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Mathabathe, Mohlamme John

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THE UNIVERSITY OF THE WITWATERSRAND
THE SCHOOL OF PUBLIC HEALTH

Accuracy of symptom-based screening for Tuberculosis in HIV-infected pregnant women attending antenatal clinics in Matlosana in 2010-2011.

Mohlamme John Mathabathe

A research report submitted to the Faculty of Health Sciences,

School of Public Health,

University of the Witwatersrand, Johannesburg

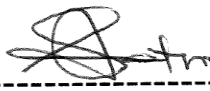
In partial fulfillment for the requirement for the degree

Master of Public Health

25 August 2014

Declaration

I, Mohlamme John Mathabathe, declare that this research report is my own work. It is submitted for partial fulfilment of Master of Public Health (Rural Health) at the University of the Witwatersrand, Johannesburg. It has not been submitted for any other degree or examination at any other university.



----------Date: 25 August 2014

Dedication

For the memories of my late father Nkgoba Philemon Mathabathe (1952-1997), and late sister Malifiane Lydia Mathabathe (1976-2006).

Acknowledgement

I would like to acknowledge the following individuals and organizations which contributed to the success of this research report:

My Supervisors, Professor Ian Couper, Professor of Rural Health and Director of the Centre for Rural Health, University of the Witwatersrand, Johannesburg, and Jabulani Ncayiyana, previously at Gillings School of Global Public Health, University of North Carolina-Chapel Hill. I also would like to thank my former supervisor, Lilo du Toit, former researcher at Centre for Rural Health, University of the Witwatersrand, Johannesburg. I would also like to thank Dr. Neil Martinson, Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, for making available the data used for this report. This report would not be possible without the assistance of Dr. Christopher Hoffmann, Aurum Institute for Health Research and Centre for TB Research, Johns Hopkins University, for helping me with the data analysis.

ABSTRACT

BACKGROUND

Tuberculosis is the leading opportunistic infection among HIV-infected adults, including pregnant women, globally. Accurate screening tools are needed to identify those requiring further laboratory testing and to initiate isoniazid preventive therapy in a timely manner. This study determined the accuracy of symptom-based screening and in particular the performance of the WHO recommended TB symptom screening algorithm in HIV-infected pregnant women.

METHODS

A cross-sectional study was conducted among consenting HIV-infected pregnant women attending routine antenatal clinics in Matlosana, South Africa recruited ≥1 week after first HIV diagnosis between June 2010 and February 2011. Sputum was collected from all women followed by a systematic TB symptom screen. The performances of each symptom (cough, fever, weight loss and night sweats) alone and in combination were assessed with TB confirmed by sputa using microscopy and liquid culture (MGIT), as reference or gold standard. The sensitivity, specificity, positive predictive value, negative

predictive value, positive likelihood ratio and negative likelihood ratio were calculated for each of the four symptoms (cough, fever, weight loss and night sweats) and their combination. Logistic regression was carried out to find associations between patient characteristics and TB.

RESULTS

Overall, Mycobacteria Growth Indicator Tube (MGIT) confirmed prevalence of TB was 2.4% (35/1456) in this sample group. Only 11/38 (29%) women with confirmed TB reported any symptoms. Cough, fever, weight-loss and night sweats, individually and in combination had sensitivities ranging from 2.7-27% and specificities ranging from 84-97%. The positive predictive and negative predictive values for any symptoms of cough, fever, night sweats, or weight loss were 4.2% and 98%, respectively. TB was associated with decreasing CD4 count, close TB contact, cough, and night sweats.

DISCUSSION

The remarkable number of asymptomatic TB in HIV-infected patients, including in the cohort included in this study highlights the limitation of symptom-based screening. The low sensitivity of the symptom screen would incorrectly stratify

patients who are being considered for Isoniazid Preventive Therapy (IPT). However, one could argue that the high negative predictive value of the symptom screen would justify its use in resource-limited settings as the initial step in identifying patients who should receive IPT. Although household TB and the father of the baby having TB were found not to have statistically significant associations with active TB, they are of public health importance as they play a role in the spread of the infection.

CONCLUSION

The WHO 4-symptom screen had low sensitive among HIV-infected pregnant women but negative predictive value was high. Few women with TB disease reported symptoms on direct questioning; the high rate of sub-clinical/asymptomatic TB is concerning. There is an urgent need for more sensitive screening tools for TB in HIV-infected pregnant women.

LIST OF TABLES

Table 1: Synopsis of studies on symptom-based screening

Table 2: Demographic and clinical characteristics of women in the study

Table 3: TB point prevalence

Table 4: Sensitivity, Specificity, Negative Predictive Value, Positive Predictive Value, Negative Likelihood Ratio, and Positive Likelihood Ratio of the symptoms

Table 5: Associations with prevalent TB

NOMENCLATURE and DEFINITIONS

Accuracy is synonymous to validity and can be defined as "a test's ability to show which individuals have the disease and which do not". This is usually assessed by two estimates, namely Sensitivity and Specificity.

ANC: Antenatal Clinic

ARV: Antiretroviral therapy

AZT: Zidovudine

CD4: Cluster of Differentiation 4 = Surrogate of Immunity

CXR: Chest X-Ray

Hb: Haemoglobin

IPT: Isoniazid Preventive Therapy

IQR: Interquartile range

HIV: Human Immunodeficiency Virus

MGIT: Mycobacterium Growth Indicator Tube

NLR: Negative Likelihood Ratio

NPV: Negative Predictive Value, which is a percentage of patients with a negative test who do not have the disease.

PMTCT: Prevention of Mother to Child Transmission

PLR: Positive Likelihood Ratio

PPV: Positive Predictive Value, which is a percentage of patients with a positive test who actually have the disease.

Point Prevalent TB is defined as TB present in the cohort of women included in the study. It is synonymous to point prevalence. In this study, it includes both the TB diagnosed prior to enrolment in the study and previously undiagnosed TB confirmed on sputum microscopy or culture.

Sens: Sensitivity, which is defined as “the chance of a true positive test.

Spec: Specificity, which is defined as “the chance of a true negative test”.

TB: Tuberculosis

WHO: World Health Organization

WHO recommended 4 Symptom screen for TB: a symptom screen involving presence of any 1 of 4 symptoms of cough, fever, night sweats, or weight loss.

