Published in final edited form as:

J Acquir Immune Defic Syndr. 2011 August 1; 57(4): e77–e84. doi:10.1097/QAI.0b013e31821ac9c1.

Active Tuberculosis Case-Finding among Pregnant Women Presenting to Antenatal Clinics in Soweto, South Africa

Celine R. Gounder¹, Nikolas I. Wada¹, Caroline Kensler¹, Avy Violari², James McIntyre³, Richard E. Chaisson¹, and Neil A. Martinson^{1,2}

¹ Center for Tuberculosis Research, Johns Hopkins University, Baltimore, MD, USA

² Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa

³ Anova Health Institute, Johannesburg, South Africa

Abstract

Background—Human immunodeficiency virus (HIV) and tuberculosis (TB) are among the leading causes of death among women of reproductive age worldwide. TB is a significant cause of maternal morbidity. Detection of TB during pregnancy could provide substantial benefits to women and their offspring.

Methods—This was a cross-sectional implementation research study of integrating active TB case-finding with delivery of antenatal and prevention of mother-to-child transmission (PMTCT) services in six clinics in Soweto, South Africa. All pregnant women ≥ 18 years of age presenting for routine care to these public clinics were screened for symptoms of active TB, cough ≥ 2 weeks, sputum production, fevers, night sweats or weight loss, regardless of their HIV status. Participants with any symptom of active TB were asked to provide a sputum specimen for smear microscopy, mycobacterial culture and drug-susceptibility testing.

Results—Between December 2008 and July 2009, 3,963 pregnant women were enrolled and screened for TB, of whom 1,454 (36.7%) were HIV-seropositive. Any symptom of TB was reported by 23.1% of HIV-seropositive and 13.8% of HIV-seronegative women ($p < 0.01$). Active pulmonary TB was diagnosed in 10/1,454 HIV-seropositive women (688 per 100,000) and 5/2,483 HIV-seronegative women (201 per 100,000, $p = 0.03$). The median CD4⁺ T-cell count among HIV-seropositive women with TB was similar to that of HIV-seropositive women without TB (352 versus 333 cells/ μ L, $p = 0.85$).

Conclusions—There is a high burden of active TB among HIV-seropositive pregnant women. TB screening and provision of isoniazid preventive therapy and antiretroviral therapy should be integrated with PMTCT services.

Keywords

tuberculosis; HIV; pregnancy; epidemiology; screening

Corresponding author: Dr. Celine Gounder, Center for Tuberculosis Research, Johns Hopkins University, CRB-2, Room M1.06, 1550 Orleans Street, Baltimore, MD 21287, USA, Tel. +1-443-287-1036, Fax +1-410-955-0740, gounder@jhmi.edu. Alternate corresponding author: Dr. Richard Chaisson, Center for Tuberculosis Research, Johns Hopkins University, CRB-2, Room M1.08, 1550 Orleans Street, Baltimore, MD 21287, USA, Tel. +1-410-955-7318, Fax +1-410-955-0740, rchais@jhmi.edu.

Meetings at which parts of the data were presented: 17th Conference on Retroviruses and Opportunistic Infections (CROI 2010). Abstract T-122. San Francisco, February 18, 2010.

Contributors: CRG and NAM conceived the study. All authors contributed to the conception and design of the study, interpretation of the data, and reviewing drafts of the manuscript. CRG and NIW analyzed the data. CRG drafted and revised the manuscript.

Conflict of interest statement: We declare that we have no conflict of interest.

Introduction

Tuberculosis (TB) is a leading cause of death among women worldwide. An estimated 700,000 women died from TB in 2008 compared to an estimated 342,900 who died from maternal causes in the same year; TB was the third leading cause of death worldwide among women aged 15–44.^{1, 2} Feminization of the HIV epidemic has increased the burden of TB among women of reproductive age.¹ TB is also a leading cause of maternal mortality in high HIV prevalence settings^{3–5} and is often under-diagnosed among women due to barriers to accessing care and low index of suspicion for TB among those presenting with symptoms.^{6–9} TB in women of reproductive age impacts not only on their own health, but also on the health of their pregnancies and children. Like HIV, TB may be transmitted from mother to child in utero, intra-partum and post-partum. Even when TB is not transmitted to an infant, it has adverse consequences for fetal and neonatal health, including increased risk of premature birth, intrauterine growth retardation, low birth weight and mortality.^{10–13} TB/HIV co-infection in pregnant women has also been shown to increase the transmission of HIV from mother to child.^{10, 13–15} There is little data however on the prevalence of TB among HIV-seronegative pregnant women, and whether TB screening should be offered to all pregnant women or only to HIV-seropositive pregnant women.

Antenatal care is an important point of contact between women, regardless of HIV status, and the health care system, and offers a unique opportunity to access large numbers of women of reproductive age. Our objective was to integrate active case-finding for TB with delivery of antenatal and PMTCT services, and to report on the number of TB cases detected by this intervention among HIV-seropositive and -seronegative women presenting for their first antenatal clinic visit.

