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Tuberculosis Infection in Women of Reproductive Age: A Cross-sectional Study at Antenatal Care Clinics in an Ethiopian City

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(See the Invited Editorial Commentary by Beckerman on pages 211–2.)

Background. Knowledge on tuberculosis (TB) infection epidemiology in women of reproductive age living in TB-endemic areas is limited. We used a composite definition of TB infection in a cohort of pregnant women recruited in an Ethiopian city as a model for TB exposure patterns, and to identify factors associated with TB infection.

Methods. Women seeking antenatal care at public health facilities underwent structured interviews, physical examination, and QuantiFERON-TB Gold-Plus (QFT) testing. Women with symptoms compatible with TB disease, and all human immunodeficiency virus (HIV)–positive women, were investigated for active TB by sputum bacteriological testing. TB infection (TB^+) was defined as either positive QFT ($\geq$0.35 IU/mL), self-reported previous active TB, or current active TB. Associations between TB infection and clinical, demographic, and socioeconomic characteristics were tested in multiple logistic regression analysis.

Results. Among 1834 participants, 679 (37.0%) met criteria for TB^+ (80 [4.4%] previous active TB, 5 [0.3%] current active TB, and 594 [32.4%] QFT-positive without previous or current active TB). Age (annual adjusted odds ratio [AOR], 1.069 [95% confidence interval {CI}, 1.045–1.093]) and HIV infection (AOR, 1.43 [95% CI, 1.033–1.988]) were independently associated with TB^+. The relationship with increasing age was only observed in HIV-negative women, and translated to an estimated annual risk of TB infection of 2.1% in HIV-negative women.

Conclusions. TB infection in women of reproductive age in Ethiopia was independently associated with HIV infection and increasing age, suggesting exposure to contagious TB and continuous acquisition of TB infection in this population.

Keywords. tuberculosis; QuantiFERON; HIV; Ethiopia; pregnancy.

In 2018, 10.0 million new cases of active tuberculosis (TB) occurred worldwide, causing 1.45 million deaths, of which 251 000 were among people living with human immunodeficiency virus (HIV), making *Mycobacterium tuberculosis* (*Mtb*) the single infectious agent responsible for the highest numbers of deaths globally [1]. Furthermore, 1.7 billion persons are estimated to have latent tuberculosis infection (LTBI) [1]. Notification rates for active TB are higher for men than women. While notification rates are biased by care-seeking behavior and access to healthcare, undiagnosed active TB is also more common in men, with a global prevalence-to-notification ratio of 2.6 for men and 1.6 for women [2]. However, the sex ratio for active TB varies considerably in different age spans, with a less prominent male predominance in early adulthood [3, 4]. Importantly, increasing proportions of cases are reported in women in sub-Saharan Africa [5]. Whereas HIV coinfection is one reason for this "feminization" of the TB epidemic [4], other factors may also be involved [6]. The rate of progression to active TB is highest during the first year after infection [7, 8], but is also related to various conditions that affect the immune control of LTBI [9, 10]. While experimental studies indicate that biological differences, including sex hormone profiles, may protect females [6], the physiological immune modulation during pregnancy could explain the relatively increased incidence of active TB in women of fertile age [11].

Whereas most studies on LTBI epidemiology have shown that prevalence is linked to male sex and increasing age, findings are discordant with regard to the impact of other conditions, such as socioeconomic status and HIV infection [12–17]. Knowledge

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on LTBI prevalence and associated factors is necessary for a better understanding of TB transmission in communities.

We aimed to study TB exposure patterns in women of reproductive age living in a TB-endemic area. For this purpose, we used a composite measure of either previous active TB, current active TB, or LTBI. This outcome was investigated in a cohort of pregnant women in Ethiopia, with analysis of clinical, demographic, and socioeconomic characteristics associated with TB infection.

MATERIALS AND METHODS

Study Setting and Participants

This study was based on a prospective cohort of women of fertile age (ClinicalTrials.gov identifier: NCT03305991), conducted at 3 antenatal care (ANC) clinics in Adama, a city with around 300 000 inhabitants in central Ethiopia. From November 2015 to February 2018, pregnant women were recruited during their first ANC visit for the current pregnancy, after providing informed consent. Repeated pregnancies were not considered. The national TB program [18] recommends screening for active TB for all pregnant women. Neither testing nor treatment for LTBI is recommended in connection to pregnancy. For HIV-positive individuals (irrespective of sex), isoniazid preventive therapy (IPT) for 6 months is recommended after exclusion of active TB.