VCT: Voluntary Counselling and Testing

Table of Contents

DECLARATION **1**

DEDICATION **2**

ACKNOLEDGEMENTS.....**3**

ABSTRACT **4**

BACKGROUND.....4

METHODS..... 4

RESULTS.....4

DISCUSSION.....5

CONCLUSION.....5

LIST OF TABLES.....**7**

NOMENCLATURE AND DEFINITIONS.....7

CHAPTER ONE: INTRODUCTION.....9

1.1 BACKGROUND.....9

1.2 LITERATURE REVIEW.....11

1.3 STATEMENT OF PROBLEM.....21

1.4 JUSTIFICATION OF THE STUDY.....21

1.5 AIM AND OBJECTIVES.....21

CHAPTER TWO: METHODOLOGY.....24

2.1 PRIMARY DATA SOURCE.....24

2.2 STUDY DESIGN AND SETTING.....25

2.3 STUDY POPULATION.....26

2.4 STUDY SAMPLE.....27

2.5 DATA COLLECTION.....27

2.6 STUDY VARIABLES……..29

2.7 DATA PROCESSING……..29

2.8 STATISTICAL ANALYSIS……..28

2.9 ETHICAL CONSIDERATIONS……..29

CHAPTER THREE: **RESULTS**……32

3.1 PARTICIPANT'S DEMOGRAPHIC AND CLINICAL CHARACTERISTICS……34

3.2 PREVALANCE OF TUBERCULOSIS (TB)……..35

3.3 SENSITIVITY AND SPECIFICITY OF SYMPTOMS……35

3.4 ASSOCIATIONS WITH PREVALENT TB……36

CHAPTER FOUR: **DISCUSSION**……..37

CHAPTER FIVE: CONCLUSION AND RECOMMENDATIONS……..39

5.1 CONCLUSION…… 45

5.2 RECOMMENDATIONS……45

REFERENCES……..47

APPENDICES……55

CHAPTER ONE: INTRODUCTION

1.1 Background

Tuberculosis (TB) remains one of the leading non-obstetric causes of maternal mortality globally [1]. It is estimated that one-third of deaths attributable to TB occur in women of child-bearing age, mainly in resource-limited countries [1]. It was estimated that 700 000 women died from TB in 2008 compared to 342 900 who died from maternal causes in the same year [2]. TB/HIV co-infection is a growing problem in Sub-Saharan Africa [1] and women of childbearing age represent a special sub-group of vulnerability because of high HIV prevalence rates in this group [3] and higher rates of progression from TB infection to disease [4; 5; 6]. TB infection in women of reproductive age impacts not only on their own health, but also on the health of both their existing families, as well as their unborn children [7]. TB increases the chance of mother to child transmission of HIV [8].

Screening for TB by using a symptom based approach during pregnancy may present a diagnostic challenge because early symptoms of the infection are not peculiar to TB, and therefore may be attributed to symptoms of pregnancy itself [9]. It is important to detect and treat TB early in pregnant women to prevent

spread to other people and complications such as disseminated disease, as well as death. Early diagnosis would involve screening women for TB during their antenatal clinic visits. Antenatal clinic visits could therefore represent a very useful point at which to screen for TB, which may go undetected at other points in the health system.

The issue of using a symptom based screening approach is well documented [10,11,12,13,14,15,16,17,18,19] especially for use in resource-poor settings, where the use of chest radiographs and laboratory tests are not always possible and are not the most cost effective way to screen.

The South African National Health Department's guidelines recommend that all HIV-infected pregnant women be screened for TB [20]. Screening for TB is usually done by asking women about the presence of TB symptoms, which in pregnancy may present a diagnostic challenge. Some symptoms can be confused with symptoms of pregnancy itself as indicated above, or may be confounded by the condition of pregnancy (for example weight loss as a symptom of TB being confounded by weight gain typical during pregnancy). The use of symptom screening for active TB in HIV-infected women is only beginning to be evaluated

for its reliability [21; 7]. Screening for TB among pregnant women by the use of a limited number of questions during routine antenatal care was found to be a feasible alternative to expensive diagnostic investigations in studies carried out in Soweto [7; 21].

1.2 Literature review

TB screening and its evaluation

The WHO recommends screening of all HIV-infected people for active TB after an HIV diagnosis has been made [22]. However, recent global data suggest that implementation of screening for tuberculosis in HIV care settings is unacceptably low, often as a result of a lack of diagnostic resources [23].

A review looking at approaches to screen for TB in people infected with HIV highlighted the fact that the best method for screening in resource-limited settings is still a matter of considerable debate [24]. The use of symptom-based screening for Tuberculosis has been used in a variety of settings. Some of the studies which looked at the use of symptom-based screening for active tuberculosis are summarised in the table 1 below:

Table 1: Synopsis of Studies on Symptom-based Screening

Reference	Study population characteristics	Sample size	Results
Kim et al., 2011 [25]	People living with HIV/AIDS at 8 outpatients facilities in Cambodia, Thailand, & Vietnam.	1745	Sensitivity for cough in the past 4 weeks was 94%. 3-symptom combination (cough in the past 24 hours, difficulty in breathing, and night sweats for > 3 weeks was 85% sensitive and 80 percent specific.
Kruk et al., 2008 [26]	Children at 3 local clinics served by Tygerberg Children's Hospital, South Africa.	252	Negative Predictive Value of symptom-based screening (cough, fever, fatigue, weight loss) varied according to case definition used; 95.6% when all of the children treated for TB, 97.2% when only children with radiologic "certain tuberculosis' were included, and 100% if the case definition excluded those with asymptomatic uncomplicated hilar adenopathy.

Corbett et al., 2010 [27]	Randomly selected participants in a community-based TB-HIV prevalence survey, Harare, Zimbabwe.	1858 HIV+, 7121 HIV-	In HIV+ participants, cough of ≥ 2 weeks' duration, any symptom (current cough, haemoptysis, fever, night sweats, and subjective weight loss) had sensitivities of 48% and 81% respectively. In HIV- sensitivities were 45% and 71% respectively. Symptoms had a higher positive and a lower negative predictive value in HIV+ participants.
Day et al., 2006 [10]	Gold miners first attending the TB preventive therapy clinic, South Africa.	1093	Most sensitive symptom combination (59.1%) was any night sweats, new or worsening cough or reported weight loss, measured weight loss > 5% increased sensitivity to 90.9%.
Mohammed et al., 2004 [12]	HIV+ with WHO clinical stage 3 or 4 disease, referred for possible participation in TB-preventive therapy trial	129	Screening instrument of two or more of measured weight loss, cough, night sweats, or fever, had a sensitivity of 100% and specificity of 88.1%, and

	in 3 hospital-based HIV clinics, South Africa.		positive and negative predictive values of 44% and 100% respectively.
Den et al., 2006 [28].	Random cluster sample of adult's aged≥ 15, Cape Town, South Africa.	1170	Chest X-ray screening had the highest sensitivity 0f 97% and individual symptoms had low sensitivities, ranging from 10% for fever to 54% for cough of ≥ 2 weeks.
Kali et al., 2006 [21].	HIV-infected pregnant women, two PMTCT program clinics, Soweto, South Africa.	545	Symptoms most associated with TB were haemoptysis (OR 8.26), fever (OR 9.55), weight loss > 5kg (OR 5.2), productive cough (OR 6.8), chest pain (OR 4.9), and tiredness (OR 5.1).

The studies presented above highlight the usefulness of symptoms for identifying active TB. Of note is that they all included participants from different backgrounds. In practice they will therefore not be easily comparable in terms of the symptom or symptom combination sensitivity and specificity for diagnosing active TB in the group of interest in the current study. For example, the study by Mohammed [12] included patients with advanced HIV disease which may have a different symptom profile than those patients presenting at HIV clinics with relatively recent symptoms. All of the mentioned studies used different symptom combinations resulting in different sensitivities. Furthermore, different case definitions for TB were used, therefore making it difficult to conclude the optimum symptom combination to use with which to specific case definition for TB.

The study by Kali et al [21], which included the study participants similar to the participants in the current study, showed that haemoptysis, fever, weight loss, productive cough, chest pain and tiredness were positively associated with active TB.

A meta-analysis of observational studies by Getahun, et al. [19] found that the best performing screening rule was the presence of any one of the following:

- Current cough (any duration);
- Fever;
- Night sweats: and/or
- Weight loss.