Methods

Setting and study population

This cross-sectional operational study was conducted between December 2008 and July 2009 at six public antenatal clinics supported by the Perinatal HIV Research Unit (PHRU) to provide prevention of mother-to-child transmission of HIV (PMTCT) services in Soweto, South Africa. Five of the clinics were community-based primary care facilities, and one was a hospital-based antenatal clinic. The vast majority of pregnant women presenting for antenatal care in Soweto are Black African, most of who are of Zulu or Sotho ethnicity. At the time of this study, the South African National Department of Health's guidelines recommended that HIV-seropositive pregnant women with CD4+ T-cell counts >200 cells/ μ L receive short-course zidovudine starting at 28 weeks gestation and single-dose nevirapine at the time of delivery, and that pregnant women with CD4+ T-cell counts $\leq$ 200 cells/ μ L or with WHO stage 4 disease receive antiretroviral therapy with a first line regimen of nevirapine, stavudine and lamivudine as soon as possible.¹⁶ The guidelines recommended that pregnant women receiving efavirenz-based ART be switched to nevirapine if in the first trimester of pregnancy, or be continued on efavirenz if in the second or third trimesters of pregnancy and be followed with fetal ultrasounds.¹⁶ The guidelines also recommended that all pregnant women with HIV be screened for TB, but this was not happening at most antenatal clinics in the country at the time of the study.¹⁶

In 2008, a total of 14,430 pregnant women attended the six study clinics for their first antenatal clinic visit, representing almost half of all such visits in Soweto that year. 98% of pregnant women attending the study clinics for antenatal services accepted HIV testing, of whom 30% were HIV-seropositive.¹⁷ Routine PMTCT services include provider-initiated counseling and testing for HIV (VCT), provision of maternal single-dose nevirapine and

short-course zidovudine, HIV support groups, infant feeding education, and free formula for infants born to HIV-seropositive mothers.

All pregnant women 18 years of age or older presenting to the six clinics were eligible to participate in the study regardless of HIV status. Women were excluded if they presented with obstetric complications or medical emergencies, declined or were unable to provide verbal consent to participate, or were prisoners or otherwise institutionalized.

Procedures

Trained and experienced counselors who provided both pre-and post-test counseling for HIV testing screened pregnant women presenting to study clinics for their first antenatal clinic visit for eligibility, and if eligible, these VCT counselors obtained verbal consent from eligible women to participate in the study. Screening of all study participants for symptoms of active pulmonary TB was then offered during the pre-test counseling session prior to HIV testing and regardless of HIV status. TB suspects were defined as participants with any symptom of active TB: cough for ≤ 2 weeks, sputum production, fevers, night sweats or weight loss. Information on demographics, HIV status, CD4+ T-cell count, and prior TB and HIV history was also collected. Clinic nurses reviewed the symptom screening questionnaire, and collected a single spontaneously expectorated sputum specimen from study participants with any symptom of active TB while they were waiting for their HIV result. Sputum induction was not performed. HIV testing was performed according to the South African national algorithm for serial rapid testing. All samples were first tested with Determine rapid test kits (Abbott Laboratories, Abbott Park, IL), and if positive, were then tested with the Uni-Gold rapid test kits (Trinity Biotech, Wicklow, Ireland). Uni-Gold reactive samples were considered confirmed positive. Uni-Gold non-reactive samples were considered indeterminate and specimens were sent to the South African National Health Laboratory Service (NHLS) for confirmatory HIV ELISA testing. HIV results were relayed to pregnant women at the same clinic visit unless an HIV ELISA was required.

Sputum specimens were transported to the public sector TB laboratory – the NHLS – for fluorescence microscopy, culture in the Mycobacterial Growth Indicator Tube System (MGIT; BD, Sparks, MD), mycobacterial identification, and conventional drug-susceptibility testing to isoniazid and rifampin. TB suspects were also referred to the TB clinic at the study site for further evaluation as indicated, the results of which were not collected by the study. TB diagnostic and treatment services were available for free at public sector TB clinics throughout Soweto. TB cases identified by the study were referred to the TB clinic at the study site for treatment. The standard TB treatment regimen, regardless of HIV status, was a 2 month intensive phase of isoniazid, rifampin, ethambutol and pyrazinamide, followed by a 4 month continuation phase of isoniazid and rifampin.¹⁸

Definitions, analysis and outcomes

TB cases were defined as participants with sputum mycobacterial cultures that were positive for *Mycobacterium tuberculosis*, or with acid fast bacilli (AFB) positive sputum smears but missing, contaminated or negative mycobacterial cultures. The primary outcome of interest was the prevalence of active pulmonary TB among HIV-seropositive and -seronegative pregnant women. The secondary outcomes of interest were risk factors for active pulmonary TB, rates of AFB positivity among TB cases, and proportion of TB suspects from whom sputum was successfully collected. We estimated that the prevalence of undiagnosed pulmonary TB among HIV-seronegative pregnant women would be 500 per 100,000 and among HIV-seropositive pregnant women would be 2,000 per 100,000.^{19, 20} Assuming a significance level of $\alpha = 0.05$, power $1 - \beta = 90\%$ and that we would enroll about twice as many HIV-seronegative as -seropositive pregnant women, we estimated that we would need