Study Procedure

Interviews covering socioeconomic and demographic characteristics, as well as medical and obstetric history, were performed using standardized questionnaires, along with physical examination. HIV serostatus was determined with rapid tests, with testing for $CD4^+$ T-cell count (CD4) and HIV viral load (VL) from HIV-positive participants. Bacteriological TB investigations (smear microscopy, MTB/RIF GeneXpert, and liquid culture) were performed on 2 spontaneously expectorated morning sputum samples for participants with symptoms or signs suggestive of active TB, and for all HIV-positive participants, irrespective of clinical presentation. Participants diagnosed with active TB were linked to TB clinics for management according to national guidelines [18].

QuantiFERON-TB Gold-Plus (QFT) was used for LTBI testing. Venous blood was collected in lithium heparin tubes, with transfer to the 4 test tubes containing TB1 or TB2 *Mtb* antigen mixtures, negative and positive controls, respectively, at the study laboratory within 8 hours of venipuncture, followed by mixing and incubation for 16–24 hours at 37°C. Supernatants were stored at −20°C after centrifugation. Interferon-γ enzyme-linked immunosorbent assay (ELISA) was performed in batches according to the manufacturer's recommendations. For indeterminate QFT results, the ELISA was repeated on the same samples.

Study Design

The primary outcome of this cross-sectional study was TB infection (TB^+), defined as a composite of either current active TB (bacteriologically confirmed or clinically diagnosed according to national guidelines), self-reported previous treatment for active TB, or LTBI. Absence of all of these criteria was defined as TB negative (TB^-).

LTBI was defined as a positive QFT result, using a cutoff of nil-corrected TB1- or TB2-stimulated interferon gamma (IFN-γ) $\geq$ 0.35 IU/mL, without past or current active TB. Since immunosuppression can reduce IFN-γ secretion after *Mtb* antigen incubation [19–21], we also separately analyzed the proportion and characteristics of women with IFN-γ levels < 0.35 IU/mL but $\geq$ 0.20 IU/mL in at least 1 antigen formulation (referred to as low borderline range [22]).

Predictive models for TB^+ in the whole study population were constructed. In addition, a model was constructed for TB^+ in the subset of HIV-positive women. A descriptive analysis comparing study participants with QFT IFN-γ levels $\geq$ 0.35 IU/mL and 0.20–0.34 IU/mL, respectively, was also performed.

Based on previous reports of characteristics associated with active or latent TB [9, 16, 17, 23–25], self-reported contact with active TB, demographic and socioeconomic factors including housing conditions, and factors related to host immunity (HIV-infection, nutritional status, and gestational age) were included in the analyses.

Statistical Analysis

Parsimonious predictive models for TB^+ were generated for analysis of each of the study objectives. The χ^2 test and Fisher exact test were used to test univariate associations for categorical variables. Subsequently, logistic regression models were constructed by stepwise forward selection, entering variables with univariate P values < .10 sequentially. Likelihood ratio tests were performed after entry of new variables to evaluate the gained additional fitness. If the fitness was significantly improved (using P < .05 as threshold), the variable remained in the model. Subsequently, interaction terms between the remaining variables were considered, based on plausibility and contribution to the model fitness. For interaction terms based on numerical variables, reference points were changed to reflect the population median of the respective variable.

Due to the possibility of false-positive significant associations because of multiple tests, Bonferroni-adjusted levels of significance for each model were calculated.

Quantile regression analysis was performed to explore the dynamics of the relationship between TB1-stimulated IFN-γ secretion and variables associated with TB^+ in prior analyses [26]. All statistical analysis was performed using R, version 3.5.1. Quantile regression analysis was performed using the quantreg R package.

Ethical Considerations

This study was performed in accordance with the Helsinki Declaration, and was approved by the ethical review committee

of Lund University, Sweden, and the national ethical review board of the Ministry of Science and Technology, Addis Ababa, Ethiopia. Individual informed consent was obtained prior to enrollment, with the assistance of proxies for illiterate participants. QFT results were not communicated to healthcare providers since testing for LTBI is not part of routine care in Ethiopia.

