive Value of Interferon-gamma Release Assays for Postpartum Active Tuberculosis in HIV-1 Infected Women

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Abstract

Background—There are limited data on prognostic utility of interferon-gamma (IFN-γ) release assays (IGRAs) for active tuberculosis (TB) among HIV-1 infected individuals.

Methods—Samples from a perinatal cohort of HIV-1 infected women in Kenya, obtained during pregnancy were tested using T-SPOT.TB IGRAs to detect Mycobacterium tuberculosis (MTB)-specific IFN-γ responses. IFN-γ (cut-off values>0,   6 and   10 spot forming cells/well (SFCs/well)) and CD4 cell count (cut-off values<250 and <350 cells/μL) were evaluated for sensitivity and specificity using a time dependent receiver operating characteristic (ROC) curve and positive predictive value (PPV) using Kaplan Meier method for future TB within one year postpartum.

Results—Of 327 women, 9 developed TB within one year postpartum (Incidence rate (IR): 3.5/100 person-years of follow-up (pyfu); 95% confidence interval: 1.6–6.7/100 pyfu). IFN-γ 6 SFCs/well was associated with an optimal trade-off between sensitivity (78%) and specificity

(55%) and PPV of 5.9%. In women with CD4<250 cells/µL, sensitivity and specificity of IFN-γ 6 SFCs/well were 89% and 63%, respectively and PPV was 19.2%.

Conclusion—Among HIV-1 infected women, IFN-γ response (6 SFCs/well) during pregnancy lacked high positive predictive value for postpartum TB but had higher sensitivity and positive predictive value among immunosuppressed women (CD4<250 cells/µL).

Keywords

TB IGRA; Predictive value; Sensitivity; Specificity; HIV-infected women

Background

Tuberculosis (TB) and HIV-1 are major health problems for women during reproductive years.[1] Latent TB infection (LTBI) during pregnancy in HIV-1 infected women is associated with increased risk of postpartum tuberculosis, maternal and infant mortality and infant HIV-1 transmission.[2–4] Although the World Health Organization (WHO) recommends isoniazid prophylaxis therapy (IPT) to all HIV-1 infected individuals, including pregnant women, global coverage of this intervention is <1%.[5] Alternative targeted strategies may be useful.

Tuberculin skin tests (TSTs) are commonly used to detect LTBI and inform IPT.[6,7] IGRAs are currently recommended for detection of LTBI, alone or with TST in TB-exposed individuals in the US, Canada and the UK. [8–12] However, WHO currently does not recommended IGRAs in low- and middle-income countries (LMICs) due to insufficient data on their utility in these settings.[13]

Several studies have shown associations between IGRA responses and development of active TB, with some evaluating magnitude of IFN-γ responses as a predictor.[14–20] Among HIV-1 infected individuals, some studies have reported associations between positive IGRA and future active TB, however, predictive value of magnitude of IFN-γ responses has not been described.[3,21,22]

Conventional test cut-offs for IGRAs were developed based on concurrent active TB as a gold-standard. The same IGRA cut-offs have been used for detection of LTBI, because there is no gold-standard for latent infection. Many studies have evaluated IGRA for diagnosis of active TB, which is distinct from using IGRA to detect LTBI and predict future active TB.[23] It is important to assess prognostic merit of IGRAs in HIV-1 infected individuals at high risk for TB.[21,24] Further, because immunosuppression might influence IGRA results and performance, combining IGRAs with CD4 counts might enhance diagnostic utility.

We previously reported a significant association between T-SPOT.TB IGRA (Oxford Immunotec) during pregnancy with postpartum active TB in HIV-1 infected women (adjusted hazard ratio (HR), 4.5; 95% confidence interval (CI), 1.1–18.0; p=0.03).[3] Using IGRA results from this cohort, we developed prognostic models to estimate sensitivity, specificity and positive predictive value (PPV) of IFN-γ response, and CD4 count measured during pregnancy for diagnosis of tuberculosis within 1 year postpartum.

Methods

Data from a historical perinatal cohort of 535 HIV-1 seropositive women in Nairobi, Kenya, accrued and followed between 1999 and 2005, were used. Details of the cohort have been described.[3,25,26] Written informed consent for the parent study was obtained. The Human Subjects Division at University of Washington and Ethical Review Committee at Kenyatta National Hospital approved the parent and current studies.