to enroll 988 HIV-seropositive and 1,976 HIV-seronegative pregnant women for a total sample size of 2,964 participants in order to detect a four-fold higher prevalence of TB among HIV-seropositive than -seronegative participants. We estimated that to measure a TB prevalence of 500 per 100,000 among HIV-seronegative women^{19, 20} with 95% confidence intervals of $\pm 1,000$, 500 and 200 per 100,000 that we would have to enroll 191, 764 and 4,778 HIV-seronegative participants respectively. We estimated that to measure a TB prevalence of 2,000 per 100,000 among HIV-seropositive women^{19, 20} with 95% confidence intervals of (CIs) $\pm 1,000$, 500 and 200 per 100,000 that we would have to enroll 753, 3,012 and 18,824 HIV-seroparticipants participants respectively. Differences in proportions were estimated using the chi-square and Fisher's exact tests. P-values were estimated using the Kruskal-Wallis test for continuous variables and the Fisher's exact test for dichotomous variables. P-values and 95% CIs for the logistic regression were estimated using the Wald test. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand and the Institutional Review Board of the Johns Hopkins University School of Medicine.

Results

Between December 2008 and July 2009, 8,862 women presented to the six study clinics for their first antenatal clinic visit, of whom 3,963 (44.7%) enrolled in the study. The median age was 26 years (IQR 22–31 years) and the median gestational age 21 weeks (IQR 16–26 weeks). 681 (17.2%) study participants reported one or more symptom of active pulmonary TB.

HIV status was known for 99.3% of participants, with 1,454 (36.7%) HIV-seropositive and 2,483 (62.7%) HIV-seronegative. Among HIV-seropositive pregnant women, the median CD4+ T-cell count was 333 cells/ μ L (IQR 214–462 cells/ μ L); 295 (20.3%) had an absolute CD4+ T-cell count ≥ 200 cells/ μ L, 1,065 (73.2%) of >200 cells/ μ L, and 94 (6.5%) were unknown. HIV-seropositive pregnant women were older than their HIV-seronegative counterparts (median age 28 versus 25 years, $p < 0.01$; Table 1). HIV-seropositive women were more likely to report symptoms (23.1%) than HIV-seronegative women (13.8%, $p < 0.01$). HIV-seropositive women were also more likely to report a prior history of TB (8.6% versus 2.5%, $p < 0.01$) and a history of household TB contact (23.8% versus 20.2%, $p = 0.01$).

The PMTCT nurses reviewed the symptom screens and further evaluated 88.4% of HIV-seropositive TB suspects and 83.0% of HIV-seronegative TB suspects. Among those TB suspects not evaluated further by the PMTCT nurses, 50.0% were HIV-seropositive and 50.0% HIV-seronegative; and 22.6% reported a cough ≥ 2 weeks, 26.7% sputum production, 35.9% cough ≥ 2 weeks or sputum production, 22.6% fevers, 12.8% sweats, 57.4% weight loss, and 61.2% no weight gain. On bivariate analysis there was no difference in rates of successful sputum collection from HIV-seropositive versus -seronegative TB suspects (49.1% versus 49.7%, $p = 0.88$), but sputum collection occurred significantly less frequently among HIV-seropositive TB suspects with CD4+ T-cell counts >500 cells/ μ L than those with CD4+ T-cell counts ≤ 500 cells/ μ L (36.7% versus 53.0%, $p = 0.04$). Sputum was successfully collected more frequently from TB suspects reporting a cough ≥ 2 weeks (60.4% versus 44.8%, $p < 0.01$), sputum production (68.6% versus 34.8%, $p < 0.01$), fevers (56.4% versus 46.8%, $p = 0.03$), prior history of TB (63.3% versus 47.9%, $p = 0.03$), or history of household TB contact (56.0% versus 45.9%, $p = 0.01$). Sputum was successfully collected less frequently from TB suspects reporting weight loss (33.6% versus 61.6%, $p < 0.01$) or poor weight gain (36.6% versus 61.5%, $p < 0.01$). On multivariate logistic regression (see Table 2a), only sputum production (OR 3.26, 95% CI 2.27–4.68, $p < 0.01$) and poor weight gain (OR 0.61, 95% CI 0.43–0.86, $p < 0.01$) remained significantly predictive of whether

sputum was collected. The same two symptoms were again predictive of sputum collection among only HIV-seropositive participants (see Table 2b). All TB suspects, including those who were unable to spontaneously expectorate sputum, were referred to the TB clinic for further evaluation, but no additional information is available regarding any investigations performed or ordered by the TB clinic.

15 TB cases were found: 10/1,454 HIV-seropositive pregnant women (688 per 100,000, [95% CI 330–1,260 per 100,000]) and 5/2,483 HIV-seronegative pregnant women (201 per 100,000, [95% CI 70–470 per 100,000], $p = 0.03$; Table 1). The clinical characteristics of the 15 TB cases identified are shown in Table 3. All HIV-seronegative TB cases but only 60% of HIV-seropositive TB cases were AFB smear positive. One HIV-seronegative participant was found to be AFB smear positive but had a negative mycobacterial culture and was included as a case. None of the TB cases had isoniazid or rifampin resistance.