RESULTS

Study Participants

Among 2088 cohort participants, 254 (12.2%) were excluded due to missing QFT results. The median age of the 1834 included women was 25 years (interquartile range [IQR], 22–28 years), the median gestational age was 18 weeks (IQR, 14–21 weeks), and 170 (9.3%) were living with HIV (Table 1). HIV-positive individuals had higher median age, a lower proportion were married, and more women reported previous pregnancies (Supplementary Table 1). The characteristics of participants excluded due to missing QFT results were similar to those included (Supplementary Table 2).

Prevalence and Associated Factors of TB Infection

According to the study definition, 679 of 1834 women were TB^+ (37.0%); 594 (32.4%) had LTBI, 80 (4.4%) reported previous treatment for active TB and 5 (0.3%) had prevalent active TB, of whom 3 were HIV-positive. Two of 3 HIV-positive women with active TB reported no symptoms suggestive of TB. Sixty-nine participants with negative QFT-result had IFN-γ levels 0.20–0.34 IU/mL. In 25 (1.4%) study participants, initial QFT results were indeterminate, but after repeat testing, QFT status could be determined in all these cases.

In univariate analysis, TB^+ was associated with higher median age compared to TB^-. In addition, TB^+ was associated with HIV infection, greater number of previous pregnancies, greater number of household members, and 1-room household residence (Table 1).

In multivariate analysis, age (annual adjusted odds ratio [AOR], 1.069 [95% confidence interval {CI}, 1.045–1.093]) and HIV infection (AOR, 1.43 [95% CI, 1.033–1.988]) were independently associated with TB^+ (Table 2).

However, the association with age was different in HIV-positive and HIV-negative participants, ranging from 19.7% among women aged < 19 years to 45.6% among women > 26 years for HIV-negative participants, whereas no such association was observed in HIV-positive women (Figure 1). Consequently, an interaction term between age and HIV serostatus was added to the model (Table 3). In that model, age remained significantly associated among HIV-negative women (annual AOR, 1.079 [95% CI, 1.053–1.105]; $P < .0001$) but not in HIV-positive women (annual AOR, 0.998; not significant). Conversely, the association with HIV serostatus varied by age, but at the population median (25 years), HIV-positive women were more likely to be TB^+ (AOR, 1.76 [95% CI, 1.21–2.54]; $P = .0029$). These findings remained significant using the Bonferroni-adjusted significance threshold ($P < .0038$). From this model, an annual risk of infection of 2.1% was derived for HIV-negative women. These results were similar in a sensitivity analysis excluding women with past and current active TB, although HIV serostatus was not associated with LTBI in this analysis (HIV negative: annual AOR, 1.081; HIV positive: annual AOR, 0.990; HIV at 25 years: AOR, 1.12; data not shown).

The 69 participants with QFT IFN-γ levels 0.20–0.34 IU/mL had similar characteristics as those with levels ≥0.35 IU/mL (Supplementary Table 3).

HIV-Specific Factors Associated With TB Infection

Among the 170 HIV-positive participants, 84 (49.4%) were TB^+, compared to 595 of 1664 (35.7%) among HIV-negative women ($P < .001$). The proportion of previous and current active TB was significantly higher among HIV-positive women: 33 of 170 (19.4%; OR, 8.3; $P < .0001$) and 3 of 170 (1.8%; OR, 14.9; $P = .0068$), respectively. In univariate analysis, TB^+ was associated with longer duration of antiretroviral therapy (ART), ART regimen, and VL > 1000 copies/mL (Table 4). The latter 2 factors remained associated with TB^+ in multivariate analysis, although not reaching the Bonferroni-adjusted threshold of significance ($P < .0031$) (Table 5).

Quantile Regression Analysis of the Relationship Between TB Infection Status and Age

As increasing age in HIV-negative women was strongly associated with TB^+ (Figure 1), we further explored this relationship using quantile regression, a semiparametric quantitative method, to determine whether these associations varied in different age ranges. Across the 20th to 80th age percentiles, TB^+ was significantly associated with higher age compared to TB^-. This difference ranged between 1 and 2 years (Supplementary Table 4).