Of 535 women in the cohort, 393 with at least one available cryopreserved peripheral blood mononuclear cell (PBMC) sample at enrollment were included for IGRA testing.[3] Of the 393, valid IGRA results were obtained for 361; 7 had no viable cells and 25 had invalid assays. Women with indeterminate IGRAs due to spot count>10 SFCs/well in the negative control were included, however 8 with spot count<20 SFCs/well in the positive control were excluded. Of the remaining 353 women (361 minus 8), 327 were seen after delivery and included in this analysis (Online Appendix Figure 1). The denominator of 327 women in this analysis differs from the past published analysis (269 women) because the prior analysis excluded women with a prior history of TB and all women with indeterminate responses (in the previous analysis, of 361 women with valid IGRAs, we excluded 28 with a history of TB, 12 with no postpartum follow-up and 52 with indeterminate IGRA responses, resulting in 269 women).[3]

PBMCs were evaluated for MTB-specific IFN-γ responses using the T-SPOT.TB manufacturer-defined procedures, previously described.[3] Measurement of CD4 counts was conducted using a FACScan flow cytometer (Becton Dickinson).[27]

None of the women included in this analysis had clinically diagnosed TB at enrollment; however women who reported prior history of TB were included.

Mothers with suspected TB during follow-up were referred to the Kenyan Ministry of Health (MOH) TB Clinic. MOH diagnostic protocol involved a chest radiograph and 3 sputum samples. Adults with at least 1 positive smear received sputum-positive pulmonary TB diagnosis and those with 3 negative smears but chest radiograph and clinical presentation suggestive of tuberculosis received sputum-negative pulmonary tuberculosis diagnosis. Culture was not routinely used for tuberculosis diagnosis.[28] Women reported the tuberculosis diagnosis and treatment they received from MOH during follow-up visits. Since the perinatal cohort was not established to address TB, data regarding specific TB diagnostic procedures and disease classification were not obtained from MOH. Use of IPT is not routine in Kenya and IGRA assays were conducted after the clinical cohort was completed. Thus, none of the women received IPT.

In our previous analysis, we determined the HR of postpartum tuberculosis and mortality in mothers with a positive IGRA, during pregnancy.[3] For the current analyses, we used results from the same IGRA assays but derived cut-off values in the quantitative IFN-γ response (spot forming cells (SFCs)/well) and CD4 count to assess their sensitivity, specificity and PPV for tuberculosis postpartum. IFN-γ response was defined as SFCs/well in the antigen-containing minus negative control. Negative values of IFN-γ response were set to 0. We calculated SFCs/well for combined IFN-γ response (maximum of ESAT-6 and CFP-10

response above background) and antigen-specific response (ESAT-6- or CFP-10-specific response above background). We defined, *a priori*, three cut-points in the combined and antigen-specific IFN-γ response: >0, 6 and 10 SFCs/well. Above background (>0) represents the least conservative cut-off, 6 represents cut-off for a positive IGRA defined by T.SPOT.TB manufacturer and 10 represents a more conservative cut-off. CD4 count cut-off values were set at <250 and <350 cells/µL. Lastly, we determined the performance of the 3 IFN-γ cut-offs within the strata of the two CD4 cell count cut-offs.

Active TB diagnosed during the first year postpartum was the gold standard for test performance. We defined sensitivity as probability of being test positive (above IFN-γ or below CD4 cut-offs) during pregnancy in women who developed tuberculosis and specificity, the probability of being test negative (below IFN-γ or above CD4 cut-offs) during pregnancy in women who did not develop tuberculosis within 1 year postpartum. PPV was defined as cumulative incidence of tuberculosis in women who were above IFN-γ or below CD4 cut-offs.

For analysis of time to tuberculosis, person-time was initiated from delivery and women were censored at initiation of antiretroviral therapy, death, last study clinic visit, or 12 months postpartum. Some women reported tuberculosis but did not report a diagnosis of TB at subsequent study visit. These women were not counted as TB cases and were censored at last visit documented to be free of TB.

Sensitivity, specificity, and area under the Receiver Operating Characteristic (ROC) curve (AUC) were calculated, from a time-dependent ROC curve using the Kaplan Meier method, taking censoring into account.[29] CI for sensitivity, specificity and AUC were based on quantiles of 1000 samples from the bootstrap procedure. AUC (95% CI) values were estimated for each cut-off value as well as using the markers as continuous measures. PPV for postpartum tuberculosis are Kaplan-Meier estimates and 95% CI, calculated for each marker cut-off (above IFN-γ or below CD4 cut-offs). Log-rank test was used to determine equality of survival curves at different levels of a marker. Cox proportional hazards (PH) regression analysis was conducted to estimated HR for incident active TB, associated with being above IFN-γ or below CD4 cut-offs.