There were no significant differences in age, gestational age, weight or median CD4+ T-cell count between HIV-seropositive pregnant women with and without TB (see Table 4a), but HIV-seropositive TB cases were significantly more likely than non-cases to report cough ≥ 2 weeks, sputum production, night sweats and weight loss. The majority of both HIV-seropositive TB cases and non-cases reported not knowing the duration of their symptoms. Similar proportions of HIV-seropositive TB cases and non-cases reported a prior history of TB or history of household TB contact.

There were no significant differences in maternal age, gestational age or weight between HIV-seronegative pregnant women with and without TB (see Table 4b). HIV-seronegative TB cases were significantly more likely than non-cases to report cough ≥ 2 weeks, sputum production and fevers. The majority of both HIV-seronegative TB cases and non-cases reported not knowing the duration of their symptoms. A higher proportion of HIV-seronegative TB cases than non-cases reported a prior history of TB (20.0% versus 2.5%, $p = 0.12$) and a history of household TB contact (60.0% versus 20.1%, $p = 0.06$), but these differences were not statistically significant.

In addition to the TB cases identified, 6 participants had negative sputum smears and grew non-tuberculous mycobacteria (NTM) on culture: 1 *M. avium intracellulare*, 3 *M. gordonae* and 2 *M. scrofulaceum*. One HIV-seropositive participant had *M. avium intracellulare* and 1 HIV-seropositive participant had *M. gordonae*. Only 1 of the 6 participants with NTM reported a cough, 3 reported sputum production, 2 fever, 2 weight loss and 0 night sweats.

In bivariate analysis, HIV-infection (OR 3.4 [95% CI 1.2–10.1], $p = 0.02$), weight loss (OR 5.63 [95% CI 1.7–18.9], $p = 0.01$) and absence of weight gain (OR 3.2 [95% CI 1.1–9.4], $p = 0.03$) were significantly associated with pulmonary TB. Multivariate analysis was not performed due to the small number of TB cases identified.

Discussion

We implemented active case-finding for TB in pregnant women through public sector health care services with existing staff and using the routine laboratory system. The prevalence of active TB among HIV-seropositive and -seronegative pregnant women in this study was high at 688 and 201 per 100,000 respectively. The prevalence of pulmonary TB among HIV-seropositive pregnant women was similar to the overall prevalence of TB in South Africa (808 per 100,000).²¹ Such a high prevalence of active TB in pregnant women with and without HIV infection is of enormous public health concern given the potential impact of the disease on pregnancy outcomes and the unique vulnerability of newborn infants exposed to infectious TB.

Five out of six of the study sites were community-based clinics. The majority of South Africans receive their health care free of charge at public sector clinics. Our study suggests that active case-finding for TB can be integrated with routine delivery of PMTCT and other antenatal clinic services, but that there are challenges to implementation. Almost all the women invited to enroll in the study and be screened for TB consented to do so; however only 44.7% of women presenting for antenatal care at the study clinics were enrolled. The routine clinical staff was not consistently adherent with offering TB screening to all eligible women, and may have been biased towards screening women who they perceived to be at higher risk for TB, as evidenced by the higher prevalence of HIV in the study population than in the general population of pregnant women at that time (36.7% versus 30%). The PMTCT nurses did not further investigate about 15% of TB suspects, despite their having had a positive symptom screen, but sputum was collected with similar frequency from HIV-seropositive and -seronegative TB suspects. There did not appear to be a bias on the part of nurses to try harder to obtain sputum specimens from HIV-seropositive than -seronegative TB suspects; however, sputum was collected more successfully from TB suspects with CD4+ T-cell counts ≤ 500 than >500 cells/ μ L. Sputum production was the only symptom that was consistently predictive of successful sputum collection, while interestingly, poor weight gain was consistently predictive against successful sputum collection. We did not utilize invasive techniques to obtain sputum specimens from TB suspects who were unable to spontaneously expectorate a specimen; however, Bell and colleagues in Malawi have demonstrated that invasive sputum collection techniques including physiotherapy-assisted sputum collection, sputum induction, gastric washing and bronchoalveolar lavage provide little additional diagnostic yield.²² Poor clinical staff morale and low motivation to take on new responsibilities without additional remuneration were important obstacles to integrating TB screening with PMTCT services in our setting, but additional training and supportive supervision could potentially improve identification and investigation of TB suspects. Operational research is needed to assess how, the order in which and by whom services are provided to minimize patient wait times and staff workloads, and to optimize patient flow and service delivery.