The overall sensitivity of this rule was 78.9% and negative predictive value was 97.7%.[19] TB in pregnancy may prove difficult to diagnose because early symptoms of the infection, such as malaise and fatigue may be attributed to the condition of being pregnant itself, and may therefore not raise a suspicion of TB [29].

Since pregnancy may present a different clinical situation than what is normally expected for HIV/TB co-infection, it presents a diagnostic challenge. There is a need for further studies to evaluate the accuracy of symptom-based screening specifically in this sub-group. Lastly, there may be differences in the timing of presentation as well as the resources available to rule out TB between urban and rural settings. The study by Nachega et al. [30] investigating a different screening strategy (screening by tuberculin skin test) among HIV-infected pregnant women

in South Africa, which found TB prevalence of 11% among women in prevention of mother to child HIV transmission, was carried out in an urban setting (Soweto).

Although the above studies demonstrate the usefulness of symptom-based screening in a variety of settings among different groups, the testing of screening instruments among the group of interest in this study (HIV infected pregnant women) is rare in the available literature, with only the study by Kali et al. [21] looking at this particular group.

Women are vulnerable to tuberculosis for a number of reasons. Culture plays a major role in the life of women, particularly rural women. Because of gender-based roles imposed on women, such as fetching water and firewood and working in the fields, women may delay seeking help when sick. McCray [31] found that culture left rural women with no ''disposable time'' for them to utilise prenatal care.
Women in rural and/ or resource-poor settings may encounter specific barriers in accessing health care, such as availability constraints caused by long distances from the health centres [32] and affordability constraints [33]. Although health services are provided free of charge to pregnant women in South Africa, the cost of

accessing health care can be high, especially in rural areas [34]. This cost may include cost of transport to a health facility, cost of food during the visit, loss of income as a result of time spent in a health facility instead of earning a living and cost of arranging child minders. For these reasons women may postpone or seek help from outside of the formal health care sector. A study by White et al. [35], looking at health seeking behaviour among pregnant women in rural Haiti found that 25% of women reported not seeking help in the formal health sector and 32% of them reported delaying help seeking.

It is estimated that half of the world's population uses solid or biomass fuel such as wood, coal and paraffin for heating and cooking; and the resultant emissions and indoor air pollution are harmful to their health [36]. Rural and/ or resource-poor households are often dependent on use of solid fuel, mainly fire wood, which is a natural resource, as part of diversified[1] livelihood strategy [37]. It is women who usually do the cooking and are therefore directly affected by the indoor air

[1] Diversification is defined as the process by which households construct increasingly diverse livelihood portfolios, making use of increasingly diverse combinations of resources and assets [37].

pollution. Sumpter and Chandramohan [36] found strong evidence for an association of indoor air pollution and the risk of Tuberculosis.

Rural women or women from resource-poor settings are likely to be malnourished compared to their urban counterparts [38] and malnutrition is one of the identified risk factors for developing Tuberculosis [39]

Lastly, HIV infection is associated with an increased risk of contracting TB [40]. As the women in our study are HIV-infected, in addition to the other factors mentioned above at play, these women are at a particularly high risk of contracting TB.

1.3 Problem Statement

Symptom-based screening is not yet fully evaluated as a reliable tool to be used for screening for TB co-infection among HIV-infected pregnant women in South Africa

and current screening algorithms need to be tested for accuracy[2] (Sensitivity[3] and Specificity[4]) for use in this particular sub-group [41, 42]

1.4 Justification of the study

The study looked at a sample drawn from a rural or resource-poor area where the lack of resources indicate a particular need for a symptom based screening tool for this specific sub-group.

There is a need to combine PMTCT services with active case finding for TB in settings where resources are often limited, as antenatal care may be one of the few opportunities to screen for TB among HIV-infected pregnant women. Screening by symptoms would be more cost-effective and therefore accessible to more people in rural and / resource-poor settings, and would also be relevant at different levels

[2] Accuracy is synonymous to validity and can be defined as "a test's ability to show which individuals have the disease and which do not". This is usually assessed by two estimates, namely Sensitivity and Specificity.
[3] Specificity is defined as "the chance of a true negative test".
[4] Sensitivity is defined as "the chance of a true positive test" [43].

of care [24]. The reliability and validity of such a screening tool needs exploration for use among HIV-infected pregnant women in different settings.

1.5 Aim and Objectives

The aim of this study is firstly, to determine the prevalence of TB co-infection among HIV-infected pregnant women attending antenatal clinics in Matlosana in 2010-2011 and secondly, to determine the accuracy of recorded symptoms (WHO 4-symptom screen[5]) in predicting active TB among HIV-infected pregnant women attending those clinics

The Specific objectives are:

- To determine the prevalence of active TB in the study population
- To describe the symptoms reported by study participants
- To determine if associations exist between symptoms reported and the laboratory results (sputum microscopy and/or culture) among HIV positive pregnant women attending PMTCT at Matlosana in 2010-2011

[5] WHO recommended 4 -Symptom screen for TB: a symptom screen involving presence of any 1 of 4 symptoms of cough, fever, night sweats, or weight loss

- To describe the symptom(s) or symptom combinations that have high sensitivity and high negative predictive value for use in screening for TB.
- To determine the accuracy of the WHO recommended symptom screening algorithm in HIV-infected pregnant women for use in resource-limited setting.

CHAPTER TWO: METHODOLOGY

2.1 Primary Data Source

Data were collected during 2010-2011 at antenatal clinics in Matlosana, as part of an earlier study by the Perinatal HIV Research Unit, the aim of which was to assess the prevalence of smear and/or culture positive sputum in pregnant HIV-infected women in whom their symptoms at screening were also recorded (See Protocol-appendix 1).

1456 patients were enrolled using the methods described below. A questionnaire was used to collect the data (see Case Report Form appendix-2). Written or verbal[6] consent was obtained. The data was never analysed previously.

The original study was approved by the Human Research Ethics Committee (Medical) at the University of the Witwatersrand in 2010

[6] Verbal consent was accepted for the original study by the Human Research Ethics Committee (Medical) at the University of the Witwatersrand.

2.2 Study design and setting.

The study is a secondary quantitative data analysis of cross-sectional data collected for the original TB prevalence study by Perinatal HIV Research Unit (June 2010 to February 2011) as outlined above.

The City of Matlosana is a sub-district in Dr. Kenneth Kaunda district of the North West Province and is one of the four local municipalities in this district [44, 45]. The Municipality covers an area of 3.162 km^2. The total population was estimated to be 398 676 in 2011 (with 1.04% growth rate) [45] with 94% of the population in urban settlements and 6 % in rural settlements [46]. Although the majority of the area is considered urban, the level of development may be considered to be similar to a rural area. The area is divided into 4 towns[7], namely, Klerksdorp (46% of the population), Orkney (26%), Stillfontein (17%) and Hartebeesfontein (5%); and rural settlements (6%) [46]. The main economic activities in this are mining (45%), trade (21%) and agriculture (9%). [46].

[7] It is important to note that Orkney, Stillfontein and Hartebeesfontein are small towns that can be in fact considered rural. There is no commonly accepted definition of rural in South Africa.