Sensitivity and specificity were derived using the *survivalROC* package and CIs using the *boot* package in R version 2.9.2.[30,31] Kaplan Meier survival analyses and Cox PH regression analyses were conducted using STATA 11.1.[32]

Results

Baseline characteristics of 327 women in this analysis are shown in Table 1. Nine of the 327 women developed tuberculosis within one year postpartum (incidence rate (IR): 3.5/100 person years of follow-up (pyfu); 95% CI: 1.6–6.7). Online Appendix Figure 2 displays the survival curve for tuberculosis.

Sensitivity of IFN-γ>0 and 6 SFCs/well was approximately 78%; IFN-γ 10 SFCs/well was associated with lower sensitivity (65%). There was gain in specificity with increasing magnitude of IFN-γ with highest specificity (60%) observed at 10 SFCs/well. T-SPOT.TB

manufacturer-defined cut-point (6 SFCs/well above background) was associated with an optimal trade-off between sensitivity and specificity (Table 2). AUC values for IFN-γ as baseline marker for postpartum tuberculosis was 0.64 (95% CI: 0.48–0.80) (Figure 1). AUC values (95% CIs) for each cut-off are shown in Table 2.

Of the women with IFN-γ >0, 6 and 10 SFCs/well, 4.3%, 5.9% and 5.9% developed tuberculosis within one year postpartum, respectively (Table 2). The PPVs associated with the cut-off values in ESAT-6 were similar to those for the combined response, whereas the PPVs associated with CFP-10 were slightly higher. Survival curves for postpartum TB for women above and below each of these cut-offs are shown in Figure 2 and the unadjusted HRs for TB associated with each cut-off are shown in Table 2. IFN-γ 6 SFCs/well was associated with a 4-fold increased risk of postpartum active TB (HR: 4.0; 95% CI: 0.8–19.3; P=0.08).

The estimates if sensitivity, specificity, PPV, AUC and HR of IFN-γ for a 2 year follow-up are presented in Online Appendix Table 1.

Sensitivity of CD4<350 and <250 cells/μL was 65% and 52%, respectively. Specificity was higher for CD4<250 cells/μL (82%) yielding 18% false positive results (1 minus specificity) compared to 35% false positive results at CD4<350 cells/μL (Table 3). ROC curve for CD4 as a baseline marker for postpartum tuberculosis had an AUC value of 0.76 (95% CI: 0.56–0.90) (Figure 3). AUC values for CD4<250 and <350 cells/μL was 0.67 (95% CI: 0.48–0.87) and 0.65 (95% CI: 0.44–0.86), respectively.

At CD4<250 and <350 cells/μL, 9.0% and 6% of women, respectively, would be expected to develop tuberculosis within 1 year postpartum (Table 3). The survival curves for incident TB associated with the two CD4 cut-offs are shown in Figure 4 and the unadjusted HR for future TB associated with CD4 cut-offs is shown in Table 3. CD4 cell count<250 cells/μL was associated with 4.7-fold increased risk of TB (HR: 4.7; 95% CI: 1.2–18.6; p=0.03).

Sensitivity associated with each IFN-γ cut-off among women with CD4<250 (85%) and <350 cells/μL (>79%) was greater than sensitivity associated with each CD4 or IFN-γ cut-off alone. Specificity estimates increased with increasing IFN-γ cut-offs in women with CD4<250 and <350 cells/μL and were greater than the corresponding estimates for IFN-γ alone (Table 3). We did not estimate AUCs for this stratified analysis because of limited number of events per stratum.

PPV of the three IFN-γ cut-offs for postpartum TB was greatest in women with CD4<250 and <350 cells/μL. Moreover, PPVs increased with increasing IFN-γ cut-offs in women with CD4<250 and <350 cells/μL (Table 3).

Discussion

We estimated sensitivity, specificity and PPV of varied IFN-γ cut-offs associated with postpartum active TB among HIV-1 infected women with baseline IGRAs performed during pregnancy. We used a time-dependent ROC method to evaluate test characteristics of varied IFN-γ cut-offs for *future* active TB, which has not been previously reported. Manufacturer

cut-offs for positive IGRAs are based on concurrent active TB as a gold standard rather than future TB. Previous studies suggest that binary positive/negative assays have some predictive ability.[19–21] It is also possible that different cut-offs may be more sensitive, specific, or predictive of future TB. Despite the difference in purpose for the cut-off threshold, we found that sensitivity and specificity of IGRA cut-offs for future active TB was best at the manufacturer cut-off (6 SFCs/well).