DISCUSSION

In this cross-sectional study of 1834 women seeking antenatal care in Ethiopia, 37% met study criteria for TB infection. Among a large set of variables, the only factors associated with TB infection in multivariate analysis were age and HIV infection. In HIV-negative study participants, the absolute annual risk of acquiring TB infection was estimated at 2.1%.

Recently acquired TB infection is recognized as a major risk factor for progression to active TB [7]. The high rate of TB exposure among women of reproductive age is of particular concern, since TB is a leading cause of maternal mortality in low-income countries [27–30] and pregnancy has been linked to an elevated incidence of active TB [31, 32].

Although 20% of HIV-negative participants had acquired TB infection at the age of 18 years, the proportion of TB-infected

Table 1. Characteristics of Pregnant Women Stratified by Tuberculosis Infection Status

Characteristic	Total		TB^-		TB^+		*P* Value
Total	1834		1155		679		
Previous active TB	80	(4.4)	…	…	80	(11.8)	
Current active TB	5	(0.27)	…	…	5	(0.7)	
Age, y							< .001
≤ 20	350	(19.1)	255	(22.1)	95	(14.0)	
21–25	725	(39.5)	490	(42.4)	235	(34.7)	
26–30	610	(33.3)	334	(28.9)	276	(40.7)	
31–35	114	(6.2)	57	(4.9)	57	(8.4)	
≥36	34	(1.9)	19	(1.6)	15	(2.2)	
NA	1	(0.1)	…	…	…	…	
Hemoglobin, g/dL, mean (SD)	12.37	(1.2)	12.39	(1.22)	12.35	(1.17)	.61
Marital status							.16[a]
Married	1757	(95.8)	1102	(95.6)	655	(96.6)	
Single	56	(3.1)	35	(3.0)	21	(3.1)	
Divorced	15	(0.8)	13	(1.1)	2	(0.3)	
Widowed	3	(0.2)	3	(0.3)	0	(0)	
NA	3	(0.2)	…	…	…	…	
Education							.017
Higher education	201	(11.0)	117	(10.1)	84	(12.4)	
6–12 grades	1038	(56.6)	669	(57.9)	369	(54.4)	
< 6 grades	360	(19.6)	239	(20.7)	121	(17.8)	
Illiterate	234	(12.8)	130	(11.3)	104	(15.3)	
NA	1	(0.1)	…	…	…	…	
Family size							
< 4	1348	(73.5)	883	(77.1)	465	(68.7)	< .001
4–6	401	(21.9)	221	(19.3)	180	(26.6)	
> 6	74	(4.0)	42	(3.7)	32	(4.7)	
NA	11	(0.6)	…	…	…	…	
One room	995	(54.3)	658	(57.2)	337	(49.9)	.003
NA	8	(0.4)	…	…	…	…	
No solid fuel combustion for cooking	441	(24.0)	264	(23.0)	177	(26.3)	.12
NA	12	(0.7)	…	…	…	…	
No electricity	76	(4.1)	47	(4.1)	29	(4.3)	.90
NA	13	(0.7)	…	…	…	…	
Occupation							.044
Housewife	1165	(63.5)	747	(64.8)	418	(61.8)	
Employed	234	(12.8)	141	(12.2)	93	(13.8)	
Self-employed	148	(8.1)	97	(8.4)	51	(7.5)	
Daily laborer	219	(11.9)	122	(10.6)	97	(14.3)	
Student	39	(2.1)	31	(2.7)	8	(1.2)	
Unemployed	23	(1.3)	14	(1.2)	9	(1.3)	
NA	6	(0.3)	…	…	…	…	
Previous pregnancies							< .001
0	671	(36.6)	465	(41.6)	206	(31.0)	
1	641	(35.0)	400	(35.8)	241	(36.3)	
2	293	(16.0)	155	(13.9)	138	(20.8)	
> 2	176	(9.6)	97	(8.7)	79	(11.9)	
NA	53	(2.9)	…	…	…	…	
Gestational age, wk							.36
< 14	301	(16.4)	178	(19.6)	123	(22.7)	
14–27	1070	(58.3)	681	(74.8)	389	(71.6)	
> 27	82	(4.5)	51	(5.6)	31	(5.7)	
NA	381	(20.8)	…	…	…	…	
MUAC < 23 cm	398	(21.7)	259	(22.8)	139	(20.9)	.38
NA	30	(1.6)	…	…	…	…	
HIV-positive	170	(9.3)	86	(7.4)	84	(12.4)	.001