Prior smaller studies that estimated even higher prevalences of TB among HIV-seropositive pregnant women in Soweto focused on higher risk populations of pregnant women attending a tertiary care hospital and a community health center located adjacent to an informal settlement.^{19, 23} Our study may have underestimated the overall burden of TB among pregnant women in Soweto because one of our screening symptoms was cough ≥ 2 weeks rather than cough of any duration;²⁴ sputum was not successfully collected from all TB suspects; we did not request sputum from asymptomatic participants; only one sputum specimen (rather than two or three) was requested from TB suspects; chest x-rays were not performed; no testing was done to assess specifically for extrapulmonary TB; and we did not collect data on further investigation and treatment of TB suspects who were negative on sputum smear and mycobacterial culture and who were referred to TB clinics. Other studies have found a high prevalence of asymptomatic tuberculosis among HIV-seropositive persons.²⁵

Different strategies are needed to more accurately and cost-effectively screen HIV-seropositive and -seronegative pregnant women for TB. The WHO has optimized a symptom screening algorithm for its sensitivity and negative predictive value in HIV-seropositive persons,²⁴ but this algorithm needs to be validated in HIV-seropositive pregnant women, HIV-seronegative pregnant women and other HIV-seronegative persons. We performed 165 sputum smears and mycobacterial cultures to diagnose 10 cases of TB among HIV-seropositive pregnant women, and 170 sputum smears and mycobacterial cultures to diagnose 5 cases of TB among HIV-seronegative pregnant women, demonstrating the need

for more specific symptom screens to allow for better targeting of laboratory resources to those most likely to have TB.

Sputum smear microscopy, the most commonly available TB diagnostic test in most high-burden areas, has a sensitivity of 50–80% and 10–40% among HIV-seronegative and -seropositive TB patients respectively,^{26–30} consistent with our finding that 100% of HIV-seronegative and 60% of HIV-seropositive TB patients were sputum smear positive. Not only is sputum smear microscopy an insensitive test for TB particularly among HIV-seropositive persons, it is unknown whether sputum smear microscopy performs as sensitively in pregnant women, in whom there appears to be an increased risk for extrapulmonary TB.^{31–33} Sputum smear microscopy is significantly less expensive than mycobacterial culture, the current gold standard for TB diagnosis (~US\$5 versus ~US\$20 at NHLS in South Africa). New rapid tests for *M. tuberculosis* and drug-resistance have the potential to be used as point-of-care diagnostics, and could improve case detection with low human resource, laboratory and infection control requirements.³⁴ Rapid diagnosis of TB with immediate initiation of treatment is likely to reduce morbidity and mortality, and may impact on transmission of TB to the fetus or neonate.¹³ Studies are also needed to assess accuracy and cost-effectiveness of combinations of different symptoms screens and diagnostic tests for TB among HIV-seropositive and -seronegative pregnant women.

The proportion of HIV-seropositive pregnant women in this study was 36.7%, the majority of whom would have been eligible for isoniazid preventive therapy (IPT), which has been shown to decrease the risk of active TB by about a third among HIV-seropositive persons.³⁵ Additionally, 55% of HIV-seropositive pregnant women in this study had CD4+ T-cell counts ≤ 350 cells/ μ L, and thus were eligible for ART based on current South African treatment guidelines. These data document the enormous health burden of TB and HIV in pregnant women and underscore the need for women-centered approaches to combat and control both diseases. Maternal and child health, reproductive health and family planning services are reliable points of contact between women and the health care system; these points of contact provide opportunities for delivering and HIV-and TB-related services including HIV testing, co-trimoxazole preventive therapy, antiretroviral therapy, TB screening and isoniazid preventive therapy.

Through the Global Health Initiative, the United States government has proposed to significantly increase funding for maternal and child health.³⁶ The Global Health Initiative aims to support horizontal, integrated health programs. The time has come for integration of TB, HIV, maternal and child health services, and health systems strengthening efforts. In high HIV and TB prevalence areas, active case-finding for TB should be integrated with routine antenatal care to prevent morbidity and mortality in both pregnant women and their children.

Acknowledgments

Sources of support: Dr. Celine Gounder was funded by NIH grant T32AI007291. This study was funded in part by a grant from the United States Agency for International Development (USAID) through Cooperative Agreement No.674-A-00-08-00009-00.

We thank the staff and patients who made this study possible. We would specifically like to thank Eunice Ramothibe, Reginah Msandiwa, Susan Raedani, Nowinile Matipile, Nick Moodley, Ravindre Panchia and Charlene Conradie. Dr. Celine Gounder was funded by NIH grant T32AI007291. Dr. Neil Martinson is partially supported by Fogarty International Center TB and HIV research training twin grants TW007370 and W007373. This study was funded in part by a grant from the United States Agency for International Development (USAID) through Cooperative Agreement No.674-A-00-08-00009-00. The contents of this report are the sole responsibility of the authors and do not necessarily reflect the views of USAID or the United States Government.