The AUC values we obtained suggest that IFN-γ and CD4 cell count, measured at baseline, are weak in their ability to discriminate or accurately classify those who would and would not develop future postpartum TB.

In a scenario of IGRA-targeted IPT provision, PPVs for this analysis suggest that IGRA-targeted IPT would be delivered to 152 of 327 IGRA-positive (IFN-γ response 6 SFCs/well) women to prevent 7 cases of TB but miss 2 TB cases in 175 IPT-untreated IGRA-negative women. In this population, CD4 cut-offs had higher sensitivity, specificity and PPV than IGRAs for the outcome of future TB. In addition, at all IGRA cut-offs the assay had higher sensitivity, specificity and PPV in immunosuppressed women (CD4 cell count<250 cells/μL) compared to women with higher CD4 counts. Together, our data suggest that IGRAs among immunosuppressed women during pregnancy would identify women most at-risk for TB.

Studies on sensitivity of IGRAs have typically used a cross-sectional study design in individuals with active TB where disease status and marker are measured concurrently and specificity is estimated in a separate healthy population at very low risk of tuberculosis exposure. A meta-analysis of IGRAs among HIV-1 infected individuals reported a pooled sensitivity of 72% for IGRAs for detection of active TB from studies in LMICs and 94% in high income countries.[23] However, IGRAs are not recommended for active TB diagnosis but to detect LTBI to identify those at risk for future active TB. Hence, we evaluated test cut-offs for risk of future rather than concurrent TB and estimated sensitivity and specificity. We would expect lower sensitivity in our prognostic model than in a concurrent model because we used future active TB as the gold-standard.

Persistent TB exposure may decrease sensitivity of a single time-point IGRA. Because our cohort was based in a high TB prevalence setting, prognostic sensitivity of IGRA would be expected to be lower than in a setting with lower TB prevalence. Thus, in contrast to our prior analysis with 2-year follow-up, we restricted this analysis to one year because we anticipated that external TB exposures would accumulate during extended follow-up and attenuate sensitivity of the one-time diagnostic test to detect future active TB. IPT was not provided in the cohort; with IPT, associations with IGRA positivity or specific cut-offs could decrease.

This study has important strengths and limitation. We assessed usefulness of two clinically and programmatically relevant biomarkers for postpartum tuberculosis. In our previous study, we observed significant association between IGRA positivity and risk of postpartum tuberculosis.[3] However, none of the IGRA cut-offs examined in the current study accurately discriminated individuals who would develop active TB, demonstrating that a marker with

significant association is not sufficient to provide high prognostic utility. Our analysis takes into account the time lag between IGRA and TB detection. IGRAs are used to detect LTBI to reduce future TB, making this approach more relevant compared to the cross-sectional studies of IGRAs in individuals with active TB. We were limited by few cases of active TB, absence of TST for comparison and absence of TB diagnostic confirmation. Limitations in TB diagnosis could contribute to non-differential under-ascertainment of TB and may not influence sensitivity but could lead to underestimated positive predictive value.