Dr. Kenneth Kaunda and Bojanala districts (formerly, Southern and Bojanala regions respectively) have the highest HIV Antenatal prevalence rates in the province (31.1% and 30.4 % respectively, 2006 data), the provincial rate being 26.7% [47]

2.3 Study population

Adult (> 18 years) HIV-infected pregnant women, attending antenatal clinics, in a sub-district of Matlosana in 2010-2011.

Inclusion criteria:

1. At least 18 years of age.
2. Pregnant.
3. Verbal or written consent to participate.
4. HIV-infected – diagnosed by a two-rapid test algorithm or HIV ELISA at least a week prior to the enrolment visit. A record of such testing was required, in the form of either an entry in the clinic register or a record on the patient held clinic card or a copy of the HIV result with the patient's name on it.

Exclusion criteria

1. Women unable or unwilling to provide verbal informed consent
2. Prisoners or other institutionalised women (at the time of recruitment)
3. Active labour or obstetric or medical complication requiring immediate intervention.

2.4 Study sample

The study analysed 1456 records that were collected in the original Perinatal HIV Research Unit study. These records represent all women who qualified for inclusion and who were willing to participate at the site. Therefore, there was no sample size calculation. Records with missing data were excluded from the analysis.

2.5 Data collection

- Primary data was collected in the original Perinatal HIV Research Unit study (see protocol: appendix 1) in the following way: HIV-infected women attending

antenatal services who had been diagnosed with HIV at a previous visit (either in the PMTCT Programme or not) and who fulfilled the eligibility criteria were approached to provide written or verbal consent to participate in the study by a lay counselor involved in the study. The consent to participate was documented by the study nurse in the patient's clinic record and in the consent log kept at the clinic.

- Sputum was collected from the women after consent was given. If a sputum sample was not initially obtainable, a supervised induced sputum sample, using hypertonic saline, was obtained, paying attention to infection control measures (well-ventilated area outside the clinic building for sputum collection). For patients from whom sputum could still not be obtained, a specimen bottle was provided for an early morning specimen to be brought to the clinic the following day.
- Sputum smear microscopy and mycobacterium culture were performed on all specimens using an accredited laboratory.
- After obtaining the sputum specimens, a systematic TB symptom screening, based on the screening method currently proposed by the National

Department of Health (see appendix-1), was done by the study nurse. This was informed by the previous work done in Soweto but the focus was on major symptoms – cough and productive cough, night sweats, fever and weight loss or no weight gain [30; 21]

- Demographic data were also obtained (age, gestational age, TB contact, at least two instances of weight recorded in the last three months).
- Contact details were also recorded in the patient's clinic record to ensure tracing of patients with positive results.
- Blood for CD4 count was obtained if not done at the time of recruitment

All data relevant to the answering of the study questions were extracted from the original database.

2.6 Study variables

1. The outcome variable was a binary variable showing either active TB confirmed on sputum smear microscopy and/or culture (binary outcome) or no active TB.

2. The binary outcome variable was tested for association with the following:
    - Demographic data: age (continuous)
    - Clinical characteristics of TB cases:
        - Gestational age of pregnancy (continuous),
        - Weight at current visit (continuous),
        - Weight from previous antenatal clinic visit (continuous)
        - Weight change (continuous)
        - Most recent CD4 count (continuous),
        - TB symptoms and their duration

2.7 Data processing

Data were extracted from the original database using a data extraction sheet and captured into a Microsoft Excel spread sheet. Data was cleaned by removing sets with missing variables (symptom data was missing for one and sputum culture data was missing for 35 sets). Data was then coded and entered into STATA version 11.1, for analysis.

2.8 Statistical analysis

Descriptive analysis included the patient's median age in years, median gestational age in weeks and median weight in kilograms. The patients were further categorized according to the reported symptoms, their CD4 count, the use of AZT for PMTCT, current use of antiretroviral treatment, and their TB status.

The Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) and Positive and Negative Likelihood Ratios of each TB-related symptom were calculated with a 95% confidence interval. The performance of each symptom independently and in combination was assessed using the prevalence of TB confirmed cases in the study population as a reference or gold standard. Microscopy and mycobacterial culture, using the BACTEC MGIT 960 system was done on the sputum samples.

Logistic regression was carried out to find associations between patient characteristics and prevalent TB (previously undiagnosed culture and smear positive TB). For the purpose of this research report, multi-variate analysis was not included.

Specificity, Sensitivity, PPV, NPV, PLR and NLR were calculated using a 2 by 2 table below [48].

		Gold standard: sputum microscopy and/ or culture		
		S+	S-	Total
Clinical test: Symptom screen	T+	a = True positive	b = False positive	a + b
	T-	c = False negative	d = True negative	c + d
	Total	a + c	b + d	

Sensitivity = a/ (a + b)

Specificity = d/ (b+ d)

Positive Predictive Value = a/ (a+ b)

Negative Predictive Value = d/ (c+ d).

Positive Likelihood Ratio = Sensitivity / (1 –Specificity)

Negative Likelihood Ratio = (1 – sensitivity)/ specificity

2.9 Ethical consideration

Ethics clearance for this study was obtained from the Wits Human Research Ethics Committee (Clearance certificate M101117. See appendix-4).

Each patient's confidentiality was maintained during the course of the study. Unique study codes were used for each data point to ensure that no patient identifiers were extracted from the original database.

CHAPTER THREE: RESULTS

1456 HIV-infected pregnant women attending antenatal clinics were enrolled. Their characteristics are illustrated in table 2. The median age of the women was 27 years (Interquartile range ((IQR): 23; 32). The median gestational age was 24 weeks (IQR: 18; 28). The median CD4 count was 396 cells /mm^3 (IQR: 277-533). 60% of the women were receiving AZT for Prevention of Mother to Child Transmission. Only 2 women (0.1%) were receiving antiretroviral therapy for treatment of HIV.

A notable burden of undiagnosed TB (2.4%) was found in this study. The majority of these TB cases were asymptomatic, with only 11/38 women with newly confirmed TB having any symptoms.

Cough was reported by 120 (8%) women, 72 (5%) reported sputum production. Fever was reported by 53 (5%) women, night sweats by 52 (4%) women and weight loss by 73 (5%) women.

12 women who were already on TB treatment (0.8%) at enrollment were not included in the symptom sensitivity and specificity analysis. Cough, fever, weight-loss and night sweats, individually and in combination had sensitivity ranging from

2.7-27% and specificity ranging from 84-97%. These four symptoms form part of the WHO recommended 4-symptom TB screen. The sensitivity of these symptoms, and therefore the WHO recommended 4-symptom TB screen, found in this study is considerably low, perhaps due to the small number in our study. The positive predictive and negative predictive values for any symptoms of cough, fever, sweats, or weight loss were 4.2% and 98%, respectively (table 3). The median CD4 count among women with previously undiagnosed prevalent TB was 251 cells/mm^3 and 14 (37%) women with undiagnosed prevalent TB[8] had a recent household contact with TB disease.

In the logistic regression analysis (table 5), some important associations with active TB were found in this study (table 5). The odds of getting TB increased with the decrease in CD4 count ($P < 0.001$). Active TB was associated with cough ($p=0.003$) and night sweats ($p=0.02$). Household TB and the baby's father having TB had a statistically non-significant association with active TB ($p > 0.05$).

[8] Prevalent TB (synonymous to point prevalence) is defined as TB present in the cohort of women included in the study. It includes both the TB diagnosed prior to enrolment in the study and previously undiagnosed TB confirmed on sputum microscopy or culture.