Data are presented as no. (%) unless otherwise indicated. Table shows characteristics of study participants with evidence of TB infection, either current or previous active TB or latent TB using the conventional cutoff (interferon-γ ≥ 0.35 IU/mL) after stimulation with TB1 or TB2 *Mycobacterium tuberculosis* antigen mixtures. The Total column reports total percentages, whereas the others report valid percentages. Univariate comparisons were made using *t* test for normally distributed variables (hemoglobin) and χ^2 test or Fisher exact test for categorical variables. Bonferroni-adjusted level of significance: 0.0038.

Abbreviations: HIV, human immunodeficiency virus; MUAC, mid-upper arm circumference; NA, not available; SD, standard deviation; TB, tuberculosis.

[a]Fisher exact test was used.

Table 2. Logistic Regression Analysis for Tuberculosis Infection

Characteristic	AOR	95% CI		*P* Value
HIV-status				
HIV-negative	Ref	Ref	Ref	
HIV-positive	1.43	1.03	1.99	.031
Age, y	1.069	1.045	1.093	< .0001

Multivariate logistic regression model for tuberculosis (TB) infection, defined as latent TB infection or previous or current active TB infection. The model was constructed in a stepwise forward selection method, with variables with univariate $P < .10$ eligible for inclusion and likelihood ratio test used to determine the contributed model fitness. Bonferroni-adjusted level of significance: 0.0038.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus.

women increased to 46% among those aged > 26 years, implying continued TB transmission in the communities where these women live. Some previous studies performed in endemic areas have found LTBI to be associated with increasing age [12, 14, 15, 33], being married, and higher socioeconomic status [15], while among South African adolescents, lower socioeconomic status, lower parental education, and crowding were associated with LTBI [33]. In our study, no differences in TB infection status were observed with regard to socioeconomic conditions, crowding, or indoor biomass combustion.

Apart from rising age, TB infection was also strongly associated with HIV infection. Interestingly, no association between TB infection and age was found among HIV-positive participants. Furthermore, the excess burden of TB infection in HIV-positive persons was due to a higher frequency of previous and current active TB, whereas the proportions with LTBI were similar with regard to HIV serostatus. This finding is in agreement with previous studies, showing no association between LTBI prevalence and HIV [15–17]. In our cohort, 9.3% of women were HIV positive, which is higher than the Ethiopian estimate of 1.4% for women of fertile age [34]. A majority of HIV-positive women had been diagnosed with HIV before the current pregnancy, and 110 (74%) were on ART since > 1 year.

Latent tuberculosis infection represents a reservoir for *Mtb*, and testing and treatment for LTBI is considered as a key component of TB control programs in low-endemic countries [35]. Although treatment of LTBI might be considered during pregnancy, this has mainly been studied in the context of HIV coinfection, and the efficacy of such treatment in areas with ongoing TB transmission for prevention of active TB is uncertain due to the high risk of reinfection. In settings such as the one in which this study was conducted, case-finding of individuals with contagious TB in the community, with adequate linkage to care and completion of treatment, should probably be prioritized for reduction of TB exposure in the community. The Global Tuberculosis Report 2019 estimated that almost one-third of active TB cases in Ethiopia are not diagnosed, demonstrating the need for improvement of existing TB control programs [1].

Early diagnosis and treatment of active TB, as well as prevention, is of special importance in pregnant women. Symptom-based screening for active TB is recommended as part of ANC in Ethiopia, but evidence is lacking on how such screening should be performed. As illustrated by the finding of 2 cases of active TB in HIV-positive women without TB-related symptoms, active TB during pregnancy can be asymptomatic or have atypical presentation [11].