In conclusion, our study estimates prognostic performance of IFN-γ and CD4 cell count, during pregnancy in identifying HIV-1 infected women at risk for postpartum tuberculosis. No IGRA cut-off provided a high predictive value or ability to discriminate those who would develop future TB. IFN-γ sensitivity and predictive value were highest in immunosuppressed women. Our study was limited in sample size and to increase precision of estimates the findings should be replicated in a cohort with more TB events. Cost-effectiveness or decision-tree analyses with these data or with larger cohort studies could inform alternative IGRA-targeted IPT strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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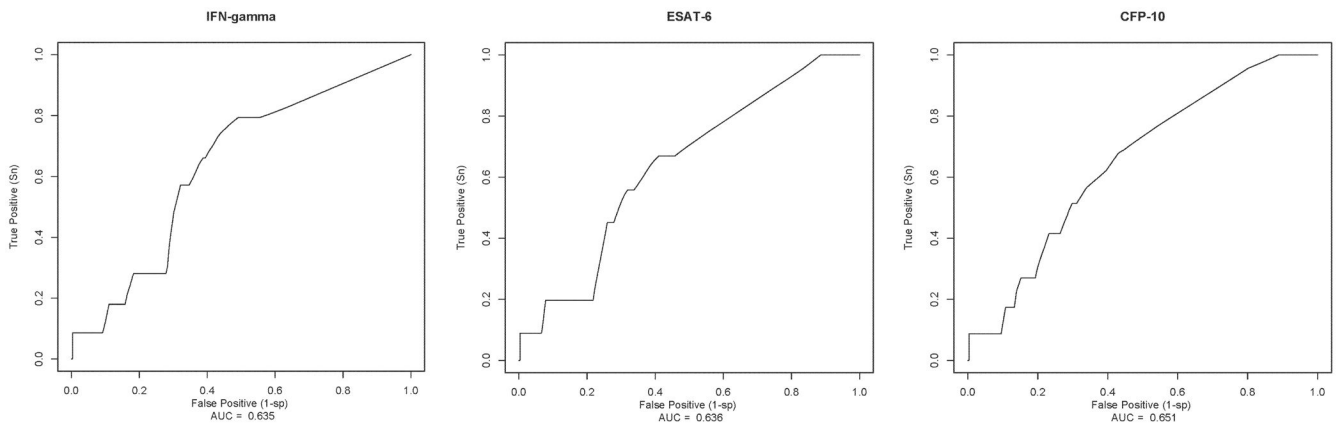32. StataCorp. Stata Statistical Software: Release 11. College Station: TSL; 2009.

Figure 1.
Receiver Operating Characteristic Curves for interferon-γ, ESAT-6 and CFP-10 as baseline markers for postpartum tuberculosis and the corresponding area under the ROC curve (AUC) value in HIV-1 infected women
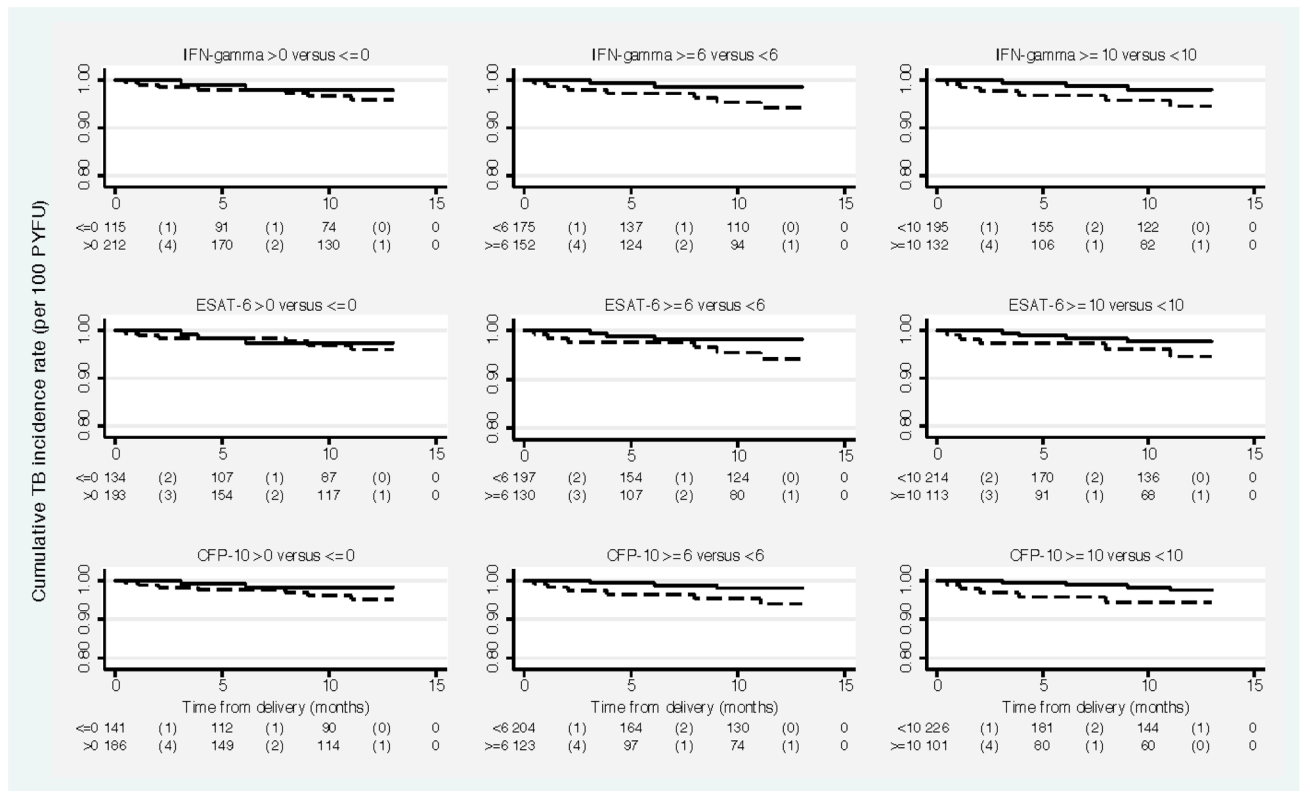
Figure 2.
Kaplan Meier estimates of cumulative tuberculosis incidence rate in HIV-1 infected women between delivery and 1 year postpartum by various cut-points in combined interferon-γ response and response to individual antigens, measured during pregnancy.