Table 2: Demographic and Clinical Characteristics women in the study

Characteristic	Totals N (%)	Median (Range)
Maternal age, years (IQR)		27 (23-32)
Gestational age, weeks (IQR)		24 (18-28)
Weight at screening, kg		68 (60-80)
Ever had TB (yes)	114/1453 (8%)	
TB treatment at screening (yes)	12/1453 (1%)	
Anyone at home with TB	362/1455 (25%)	
Childs father with TB now	12/73 (0.16%)	
Mothers smokes	41/1455 (25%)	
Median Hb at screening		11.2 (10.1 - 12.4)
CD4 (most recent)		396 (272 - 533)
CD4 group count (most recent)		
≤ 200	185 (13)	
201-300	249 (17)	
301-400	294 (21)	
401-500	263 (18)	
> 500	436 (30)	
Antiretroviral management at screening		
AZT pMTCT	881/1455 (60%)	
Current ART	2/1455 (0.1%)	
No ART	572/1455 (39%)	
Prior ANC visit (yes)	1424/1455 (98%)	
Participants reporting:		
Cough > 1 day	120/1455 (8%)	
Cough > 2 weeks	62/1455 (4%)	
Sputum production	72/1455 (5%)	
Coughing of blood or blood-stained sputum	11/1455 (1%)	
Night sweats	52/1455 (4%)	
Weight loss (self-reported)	113/1342 (8%)	
Weight loss > 2kg (from prior ANC visit)	73/1455 (5%)	
Tiredness	53/1455 (3.6%)	
Swellings in the neck, armpits or elsewhere	43/1455 (35%)	
Chest pains, fast breathing, dyspnoea	36/1455 (2.5%)	
Fever	53/1455 (4%)	

Table 3: TB point prevalence

Diagnosed prevalent TB	12/1456 (0.8%)
Undiagnosed prevalent TB (culture positive)	35/1456 (2.4%)
Undiagnosed prevalent TB (smear positive & CXR confirmed)	1
Undiagnosed prevalent TB (smear positive, No CXR)	2
Total TB at screening)	49/1456 (3.3%)

Table 4: Sens, Spec, NPV, PPV, NLR, and PLR of the symptoms

Symptoms/ Symptoms combination	Participants with defined symptoms	Participants with defined symptoms without TB	TB cases with defined symptoms	Spec%	Sens%	NPV	PPV	NLR	PLR
Cough (C)	115	107	8	92	22	98	7.0	0.85	2.8
Fever (F)	52	51	1	96	2.7	97	1.9	1.0	0.74
Weight loss (W)	109	106	3	92	8.1	97	2.7	0.99	1.1
Night sweats (S)	50	46	4	97	11	98	08.0	0.92	3.3
CFSW	237	227	10	84	28	98	4.2	0.87	1.7

Table 5: 2 by 2 table for calculation of Sens, Spec, PPV, and NPV for CFSW.

		Gold standard: sputum microscopy and/ or culture		
		S+	S-	Total
Clinical test: Symptom screen	T+	a = True positive 10	b = False positive 227	a + b 237
	T-	c = False negative 25	d = True negative 1152	c + d
	Total	a + c 35	b + d 1379	

Below is few Calculations to show how the values were obtained using CFSW as an example. In reality the calculations are done by STATA software.

Sensitivity = 10/ 35 = 28%

Specificity = 1152/ 1374 = 84%

PPV = 10/ 237 = 4.2%

NPV = 1152/ 1177 = 98%

Table 6: Associations with point prevalent TB (undiagnosed at screening): logistic regression

	OR (95% CI)	P-Value
CD4		
<200	1	< 0.001
200-300	0.47 (0.21 - 1.1)	
301-400	0.11 (0.033 - 0.41)	
401-500	0.17 (0.057 - 0.53)	
>500	0.13 (0.047 - 0.36)	
Hb		
≤ 10 g/dL	1.1 (0.50 - 2.3)	0.8
> 10g/dL	1	
Previous TB		
No	1	0.3
Yes	0.32 (0.043 - 2.4)	
Household with TB		
No	1	0.1
Yes	1.7 (0.85 - 3.3)	
Baby's father with TB		
No	1	0.9
Yes	1.0 (0.25 - 4.5)	
Mother smokes		
No	1	0.4
Yes	2.0 (0.46 - 8.6)	
Cough		
No	1	0.003
Yes	3.3 (1.5 - 7.5)	
Night sweats		
No	1	0.02
Yes	3.6 (1.2 - 10)	
Weight loss		
No	1	0.9
Yes	1.1 (0.33 - 3.6)	
Fever		
No	1	0.8
Yes	0.74 (0.099 - 5.5)	

CHAPTER FOUR: DISCUSSION

This study found pulmonary TB prevalence of more than three percent, which is moderately high as compared to the prevalence found in HIV negative patients from a high TB burden community [14]. 2.4% of the cases of TB were undiagnosed prior to the study. A previous study done in Soweto also showed a high burden of TB among HIV-infected pregnant women attending voluntary counselling and testing (VCT) sessions for HIV [21]. The noteworthy prevalence of undiagnosed TB in this cohort is in keeping with generally high levels of undiagnosed TB reported among HIV-infected patients. Bassett, et al., found that nearly 20% of patients starting ART in Durban had undiagnosed, culture positive TB [49]. Active TB is strongly associated with increased mortality risk [50] and undiagnosed TB is associated with the risk of transmission to the unborn baby and to other patients in crowded clinic settings [51], which is a common reality in South Africa and these patients remain reservoirs of TB in the community.

Women have specific additional factors which predispose them to contracting HIV and developing TB. The factors which make women vulnerable to HIV and TB occur

at individual, societal, health systems and political levels. As such, multidisciplinary, broad-based strategies, addressing social determinants of health would need to be used in order to address these factors. Lönnroth et al. [58], have highlighted the importance of addressing the underling risk factors of TB as well as social determinants in the current TB strategies in order to reach long-term control targets. They suggest the framework below (Figure 1):