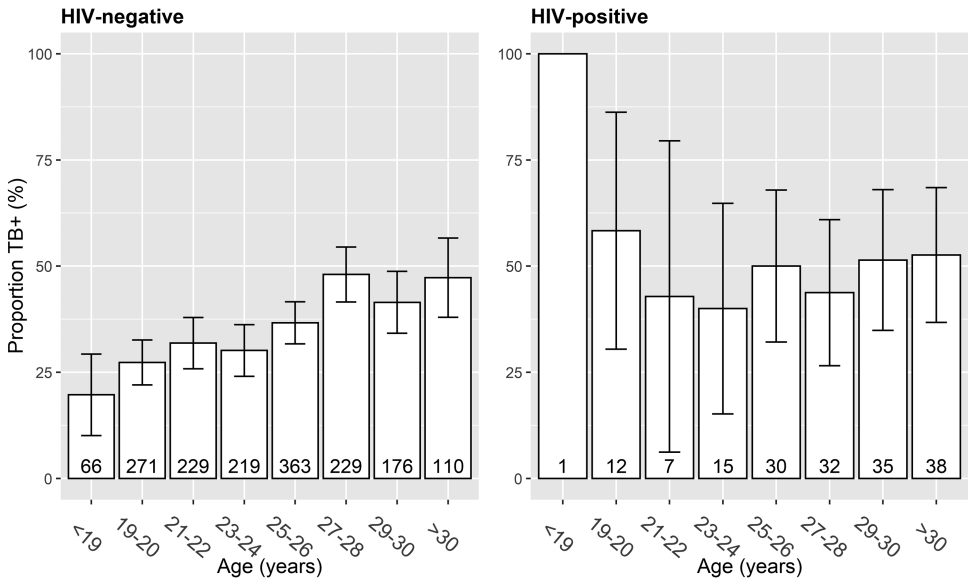

Figure 1. Proportion of tuberculosis (TB) infection stratified by age and human immunodeficiency virus (HIV) serostatus. Bar chart depicting the distribution of TB^+ across age categories in HIV-negative and HIV-positive study participants. TB^+ was defined as past or present active TB and/or positive QuantiFERON-TB Gold-Plus using the recommended cutoff of 0.35 IU/mL. Whiskers represent 95% confidence intervals for the proportion; the group size is denoted at the bottom of each bar.

Table 3. Logistic Regression Analysis for Tuberculosis Infection, model with interaction

Characteristic	AOR	95% CI		*P* Value
HIV status, at age 25 y				
HIV-negative	Ref	Ref	Ref	
HIV-positive	1.76	1.21	2.54	.0029
Age in HIV-negative women (years)	1.079	1.053	1.105	< .0001
Age in HIV-positive women (years)	0.998	0.931	1.069	.028[a]

Multivariate logistic regression model for tuberculosis infection (TB^+), defined as latent TB infection, previous or current active TB infection. The model was constructed in a stepwise forward selection method, with variables with univariate $P < .10$ eligible for inclusion and likelihood ratio test used to determine the contributed model fitness. There was an interaction between age and HIV status; although the AOR in the HIV-negative group increased by 1.079 per living year, age did not affect the rate of TB^+ in the HIV-positive group. Bonferroni-adjusted level of significance: 0.0038.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus.

[a] *P* values indicate the level of evidence that the age association was different in HIV-positive and HIV-negative individuals (ie, the interaction).

Our findings highlight the need of improved TB control in connection to pregnancy. Since the incidence of active TB has been reported to be higher postpartum compared to during pregnancy [31, 32], assessment of women after delivery should also be considered. Further research is required in this field, including the role of diagnosis and treatment of LTBI.

To reflect the cumulative burden of TB in young women, we used a broad definition of TB infection, including both active and latent infection as well as self-reported history of previous treatment for active TB. For determination of LTBI status among women without active TB, we used the novel QFT assay. Similar to previous versions of QFT assays, this method is based on measurement of IFN-γ in plasma after whole-blood incubation with *Mtb* specific antigens. While initially considered as a binary test, the choice of a threshold level for definition of a positive reaction has been debated, especially since results close to the recommended cutoff level (0.35 IU/mL) are subject to variability on repeat testing [36]. We and other researchers have presented data suggesting that a lower threshold level (0.20 IU/mL) could be considered for identification of LTBI in persons with immunosuppressive conditions [37–39], to increase assay sensitivity in such individuals. In our cohort, 69 of 1749 women had IFN-γ levels in the low borderline range (0.20–0.34 IU/mL). The proportions of persons displaying this pattern did not differ with regard to HIV serostatus, nor for other characteristics.