Note: In each plot, dashed line represents the survival curve for women below the cut-off value and bold line represents the survival curve for women above the cut-off value. The risk table shown below each plot shows the number at risk (number of events) within each time interval represented on the x-axis.

p-values for Log-rank test for equality of survival functions at each of the cut-off values displayed were >0.05.
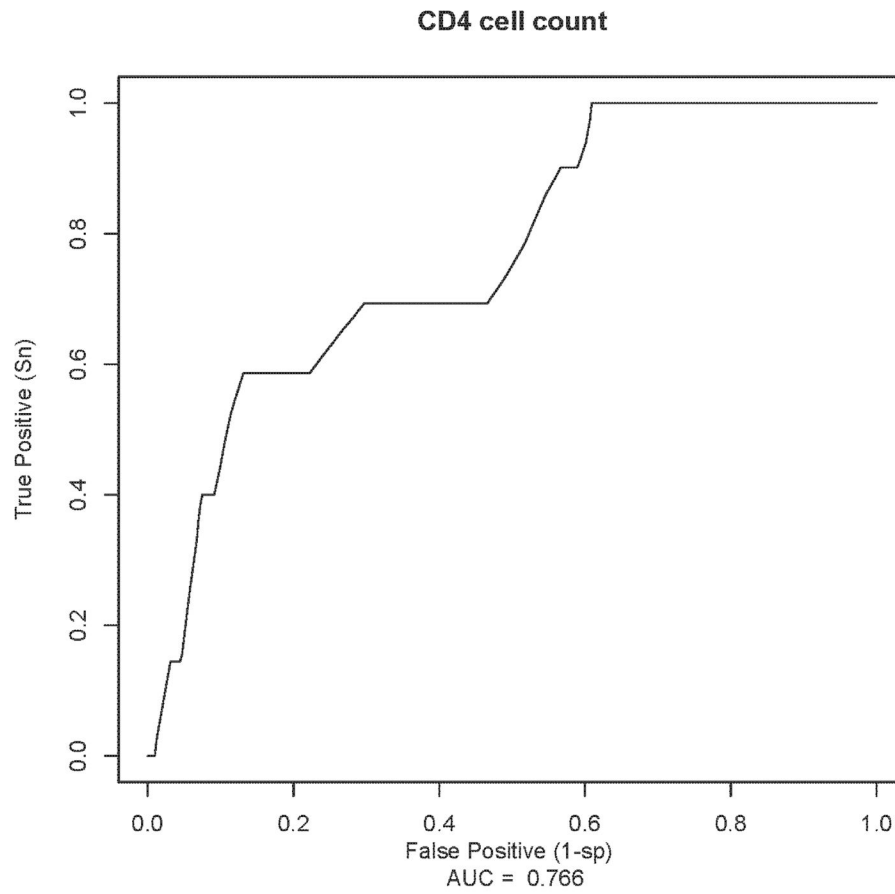
CD4 cell count