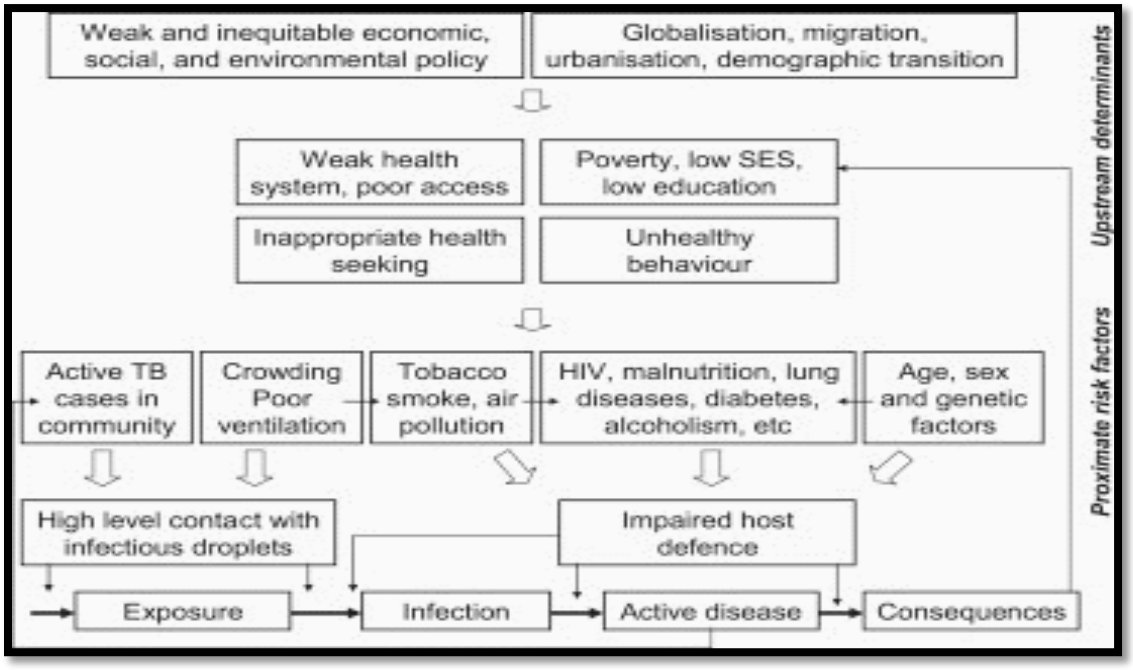


Figure 1: Framework for proximate risk factors and upstream determinants of TB [58].

The high level of TB in HIV-infected patients re-emphasizes the need for an accurate, cheap and easy to use screening tool for use during antenatal visits. Hence, there was a need to determine the specificity and sensitivity of the symptom-based screening for early TB in women attending antenatal care in order to treat those with active TB and offer Isoniazid Preventive Therapy to those with no TB [52]. In resource-poor settings it is not always possible to use the diagnostic tools such as microscopy and culture to rule out tuberculosis. Symptom-based screening has been shown to offer an alternative to high- technology tools in screening for tuberculosis [53] and the new joint guidelines on Isoniazid and intensified case-finding from WHO state that screening for tuberculosis by using only a symptom-based screening algorithm is sufficient to start Isoniazid Preventive Therapy (IPT) for people living with HIV [54].

Tuberculin Skin Test has been used in resource-poor settings previously to screen patients for active TB. Those who were found to have a positive reaction were then investigated further for active TB [30). In our setting where BCG is widely used, there might be issues of false positive results.

The main aim of this study was to determine the accuracy of reported symptoms in predicting TB among HIV-infected pregnant women attending antenatal clinics in a resource-poor settings, using the prevalence of TB confirmed cases in the study population as a reference or gold standard. The study by Kali, et al. [21], showed that haemoptysis and fever were the symptoms most associated with TB in HIV-infected women. In this study, the majority of women with confirmed TB reported no symptoms suggestive of TB. The high level of subclinical TB in this population made it difficult to determine whether a relationship existed between TB symptoms and confirmed TB. The sensitivity of the symptoms was too low to be useful in diagnosing TB in this population. Thus the 4-symptom screen recommended by the World Health Organization, was only useful in *ruling out* TB (as seen by the high negative predictive value), but performed poorly in diagnosing TB, even in participants who had smear-positive TB (as seen by a poor sensitivity). The reality in practice is that relying only on a symptom screen will miss a large number of patients who need treatment.

The symptom-based screening will continue to be of value in stratification of patients in terms of their likelihood of not having TB, such that in those without any symptoms, which would constitute a negative screen test, the likelihood of having TB would be low and that they could be started on IPT. The negative predictive value for cough, fever, weight loss and night sweat and all the four symptoms combined ranged from 97% to 98%.

The symptom screen however would have limitations in those who are at an increased risk of developing TB, such as HIV-infected patients; and in those where the symptoms of TB could be masked by other conditions, such as pregnancy, in which case further investigations including sputum microscopy and/or culture would still be required. The high level of asymptomatic TB in this study highlights this limitation. A meta-analysis of intensified case finding for HIV-associated TB found that microbiological examination of sputum from all HIV-infected persons, without prior selection by symptoms screening yields an additional 4 cases per 100 individuals screened, compared to when the symptoms were used to trigger microbiological examination [55].

In resource poor settings, symptom-based screening should be the starting point. The utility of the 4 symptom screen recommended by World Health Organization has been proven in other studies, including the meta-analysis by Getahun et al, [19] and this study reaffirms its high negative predictive value in HIV-infected pregnant women. HIV-infected pregnant women who are categorized by the 4 symptom screen as less likely to have tuberculosis can be started on Isoniazid Preventive Therapy. The health care providers should however bear in mind that not all women with active tuberculosis would have any symptoms and that the screen needs to be repeated on subsequent visits. Close monitoring of the women who are HIV-infected is required and if in doubt, sputum should be taken for microscopy, culture and / or Xpert MTB/RIF[9] assay, if this test is available.

Although found not to be statistically significant in the current study, household TB and the father of the baby having TB, are associations of public health importance in the context of South Africa. Overcrowding is not uncommon in South Africa.

[9] Xpert MTB/RIF assay is a real-time PCR assay for *Mycobacterium tuberculosis* that simultaneously detects rifampicin resistance (Cepheid, Sunnyvale CA, USA) [59].

Having a household TB contact would increase the chance of HIV-infected pregnant woman contacting the infection as close social interaction and overcrowding may play a role in the transmission [56]. Mining is one of the major economic activities in Matlosana Sub-district [46]. TB is epidemic among workers in South African gold mines [57]. Some of the men who are fathers of the babies and employed in the gold mining sector may be exposed to TB, and in turn expose their partners to it.

There are some limitations in this study inherent to the design of the primary study. Firstly, this study was only limited to one South African setting and therefore the results would not be generalizable to all HIV-infected pregnant women in resource-poor settings; however one could expect similar results in other contexts.

Secondly, the sample size was predetermined by the primary study and therefore power calculation for this study was not done prospectively as the study was secondary data analysis. However the power calculation could have been done retrospectively. The number of women included in the study proved to be small. Only a small number of women who had TB reported symptoms. The few reported

symptoms were not sufficient to allow determination of the accuracy of different symptom combinations in addition to the WHO 4-symptom screen.

Thirdly, only one sputum sample was collected. This would have an impact on the chance of finding acid-fast bacilli on microscopy and may also have an impact on the culture yield. Multiple and especially early morning specimens would have been ideal.

Lastly, there was a chance of bias in our study. This includes selection bias and recall bias. In terms of the selection bias, only women who attended the antenatal clinic were included in the study. These women may be different to the women in the general population. Selection bias may arise from the fact that women who have more advanced disease may recall the presence of symptoms better compared to those who have mild disease or those who are at an early stage of the disease. This might influence the accuracy of symptom-based screening as the tool is dependent on the participant's recollection of their disease experience.

One of the lessons learned from this study is that all women who are HIV-infected and therefore at a significant risk of having TB, will need to have their sputa taken

for microscopy and culture, in addition to the symptom screen. This will ensure that those who are not having an active disease receive the necessary isoniazid prophylaxis to prevent them from getting an active disease and that those with an underlying but subclinical TB will not be missed and given the necessary treatment.

This study is one of the few studies which looked at the accuracy of symptoms-based screening for TB in HIV-infected pregnant women.