References

1. WHO. Women and TB Fact Sheet. 2009.
2. Hogan MC, Foreman KJ, Naghavi M, et al. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. *Lancet*. 2010; 375:1609–23. [PubMed: 20382417]
3. Majoko F, Chipato T, Iliff V. Trends in maternal mortality for the Greater Harare Maternity Unit: 1976 to 1997. *Cent Afr J Med*. 2001; 47:199–203. [PubMed: 12808767]
4. Ahmed Y, Mwaba P, Chintu C, et al. A study of maternal mortality at the University Teaching Hospital, Lusaka, Zambia: the emergence of tuberculosis as a major non-obstetric cause of maternal death. *Int J Tuberc Lung Dis*. 1999; 3:675–80. [PubMed: 10460099]
5. Khan M, Pillay T, Moodley JM, et al. Maternal mortality associated with tuberculosis-HIV-1 co-infection in Durban, South Africa. *AIDS*. 2001; 15:1857–63. [PubMed: 11579249]
6. Thorson A, Hoa NP, Long NH, et al. Do women with tuberculosis have a lower likelihood of getting diagnosed? Prevalence and case detection of sputum smear positive pulmonary TB, a population-based study from Vietnam. *J Clin Epidemiol*. 2004; 57:398–402. [PubMed: 15135842]
7. Becerra MC, Pachao-Torreblanca IF, Bayona J, et al. Expanding tuberculosis case detection by screening household contacts. *Public Health Rep*. 2005; 120:271–7. [PubMed: 16134567]
8. Borgdorff MW, Nagelkerke NJ, Dye C, et al. Gender and tuberculosis: a comparison of prevalence surveys with notification data to explore sex differences in case detection. *Int J Tuberc Lung Dis*. 2000; 4:123–32. [PubMed: 10694090]
9. Khan MS, Dar O, Sismanidis C, et al. Improvement of tuberculosis case detection and reduction of discrepancies between men and women by simple sputum-submission instructions: a pragmatic randomised controlled trial. *Lancet*. 2007; 369:1955–60. [PubMed: 17560448]
10. Gupta, A.; Gupte, N.; Patil, S., et al. [Accessed 10 May 2010] Maternal TB is associated with increased risk of HIV mother-to-child transmission. Conference on Retroviruses and Opportunistic Infections. 2010. Abstract 899. Available from: <http://retroconference.org/2010/Abstracts/37899.htm>
11. Figueroa-Damian R, Arredondo-Garcia JL. Neonatal outcome of children born to women with tuberculosis. *Arch Med Res*. 2001; 32:66–9. [PubMed: 11282183]
12. Lin HC, Lin HC, Chen SF. Increased risk of low birthweight and small for gestational age infants among women with tuberculosis. *BJOG*. 2010; 117:585–90. [PubMed: 20156210]
13. Pillay T, Sturm AW, Khan M, et al. Vertical transmission of *Mycobacterium tuberculosis* in KwaZulu Natal: impact of HIV-1 co-infection. *Int J Tuberc Lung Dis*. 2004; 8:59–69. [PubMed: 14974747]
14. Pillay T, Adhikari M, Coovadia HM, et al. In utero HIV infection in pregnancies complicated by tuberculosis in Durban, South Africa. *Arch Dis Child Fetal Neonatal Ed*. 2004; 89:F468–9. [PubMed: 15321976]
15. Adhikari M, Pillay T, Pillay DG. Tuberculosis in the newborn: an emerging disease. *Pediatr Infect Dis J*. 1997; 16:1108–12. [PubMed: 9427454]
16. South African National Department of Health. [Accessed 19 August 2010] Policy and guidelines for the implementation of the PMTCT programme. February 11. 2008 Available from: <http://www.doh.gov.za/docs/policy/pmtct.pdf>
17. Gray, G.; McIntyre, J. Responding to the HIV epidemic in Soweto, South Africa. 14th Bernard Fields Memorial Lecture. 3rd N'galy-Mann Lecture. 16th Conference on Retroviruses and Opportunistic Infections; February 8, 2009;
18. South African National Department of Health. [Accessed 19 August 2010] The South African tuberculosis control programme practical guidelines. 2000. Available from: <http://www.doh.gov.za/tb/docs/ntcpguidelines01.pdf>, <http://www.doh.gov.za/tb/docs/ntcpguidelines02.pdf>
19. Kali PB, Gray GE, Violari A, et al. Combining PMTCT with active case finding for tuberculosis. *J Acquir Immune Defic Syndr*. 2006; 42:379–81. [PubMed: 16645548]
20. World Health Organization. [Accessed 10 November 2010] Global tuberculosis control - surveillance, planning, financing. WHO Report. 2007. WHO/HTM/TB/2007.376. Annex 1:

Profiles of high-burden countries. South Africa. Available from:
http://www.who.int/tb/publications/global_report/2007/pdf/zaf.pdf