Figure 3.
Receiver Operating Characteristic Curves for CD4 cell count as baseline marker for postpartum tuberculosis and the corresponding area under the ROC curve (AUC) value in HIV-1 infected women
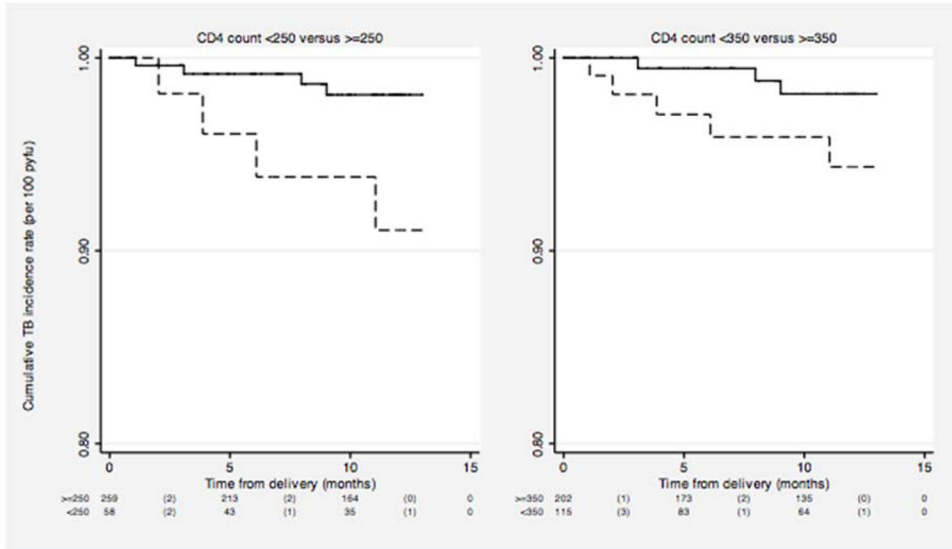
Figure 4.
Kaplan Meier estimates of cumulative tuberculosis incidence rate in HIV-1 infected women between delivery and 1 year postpartum by various cut-points in CD4 cell count measured during pregnancy.

Note: In each plot, dashed lines represent the survival curve for women with CD4 <250 and <350 cells/μL and the bold lines represent survival curves for women with CD4>250 and >350 cells/μL. The risk table below each plot shows the number at risk (number of events) within each time interval represented on the x-axis.

p-values for the Log-rank test for equality of survival functions is 0.02 for CD4<250 compared to >=250 cells/μL and 0.08 for CD4<350 compared to >=350 cells/μL.

Table 1

Baseline sociodemographic and clinical characteristics and distribution of baseline markers in pregnant HIV-1 infected women

Indicator	Women,[a] no.(n=327)	Value[b]
Sociodemographic characteristic		
Age, years	326	25.0 (22.0–28.0)
Ever married	327	302 (92.4)
More than primary education	323	139 (43.0)
Employed	327	111 (33.9)
Living in >1 room household	325	67 (20.6)
Number of rooms	325	1.0 (1.0–1.0)
Use of flush toilet	327	164 (50.2)
Use of shared toilet	327	297 (90.8)
Number of persons per room	326	3.0 (2.0–4.0)
Medical history		
History of tuberculosis	327	28 (8.6)
History of HIV-1 related illness	327	40 (12.2)
T-SPOT.TB IGRA response	327	
Positive		125 (38.2)
Negative		157 (48.0)
Indeterminate		45 (13.8)
ESAT-6 spot count[c]	327	
>0		193 (59.0)
6		130 (39.8)
10		113 (34.6)
CFP-10 spot count[c]	327	
>0		186 (56.9)
6		123 (37.6)
10		101 (30.9)
Maximum (ESAT-6, CFP-10) [c]	327	
> 0		212 (64.8)
6		152 (46.5)
10		132 (40.4)
HIV-1 markers		
CD4 cell count, cells/μL	317	413.0 (300.0–618.0)
<250		58 (18.3)
<350		115 (36.3)
HIV-1 viral load, copies/mL	326	4.8 (4.2–5.3)
>50,000		170 (52.0)

[a]For whom data was available

[b]Median (interquartile range) or number (percent) of women

[c]Spot count above background

Table 2

Sensitivities, specificities and positive predictive values (PPVs) for tuberculosis within 1 year postpartum associated with cut-off values in IFN-γ response measured at 32 weeks' gestation in HIV-1 infected women.