CHAPTER FIVE: CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

There was a high prevalence of asymptomatic TB in the group of women enrolled in the study. Symptom-based screening had low sensitivity in HIV-infected pregnant women attending antenatal clinics in Matlosana. This means that the symptom screen could not accurately identify all women who had active tuberculosis as diagnosed by microscopy and/or culture. Negative predictive value was however high which means the 4 symptom screen could be used to identify women who are less likely to have active tuberculosis and therefore eligible for Isoniazid preventive therapy.

5.2 RECOMMENDATIONS

The following are recommended, which cut across the individual, health system, and policy levels:

1. All HIV-infected women should have their sputa taken for exclusion of TB in addition to the symptom screen as part of PMTCT. A new diagnostic algorithm would be needed to take into account the use of Xpert MTB/RIF

test for diagnosis of TB and Multidrug resistance. A study done in South Africa and other low income countries to evaluate the feasibility, diagnostic accuracy and effectiveness of decentralized use of Xpert MTB/RIF test for TB diagnosis and multidrug resistance found that the test can effectively be used in low-resource settings to simplify patient's access to early and accurate diagnosis, thereby potentially decreasing morbidity associated with diagnostic delay in the case of microscopy and culture [59].

2. Women who are found to have a negative symptom screen may be started on IPT. Even in these women, sputa should be considered if in doubt and the screen should be repeated on each subsequent visit.
3. Further research looking at more accurate diagnostic test for TB in resource-poor settings is essential.

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Appendices

1. Martinson N (2010). Screening for active tuberculosis during mother to child prevention at antenatal clinics, South Africa. Study Protocol, Version 0.1 January (not published).
2. CRF Active TB-MTCT (DEM-1).
3. Ethics approval certificate
4. Permission letter for using data

SCREENING FOR ACTIVE TUBERCULOSIS DURING MOTHER TO CHILD PREVENTION AT ANTENATAL CLINICS, SOUTH AFRICA (2)

Study Team

Dr. Neil Martinson, Perinatal HIV Research Unit, the University of the Witwatersrand, South Africa;
and the Johns Hopkins University Center for TB Research, Baltimore, USA

Ms Modiehi Rakgokong
Perinatal HIV Research Unit

Dr E Variava, Tshepong Hospital and University of the Witwatersrand, Johannesburg

Dr. Richard Chaisson, the Johns Hopkins University Center for TB Research, Baltimore, USA

Introduction

HIV and tuberculosis (TB) have emerged as a leading infectious cause of death among women of reproductive age worldwide (6-13). Current approaches to TB control are failing in areas with a high prevalence of HIV (2, 3). Active case finding in settings with a high prevalence of HIV could be necessary to strengthen TB control programs. Research has shown that tuberculosis is a significant cause of infant and maternal morbidity and mortality. Co-infection with TB and HIV increases vertical transmission of HIV (9, 11).

Effective strategies to control TB include early identification and treatment of active cases of TB, providing prophylaxis to patients with latent TB infection, and infection control to reduce transmission of TB. In South Africa there is a high prevalence of undiagnosed, active TB among HIV-infected persons; therefore it is likely that targeting HIV-infected adults would strengthen TB control programs. Settings with a known higher prevalence of HIV include hospitals, clinics, HIV testing and counseling centers, HIV clinics, TB Clinics, STI clinics and prisons (1, 4, 5). Women presenting to antenatal clinics are also at a higher risk for HIV.

Perinatal transmission of TB to a neonate may occur through intrauterine, intra-partum or postpartum transmission. Intrauterine transmission of TB occurs via hematogenous spread through the umbilical vein or via inhalation and ingestion of TB contaminated amniotic fluid. Intra-partum transmission of TB occurs through inhalation or ingestion of amniotic fluid or genital secretions. Postpartum transmission of TB occurs primarily through inhalation or ingestion of respiratory droplets from the mother or through infected breast milk. Infants with perinatal TB have high mortality – up to 38% (9). Perinatal TB is also associated with an increased risk of HIV transmission from mothers with HIV/TB co-infection (9). The prevalence of TB in pregnancy at King Edward VIII Hospital in Durban, South Africa in the late 1990s was 775/100,000 among HIV-infected women (12). Among HIV-infected women at an antenatal clinic at Chris Hani Baragwanath Hospital in 2001, about half were TB skin positive, and among these, 11% had active TB (10).

Tuberculosis is a significant cause of maternal mortality. In a study of over 50,000 deliveries in Durban, South Africa, the mortality rate among those with tuberculosis and HIV co-infection was 121.7/100,000 (8). Tuberculosis was the third leading cause of maternal mortality after sepsis and hypertensive disorders of pregnancy (8).

Tuberculosis is also a significant cause of infant morbidity and mortality. In a small prospective study of 82 HIV/TB co-infected women and 25 HIV-uninfected and TB-infected women at King Edward VIII Hospital in Durban, South Africa, the perinatal mortality among neonates born to

HIV/TB co-infected women was 85.4/1,000 (13). The rate of vertical-transmission of TB was 16%, with no difference between HIV-infected and HIV-uninfected women. 66% of neonates born to women with TB had intrauterine growth retardation (13). 49% of neonates born to women with TB had low birth weights (13). Infants born to HIV/TB co-infected women at a large, urban, public teaching hospital in Pune, India were found to have a 3-fold increased mortality rate compared to infants born to HIV-infected women without TB (6).

Vertical transmission of HIV also appears to be impacted by co-infection of the mother with tuberculosis. In a study of 42 women in Durban, South Africa with HIV/TB co-infection, the intrauterine transmission rate of HIV was 19%, compared to the 5-10% observed among HIV-infected women in resource-limited settings (11).

Different approaches have been used to screen for TB including: symptom screening, TB skin testing, sputum smear microscopy, mycobacterial culture and chest x-ray. Some investigators have screened only HIV-infected women for TB during the peripartum period, while others have screened all women for TB during the peripartum period. In Soweto, the prevention of mother to child transmission program tests about 30 000 women per annum of whom approximately 30% are found to be HIV-infected of whom almost all receive an intervention to prevent MTCT of HIV. In 2009, our group completed a study of the prevalence of TB in HIV-infected and uninfected pregnant women in six of the 13 antenatal clinics in Soweto. In that study we showed that in HIV-infected women the prevalence of previously undiagnosed pulmonary TB was 696/100,000 and (10 cases), and in HIV-uninfected pregnant women (5 cases) 200 per 100,000 . The Soweto prevention of mother-to-child transmission of HIV (PMTCT) program is offered in 13 community clinics and a hospital-based antenatal clinic in Soweto. The PMTCT program tests approximately 30,000 pregnant women per year, of whom about 30% are HIV-infected (7).

The feasibility of active case finding for tuberculosis has been studied in two community clinics in Soweto where the PMTCT program is offered (7). Women found to be HIV-infected were then screened for active symptoms of TB during their post-counseling session, and if their symptom screen was positive, they were tested for TB with sputum smear and mycobacterial culture. The prevalence of active TB was 2%, none of whom were sputum smear positive (7). The acceptance rate for TB screening during post-test counseling was low (66%). The authors hypothesized that the informed consent procedure and need for additional phlebotomy may have decreased acceptance rates. They also conjectured that having just learned they had HIV, these women were reluctant to be tested for another serious disease (7). In our prevalence study in Soweto, we therefore used verbal consent at the pre-test HIV counseling session and uptake to that study was close to 100% of the women approached.