To our knowledge, this study is the largest survey of TB infection among women of fertile age from an endemic setting using an IFN-γ release assay for LTBI detection. The study protocol included a large set of variables potentially associated with TB infection.

We acknowledge certain study limitations. This study was conducted in women seeking ANC at public health facilities, which we consider to be a representative population for women of reproductive age. However, certain categories of women in this age range were not included, especially nonpregnant women, but also women seeking ANC at private clinics or those who do not seek

Table 4. Characteristics Associated With Tuberculosis Infection in Human Immunodeficiency Virus–Positive Pregnant Women

Characteristic	TB^-		TB^+		*P* Value
Total	86		84		
Previous active TB	NA		33	(39.3)	
Current active TB	NA		3	(3.6)	
QFT ≥ 0.35 IU/mL	NA		62	(75.6)	
Age, y					.51[a]
≤ 20	5	(5.8)	8	(9.5)	
21–25	24	(27.9)	18	(21.4)	
26–30	39	(45.3)	38	(45.2)	
31–35	12	(14.0)	17	(20.2)	
≥36	6	(7.0)	3	(3.6)	
Hemoglobin, g/dL, mean (SD)	11.97	(1.44)	12.37	(1.37)	.11
Marital status					.23[a]
Married	74	(86.0)	79	(94.0)	
Single	9	(10.5)	3	(3.6)	
Divorced	2	(2.3)	2	(2.4)	
Widowed	1	(1.2)	0	(0)	
Education					.061[a]
Higher education	2	(2.3)	5	(6.0)	
6–12 grades	61	(70.9)	43	(51.2)	
< 6 grades	13	(15.1)	18	(21.4)	
Illiterate	10	(11.6)	18	(21.4)	
Family size					
< 4	57	(66.3)	44	(52.4)	.15
4–6	23	(26.7)	34	(40.5)	
> 6	6	(7.0)	6	(7.1)	
One room	36	(41.9)	32	(38.1)	.73
No solid fuel combustion for cooking	15	(17.6)	17	(20.5)	.79
No electricity	5	(5.8)	6	(7.2)	.95
Occupation					.22[a]
Housewife	49	(57.6)	54	(64.3)	
Employed	14	(16.5)	5	(6.0)	
Self-employed	8	(9.4)	12	(14.3)	
Daily laborer	11	(12.9)	9	(10.7)	
Student	0	(0)	0	(0)	
Unemployed	3	(3.5)	4	(4.8)	
No. of previous pregnancies					.47
0	11	(13.8)	10	(12.2)	
1	34	(42.5)	29	(35.4)	
2	15	(18.8)	24	(29.3)	
≥3	20	(25.0)	19	(23.2)	
Gestational age, wk					.36[a]
< 14	16	(25.4)	19	(27.5)	
14–27	40	(63.5)	47	(68.1)	
> 27	7	(11.1)	3	(4.3)	
Wasted (MUAC < 23 cm)	18	(21.4)	18	(22.0)	1
ART duration, mo					.010[a]
< 3	23	(30.7)	10	(13.5)	
3–11	5	(6.7)	1	(1.4)	
12–35	15	(20.0)	15	(20.3)	
≥36	32	(42.7)	48	(64.9)	
NA	11	(12.8)	10	(11.9)	
ART regimen					.0085[a]
ZDV + 3TC + NVP	4	(5.6)	17	(23.6)	
ZDV + 3TC + EFV	2	(2.8)	3	(4.2)	

Table 4. Continued

Characteristic	TB⁻		TB⁺		*P* Value
TDF + 3TC + EFV	55	(77.5)	46	(63.9)	
TDF + 3TC + NVP	10	(14.1)	5	(6.9)	
Second line	0	(0)	1	(1.4)	
NA	15	(17.4)	12	(14.3)	
CD4 count, cells/μL					.17[a]
< 350	12	(32.4)	4	(16.0)	
350–599	13	(35.1)	7	(28.0)	
≥ 600	12	(32.4)	14	(56.0)	
NA	49	(57.0)	59	(70.0)	
Viral load, copies/mL					.007
< 1000	40	(52.6)	58	(69.0)	
≥ 1000	26	(34.2)	9	(13.4)	
NA	10	(11.6)	17	(20.2)	