21. World Health Organization. [Accessed 29 November 2010] Global TB database. Country Profile: South Africa. 2010. Available from: <http://www.who.int/tb/country/data/profiles/en/index.html>
22. Bell DJ, Dacombe R, Graham SM, et al. Simple measures are as effective as invasive techniques in the diagnosis of pulmonary tuberculosis in Malawi. *Int J Tuberc Lung Dis.* 2009; 13:99–104. [PubMed: 19105886]
23. Nachega J, Coetzee J, Adendorff T, et al. Tuberculosis active case-finding in a mother-to-child HIV transmission prevention programme in Soweto, South Africa. *AIDS.* 2003; 17:1398–400. [PubMed: 12799565]
24. Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med.* 2011; 8:e1000391. [PubMed: 21267059]
25. Mtei L, Matee M, Herfort O, et al. High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania. *Clin Infect Dis.* 2005; 40:1500–7. [PubMed: 15844073]
26. Aber VR, Allen BW, Mitchison DA, et al. Quality control in tuberculosis bacteriology. 1. Laboratory studies on isolated positive cultures and the efficiency of direct smear examination. *Tubercle.* 1980; 61:123–33. [PubMed: 6777919]
27. Harries, AD. What is the additional yield from repeated sputum examinations by microscopy and culture?. In: Frieden, TR., editor. *Toman's Tuberculosis: Case Detection, Treatment and Monitoring.* 2. Geneva: World Health Organization; 2004. p. 46-50.
28. Kivihya-Ndugga LE, van Cleeff MR, Githui WA, et al. A comprehensive comparison of Ziehl-Neelsen and fluorescence microscopy for the diagnosis of tuberculosis in a resource-poor urban setting. *Int J Tuberc Lung Dis.* 2003; 7:1163–71. [PubMed: 14677891]
29. Steingart KR, Ng V, Henry M, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis.* 2006; 6:664–74. [PubMed: 17008175]
30. Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis.* 2006; 6:570–81. [PubMed: 16931408]
31. Knight M, Kurinczuk JJ, Nelson-Piercy C, et al. Tuberculosis in pregnancy in the UK. *BJOG.* 2009; 116:584–8. [PubMed: 19250368]
32. Kothari A, Mahadevan N, Girling J. Tuberculosis and pregnancy--Results of a study in a high prevalence area in London. *Eur J Obstet Gynecol Reprod Biol.* 2006; 126:48–55. [PubMed: 16154251]
33. Llewelyn M, Copley I, Wilkinson RJ, et al. Tuberculosis diagnosed during pregnancy: a prospective study from London. *Thorax.* 2000; 55:129–32. [PubMed: 10639530]
34. Boehme CC, Nabeta P, Hilleman D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med.* 2010; 363:1005–15. [PubMed: 20825313]
35. Akolo C, Adetifa I, Shepperd S, et al. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev.* 2010; (1):CD000171. [PubMed: 20091503]
36. The Henry J. Kaiser Family Foundation. [Accessed 6 May 2010] Budget tracker: Status of US funding for key global health accounts. Available from: <http://www.kff.org/globalhealth/8045.cfm>

Table 1

Demographic and clinical characteristics of HIV-seropositive and -seronegative pregnant women presenting for their first antenatal clinic visit.

	HIV-seropositive (n = 1,454)	HIV-seronegative (n = 2,483)	p-value
Maternal age, median years (IQR)	28 (24,32)	25 (21,30)	<0.01
Gestational age, median weeks (IQR)	21 (16,26)	21 (16,27)	0.25
Weight, median kg (IQR)	68.5 (61.0,78.9)	68.2 (60.0,80.3)	0.73
Participants reporting:			
Cough ≥2 weeks	105 (7.2%)	91 (3.7%)	<0.01
Sputum production	156 (10.7%)	136 (5.5%)	<0.01
Either cough ≥ 2 weeks or sputum production	188 (12.9%)	173 (7.0%)	<0.01
Fevers	83 (5.7%)	96 (3.9%)	0.01
Night sweats	49 (3.4%)	47 (1.9%)	0.01
Weight loss	152 (10.5%)	145 (5.8%)	<0.01
Any symptom of TB (i.e. a TB suspect)	336 (23.1%)	342 (13.8%)	<0.01
Absence of weight gain	252 (17.3%)	286 (11.5%)	<0.01
Duration of TB symptoms if any reported, median weeks (IQR)	3 (2,8)	3 (2,6)	0.43
<2 weeks	0 (0.0%)	1 (0.3%)	–
2–3 weeks	51 (15.2%)	49 (14.3%)	–
>3 weeks	35 (10.4%)	38 (11.1%)	–
Don't know	250 (74.4%)	254 (74.3%)	–
Prior history of TB	125 (8.6%)	63 (2.5%)	<0.01
History of household TB contact	346 (23.8%)	502 (20.2%)	0.01
TB cases per 100,000 (95% CI)	688 (330–1,260)	201 (70–470)	0.03

Table 2a

Multivariate logistic regression of predictors of sputum collection from TB suspects by PMTCT nurses

Predictor	Odds ratio (OR)	95% confidence interval (CI)	p-value
Cough	1.13	0.78–1.65	0.52
Sputum	3.26	2.27–4.68	<0.01
Fever	1.25	0.85–1.82	0.26
Sweats	1.44	0.90–2.31	0.13
Poor weight gain	0.61	0.43–0.86	0.01
TB history	1.56	0.86–2.83	0.14
TB contact history	1.28	0.90–1.81	0.17
HIV-seropositive	0.87	0.62–1.21	0.41

Table 2b

Multivariate logistic regression of predictors of sputum collection from HIV-seropositive TB suspects by PMTCT nurses

Predictor	Odds ratio (OR)	95% confidence interval (CI)	p-value
Cough	0.91	0.53–1.58	0.75
Sputum	2.27	1.34–3.84	<0.01
Fever	1.17	0.67–2.05	0.58
Sweats	0.93	0.47–1.84	0.83
Poor weight gain	0.50	0.30–0.83	0.01
TB history	1.50	0.74–3.03	0.26
TB contact history	1.06	0.64–1.75	0.83
Absolute CD4+ T-cell count, cells/ μ L			
≤200	1.62	0.78–3.35	0.19
201–350	2.20	1.10–4.39	0.03
351–500	1.77	0.85–3.71	0.13