However, concern has recently been expressed about "asymptomatic" or "sub-clinical" TB in HIV-infected adults. In a study from Ethiopia by Shah, 15% of HIV-infected adults diagnosed with TB were found to be asymptomatic. Our previous study used the presence of symptoms to identify women who then had a smear and mycobacterial culture performed on a sputum specimen. However, asymptomatic pregnant women were not included. In the proposed study we will assess the prevalence of pulmonary TB in pregnant women - irrespective of whether or not they have symptoms suggestive of TB.

Objectives

Primary objectives

- To assess the prevalence of smear and/or culture positive sputum in pregnant HIV-infected women stratified by reported symptoms.

Methodology

Sites: Antenatal clinics in Matlosana

Population: HIV-infected pregnant women attending antenatal PMTCT services.

Eligibility:

Inclusion Criteria:

1. At least 18 years of age.
2. Pregnant
3. HIV-infected - diagnosed by a two-rapid test algorithm or HIV ELISA at least a week prior to the enrollment visit. Some form of documentation will be required – either an entry in the clinic register or a record on the patient held clinic card or a copy of the HIV result with the patient's name on it.
4. Verbal or written consent to participate.

Exclusion Criteria:

1. Women unable or unwilling to provide verbal informed consent.
2. Prisoners or other institutionalized women (at the time of recruitment).
3. Active labour or obstetric or medical complication requiring immediate intervention.
4. Taking HAART at the time of enrollment

Study Procedures:

HIV-infected women attending antenatal services who have been diagnosed with HIV at a previous visit (either in the PMTCT program or not) and fulfilling other eligibility criteria will be approached to provide written or verbal verbal consent by the lay counselor involved in the study to participate in this study. Consent to participate will be documented by the lay counselor in a source document. No signature will be required or obtained from the participant.

Sputum Specimen: Once ~~verbal~~ consent has been obtained and documented, a sputum specimen will be obtained from the pregnant women. If a sputum sample is unable to be obtained, a supervised induced sputum sample will be obtained using nebulised hypertonic saline. For infection control purposes, nebulization procedures will be performed in a well ventilated area, such as outside of the clinic building. If no specimen is obtained, a specimen bottle will be provided with a request for an early morning specimen to be brought to the clinic the following day. Sputum smear microscopy and mycobacterial culture will be performed on all specimens from symptomatic women using an accredited laboratory.

If a woman is identified as having active pulmonary TB, she will be contacted and referred to the nearest TB treatment facility in her area for TB treatment. Drug susceptibility testing for isoniazid and rifampin will be performed if the culture specimen is suitable.

Symptom screening: At the visit when the sputum specimen is obtained, after obtaining the sputum specimen, a systematic TB symptom screen will be administered based on the one currently proposed by the National Department of Health. Symptom screening for active pulmonary TB will be performed by a lay counselor. This will be informed by our previous work in Soweto but will focus on the major symptoms – Cough and productive cough, night sweats and weight loss or no weight gain will feature prominently.

Investigations: The participant's CD4 count will be recorded but if not done at the time of recruitment, a blood specimen will be taken at that visit and the result provided to the woman and recorded on her antenatal record within two weeks of it being taken. If CD4 count is less than 350 cells the pregnant woman will be immediately referred for initiation of highly active antiretroviral therapy (HAART). Similarly if the CD4 count is above 350 and not already taking azothiaprine (AZT), the woman will be referred for AZT initiation. This study will not provide antiretrovirals for pregnant women.

Demographic Details: Women's age, gestational age, most recent known contact with a case of

TB, prior episodes of TB, month of first diagnosis of HIV and at least two documented weights in the past three months will be will be recorded for analytical purposes. As will the clinic where she was enrolled. In addition, contact details: contact cell phone number and address will be recorded in the source document to ensure that if a specimen is found to be positive, the woman can be re-contacted and referred for TB treatment. Contact details will not be collected for analytical purposes.

Referral: Women diagnosed with active TB will be contacted and referred to their most convenient TB Clinic for TB treatment after being notified. We will not provide treatment for TB as part of this study. We will follow the women with active TB to verify that they follow up in TB Clinic. If necessary, the study coordinator will make home visits to make sure that the women receive their test results and to encourage them to follow up in TB Clinic.

Sample size estimation: The prevalence of HIV in the antenatal clinics in Matlosana is approximately 33%, resulting in 2000 HIV-infected pregnant women being diagnosed with HIV annually in the PMTCT programme. In our previous symptom-based study, we found that six percent [600 cases per 100 000] of pregnant, HIV-infected women had active TB. From prior reports in non-pregnant adults, we assume that this figure could be elevated by 10% to 660 cases per 100 000 population in the Matlosana district. Moreover, we expect the TB prevalence may be even higher as a proportion of women may be asymptomatic at screening. For the purposes of this study we assume that a further 15% of cases were asymptomatic or sub-clinical. We therefore estimate that 7.6% of HIV-infected pregnant women in the Matlosana district will have active pulmonary TB. We will recruit 1500 HIV-infected pregnant women and estimate that 114 will have active TB of whom 15 will be asymptomatic. We will report the prevalence of active pulmonary TB with 95% confidence intervals in pregnant women, stratified by whether or not they had symptoms suggestive of TB.

Ethical issues

We will be obtaining written or if someone does not want to sign consent but syill wants to be in the study verbal consent will be accepted from pregnant women for participation in the study. We feel it is appropriate to do so because our intervention is not invasive. Moreover, we the questions we will ask of the women are not intrusive but relate to TB and will be asked in a private room. ~~A dated record of obtaining verbal consent will be made in the source document by the lay counselor who discussed the study with the participant.~~ In response to concerns of the local IRB, a consent log will be maintained at each site of recruitment.

Timeline

We anticipate Ethics approval will be obtained for this study by end January 2010. Site

preparation and study nurse recruitment will also take place in January 2010. First enrollment of pregnant women will be in February 2010. We will recruit approximately 150 HIV-infected pregnant women each month for 10 months. Results will be available end November 2010. Meetings will be held on site with National TB Control Personnel in March, June and September 2010.

Budget

This study is funded by a grant from the National Department of Health TB Control Programme

LABORATORY	Number	Cost/item	ZAR
Auramine smear	1500	75.1	R112,650.00
MGIT Culture	1500	104.85	R157,275.00
ZN stain for mycobacterial culture positive	25	27	R675.00
Speciation of mycobacterial culture pos	25	250	R6,250.00
			R276,850.00
SALARY			
Study Nurse	10	14500	R145,000.00
SUPPLIES			
Stationary	1	8012	R8,012.00
Ethics submission	1	1000	R1,000.00
Transport	10	2200	R22,000.00
telephony	10	400	R4,000.00
translations	3	1000	R3,000.00
			R38,012.00
SUBTOTAL			R459,862.00
Wits Health Consortium Indirect (8%)			R36,788.96
TOTAL			**R496,650.96**

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Mohlamme J Mathabathe

CLEARANCE CERTIFICATE	M101117
PROJECT	The Accuracy of Systoms-Based Screening for Tuberculosis in HIV-Infected Pregnant Women Attending Antenatal Clinics in Matlosna in 2010-2011
INVESTIGATORS	Dr Mohlamme J Mathabathe.
DEPARTMENT	Schoo of Public Health
DATE CONSIDERED	28/10/2011
M1011170DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 28/10/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Lilo du Toit

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...