Data are presented as no. (%) unless otherwise indicated. Characteristics of human immunodeficiency virus–positive study participants with evidence of TB infection, either current or previous active TB or latent TB, using the conventional cutoff (interferon-γ ≥ 0.35 IU/mL) after stimulation with either TB1 or TB2 antigen mixtures. Univariate comparisons were made using *t* test for normally distributed variables (hemoglobin) and using χ^2 test or Fisher exact test for categorical variables. Bonferroni-adjusted level of significance: 0.0031.

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; EFV, efavirenz; MUAC, mid-upper arm circumference; NA, not available; NVP, nevirapine; QFT, QuantiFERON-TB Gold-Plus; SD, standard deviation; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

[a] Fisher exact test.

Table 5. Logistic Regression Analysis for Tuberculosis Infection in Women With Human Immunodeficiency Virus

Regimen and Viral Load	AOR	(95% CI)	*P* Value
ART regimen			
ZDV + 3TC + NVP	Ref	…	
ZDV + 3TC + EFV	0.261	(.027–2.50)	.24
TDF + 3TC + EFV	0.288	(.086–.971)	.045
TDF + 3TC + NVP	0.125	(.024–.640)	.013
Viral load, copies/mL			
< 1000	Ref	…	
≥ 1000	0.275	(.098–.773)	.014

Multivariate logistic regression for tuberculosis infection (TB⁺) in women with human immunodeficiency virus using the conventional cutoff (0.35 IU/mL) for QuantiFERON-TB Gold-Plus. The model was constructed in a stepwise forward selection method, with variables with univariate $P < .10$ eligible for inclusion and likelihood ratio test used to determine the contributed model fitness. Bonferroni-adjusted level of significance: 0.0031.

Abbreviations: 3TC, lamivudine; AOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; EFV, efavirenz; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

ANC during pregnancy. Three criteria were used to define TB infection. Compared to tuberculin skin test, which has previously been the reference method for LTBI diagnosis, QFT is considered to have higher specificity for *Mtb* infection, as well as greater sensitivity, especially in persons with immunosuppression. Yet, it has been suggested that false-negative QFT results might occur during pregnancy [19, 21]. As immunosuppression is most pronounced in the third trimester, and only 5.6% of our participants were tested during this period, we believe this is unlikely to bias our conclusions. The inclusion of 2 sets of *Mtb* antigen in the QFT assay could also improve sensitivity in immunocompromised individuals. We did not collect data on IPT for HIV-positive women, but it is possible that a majority of them had received such treatment according to Ethiopian guidelines previously. Although this intervention could have reduced rates of active TB in these individuals, we consider it unlikely that IPT has affected QFT results [40].

For detection of current active TB, bacteriological TB testing was performed on sputum samples. The number of diagnosed cases of active TB was relatively low. Although this testing strategy could have missed cases of extrapulmonary TB, only 2 additional TB cases were observed during subsequent follow-up. As a measure of cumulative TB exposure, we also recorded self-reported treatment for active TB. In the study setting, we were not able to check these reports, and recall bias is possible.

Simultaneous testing of many risk factors increases the risk for spurious associations. The association with ART regimen could represent such an example. To reduce the risk of false-positive associations, we used Bonferroni adjustment of the significance threshold following which only age and HIV serostatus remained significantly associated with TB infection.

Data for certain variables were missing; however, with the exception of CD4 count this proportion was low, and unlikely to bias the conclusions.

CONCLUSIONS

In this large cohort of Ethiopian women of reproductive age, 37% met criteria for TB infection, which was independently associated with HIV infection and increasing age. The absolute risk of acquiring TB infection was estimated at 2.1% per year, suggesting continuous exposure to contagious TB among young women living in Ethiopia.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. P. B. is the principal investigator and provided the funds for this project and initiated it together with N. W., T. T. B., S. H., M. J., and E. S. Data were collected by J. W., F. T., G. M., and M. K.; J. W. performed the statistical analysis and prepared the first draft of the manuscript. All authors have contributed to the intellectual content and have given their final approval for the version submitted for publication.

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