Table 3

Clinical characteristics of TB cases

	HIV-seropositive (n = 10)		HIV-seronegative (n = 5)
	AFB smear positive (n = 6)	AFB smear negative (n = 4)	AFB smear positive (n = 5)
Maternal age, median years (IQR)	31.5 (22,36)	28 (26,31)	26 (25,26)
Gestational age, median weeks (IQR)	25 (23,28)	29 (23,31)	24 (22,28)
Weight, median kg (IQR)	68.4 (53.7,79.5)	64.9 (63.0,67.0)	75.9 (66.9,87.7)
Absolute CD4+ T-cell count, median cells/ μ L (IQR)	353 (257,447)	352 (245,576)	–
Participants reporting:			
Cough $\geq$ 2 weeks	3	1	3
Sputum production	3	2	3
Cough $\geq$ 2 weeks or sputum production	3	2	3
Fevers	2	1	2
Night sweats	2	0	1
Weight loss	3	1	0
Absence of weight gain	3	1	1
Prior history of TB	1	1	1
History of household TB contact	2	2	3
Mycobacterial culture			
TB	1	4	1
Contaminated	1	0	1
Negative	4	0	2
Not done*	0	0	1

* All were sputum smear positive.

Table 4a

Clinical characteristics of HIV-seropositive pregnant women with and without TB

	TB cases (n = 10)	Non-TB cases (n = 1,444)	p-value
Maternal age, median years (IQR)	34 (30,37)	28 (24,32)	0.53
Gestational age, median weeks (IQR)	28 (25,30)	21 (16,26)	0.16
Weight, median kg (IQR)	67.0 (62.9,69.5)	68.5 (61.0,78.9)	0.43
Absolute CD4+ T-cell count, median cells/ μ L (IQR)	352 (257,447)	333 (214,462)	0.85
0–200	1 (10.0%)	294 (20.4%)	–
201–350	3 (30.0%)	443 (30.7%)	–
351–500	4 (40.0%)	331 (22.9%)	–
>500	1 (10.0%)	283 (19.6%)	–
Unknown	1 (10.0%)	93 (6.4%)	–
Participants reporting:			
Cough $\geq$ 2 weeks	6 (60.0%)	99 (6.9%)	<0.01
Sputum production	6 (60.0%)	150 (10.4%)	<0.01
Either cough $\geq$ 2 weeks or sputum production	7 (70.0%)	181 (12.5%)	<0.01
Fevers	2 (20.0%)	81 (5.6%)	0.11
Night sweats	2 (20.0%)	47 (3.3%)	0.04
Weight loss	4 (40.0%)	148 (10.2%)	0.01
Any symptom of TB (i.e. a TB suspect)	10 (100.0%)	326 (22.6%)	<0.01
Absence of weight gain	4 (40.0%)	248 (17.2%)	0.08
Duration of TB symptoms if any reported, median weeks (IQR)	18 (–)	3 (2,7)	0.12
<2weeks	0 (0.0%)	0 (0.0%)	–
2–3 weeks	0 (0.0%)	51 (15.6%)	–
>3 weeks	1 (10.0%)	34 (10.4%)	–
Unknown	9 (90.0%)	241 (73.9%)	–
Prior history of TB	1 (10.0%)	124 (8.6%)	0.56
History of household TB contact	3 (30.0%)	343 (23.8%)	0.46

Table 4b

Clinical characteristics of HIV-seronegative pregnant women with and without TB

	TB cases (n = 5)	Non-TB cases (n = 2,478)	p-value
Maternal age, median years (IQR)	26 (25,26)	25 (21,30)	0.56
Gestational age, median weeks (IQR)	24 (22,28)	21 (16,27)	0.55
Weight, median kg (IQR)	75.9 (66.9,87.7)	68.2 (60.0,80.3)	0.45
Participants reporting:			
Cough ≥2 weeks	3 (60.0%)	88 (3.6%)	<0.01
Sputum production	3 (60.0%)	133 (5.4%)	<0.01
Either cough ≥2 weeks or sputum production	3 (60.0%)	170 (6.9%)	<0.01
Fevers	2 (40.0%)	94 (3.8%)	0.01
Night sweats	1 (20.0%)	46 (1.9%)	0.09
Weight loss	0 (0.0%)	145 (5.9%)	1.00
Any symptom of TB (i.e. a TB suspect)	4 (80.0%)	338 (13.6%)	<0.01
Absence of weight gain	1 (20.0%)	285 (11.5%)	0.46
Duration of TB symptoms if any reported, median weeks (IQR)	2 (1,24)	3 (2,6)	0.71
<2 weeks	0 (0.0%)	1 (0.3%)	–
2–3 weeks	1 (25.0%)	48 (14.2%)	–
>3 weeks	1 (25.0%)	37 (10.9%)	–
Unknown	2 (50.0%)	252 (74.6%)	–
Prior history of TB	1 (20.0%)	62 (2.5%)	0.12
History of household TB contact	3 (60.0%)	499 (20.1%)	0.06