Predictor	Cut-off value	Events	PYFU	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive value (95% CI)	AUC (95% CI)	Hazard Ratio* (95% CI)	p-value
IFN-γ	>0	7	164.3	78.9 (47.8–100.0)	35.7 (30.3–41.4)	4.3 (1.7–8.8)	0.57 (0.41–0.69)	1.9 (0.4–9.3)	0.41
	6	7	118.7	77.7 (45.7–100.0)	54.6 (49.3–60.1)	5.9 (2.4–12.2)	0.66 (0.50–0.78)	4.0 (0.8–19.3)	0.08
	10	6	102.1	65.0 (29.0–98.7)	60.5 (55.2–65.7)	5.9 (2.2–12.8)	0.63 (0.45–0.80)	3.0 (0.7–12.0)	0.12
ESAT-6	>0	6	148.6	69.1 (36.3–100.0)	41.3 (35.9–46.8)	4.0 (1.5–8.8)	0.55 (0.37–0.70)	1.4 (0.4–5.7)	0.61
	6	6	101.8	67.4 (30.7–98.0)	61.2 (56.1–66.8)	5.9 (2.2–12.8)	0.64 (0.45–0.80)	3.0 (0.8–12.1)	0.12
	10	5	86.7	55.5 (21.3–90.2)	66.2 (60.8–71.5)	5.8 (1.9–13.5)	0.61 (0.43–0.79)	2.4 (0.7–9.1)	0.18
CFP-10	>0	7	143.9	78.9 (44.1–100.0)	43.9 (38.3–49.1)	4.9 (2.0–10.0)	0.61 (0.46–0.74)	2.7 (0.6–13.1)	0.21
	6	6	93.6	66.0 (28.5–99.2)	63.4 (57.7–68.6)	6.4 (2.4–14.0)	0.65 (0.46–0.82)	3.4 (0.9–13.8)	0.08
	10	5	76.7	50.5 (13.9–85.2)	69.8 (64.7–74.8)	6.5 (2.1–15.2)	0.60 (0.43–0.78)	2.9 (0.8–10.8)	0.11

Note: PYFU Person years of follow-up; CI Confidence Interval

*
Crude Hazard Ratio for active TB in women above IFN-γ cut-off value compared with women below IFN-γ cut-off value

Table 3

Sensitivities, specificities and positive predictive values for tuberculosis within one year postpartum associated with cut-off values in CD4 cell count alone and in combination with IFN-γ responses measured at 32 weeks' gestation in HIV-1 infected women

Predictor cut-off value		Events	PYFU	Sensitivity*	Specificity	Positive Predictive value	Hazard Ratio** (95% CI)	p-value
CD4 cell count								
<250		4	44.4	51.5 (14.1–91.7)	82.8 (78.4–87.0)	9.0 (2.5–23.1)	4.7 (1.2–18.6)	0.03
<350		5	84.4	64.6 (24.6–100.0)	64.7 (59.3–69.8)	5.9 (1.9–13.8)	3.3 (0.8–13.7)	0.10
CD4 cell count	IFN-γ							
250	>0	3	137.5	78.0	33.4 (27.3–39.5)	2.2 (0.4–6.4)	1.5 (0.2–14.4)	0.73
	6	3	98.9	76.3	53.5(47.1–59.8)	3.0 (0.6–8.9)	3.3 (0.3–31.6)	0.30
	10	2	85.4	47.5	59.2(53.3–65.2)	2.3 (0.3–8.5)	1.4 (0.2–10.1)	0.72
<250	>0	3	21.7	84.6	47.7(33.8–61.4)	13.8 (2.9–40.4)	3.2 (0.3–30.7)	0.32
	6	3	15.6	89.4	63.3(50.4–78.4)	19.2 (4.0–56.2)	5.8 (0.6–55.9)	0.13
	10	3	13.6	87.5	68.8(56.0–82.2)	22.1 (4.5–64.5)	7.0 (0.7–67.8)	0.09
350	>0	2	113.7	74.5	30.3(24.1–36.2)	1.8 (0.2–6.4)	1.0 (0.1–10.6)	0.97
	6	2	81.1	73.8	51.0(44.0–58.2)	2.5 (0.3–8.9)	2.2 (0.2–23.8)	0.53
	10	1	69.5	35.6	57.3(50.5–64.1)	1.4 (0.04–8.0)	0.7 (0.1–7.8)	0.78
<350	>0	4	45.5	80.8	45.9(36.8–55.8)	8.8 (2.4–22.5)	3.4 (0.4–30.5)	0.27
	6	4	33.5	78.9	62.3(54.0–71.7)	11.9 (3.3–30.6)	6.0 (0.7–54.1)	0.11
	10	4	29.4	79.4	67.0(57.6–75.7)	13.6 (3.7–34.8)	7.4 (0.8–66.1)	0.07

Note: PYFU Person years of follow-up;

*
Confidence Intervals for sensitivity could not be calculated due to the very small number of events that the sensitivity estimate was based on.

**
Crude Hazard Ratio for active TB in women below CD4 cut-off value compared with women above CD4 cut-off value