Integration of Tuberculosis Prevention Into Antenatal Care Clinics in Matlosana, South Africa from November 2017 through July 2018

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# TABLE OF CONTENTS

**ACKNOWLEDGMENTS** ........................................................................................................ ii

**ACRONYMS** .................................................................................................................. ii

**EXECUTIVE SUMMARY** .............................................................................................. 1

**INTRODUCTION** ............................................................................................................. 4

**METHODOLOGY** .............................................................................................................. 6

- Objectives ......................................................................................................................... 6
- Study design ...................................................................................................................... 6
- Description of intervention ............................................................................................... 6
- Data collection methods ................................................................................................... 8
- Ethical review .................................................................................................................... 8
- Data analysis ..................................................................................................................... 8

**KEY FINDINGS** ............................................................................................................ 9

- Characteristics of the participants ................................................................................... 9
- Treatment and prevention of TB among pwlhiv ............................................................... 12

**DISCUSSION** ................................................................................................................. 13

- Limitations ....................................................................................................................... 14

**CONCLUSION AND RECOMMENDATIONS** ................................................................. 16

- Conclusions ..................................................................................................................... 16
- Recommendations .......................................................................................................... 16

**REFERENCES** .................................................................................................................. 17
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ACRONYMS

ANC       Antenatal care
ART       Antiretroviral therapy
ATT       Anti-tuberculous therapy
cART      Combined antiretroviral therapy
HIV       Human immunodeficiency virus
IPT       Isoniazid preventive therapy
PEPFAR    United States President’s Emergency Plan for AIDS Relief
PLHIV     People living with HIV
PMTCT     Prevention of mother-to-child transmission (HIV)
PWLHIV    Pregnant women living with HIV
TB        Tuberculosis
TPT       Tuberculosis preventive therapy
TST       Tuberculin skin testing
USAID     United States Agency for International Development
WHO       World Health Organization
EXECUTIVE SUMMARY

In 2015, the World Health Organization (WHO) estimated there were 10.4 million new tuberculosis (TB) cases worldwide affecting 3.5 million women and at least 1 million children (WHO 2018). TB remains a leading cause of death among women of childbearing age (20–49 years), killing 480,000 women in 2014 (WHO 2015). While the epidemiology of TB in pregnancy is unknown, estimates suggest that at least 216,500 TB cases occurred in pregnant women in 2010 (Sugarman et al. 2014). In sub-Saharan Africa, where women of childbearing age are disproportionately affected by HIV and TB, the WHO estimates HIV-positive pregnant women are 10 times more likely to develop TB disease than HIV-negative pregnant women (WHO 2015).

The institutional maternal mortality rate in South Africa peaked in 2009 (~189 maternal deaths/100,000 live births) and has steadily decreased since that time (134 maternal deaths/100,000 live births in 2016) (Moodley, Fawcus, and Pattinson 2018). This decline in mortality is largely attributed to a decrease in maternal deaths due to non-pregnancy-related infections that predominantly occur in HIV-infected women (>95%) and are due to tuberculosis, pneumonia, meningitis, and malaria. The proportion of these deaths attributable to tuberculosis is unknown. Studies have shown, however, substantial TB disease among pregnant women living with HIV in South Africa with high rates of maternal and infant mortality (Gounder et al. 2011, Salazar-Austin et al. 2017). In 2017, TB incidence in South Africa was 567 per 100,000 population. Sixty percent of these cases had TB/HIV co-infection and nearly 25 percent died.

In Matlosana, the incidence of TB disease remains high (772/100,000 population) (Massyn et al. 2014). In sub-Saharan Africa, TB is driven by the HIV epidemic, which women of child-bearing age bear the brunt of. In Matlosana, nearly 30 percent of pregnant women are HIV-positive (Massyn et al. 2014). Currently, diagnosis of active TB disease among pregnant women in resource-limited settings relies on the presence of clinical symptoms, which often overlap with or are masked by the symptoms of pregnancy, resulting in low sensitivity of the WHO-recommended screening tool among HIV-positive pregnant women (Gounder et al. 2011, Getahun et al. 2011, Sheriff et al. 2010, Hoffmann et al. 2013). In our recently completed cluster randomized study in Matlosana, clinics performing universal screening of HIV-infected pregnant women using sputum uncovered 10 times more TB than clinics following the WHO-recommended symptom screening (Martinson et al. 2017).

Early identification of maternal TB disease is important given the serious health consequences for both the mother and infant, particularly in the context of maternal HIV co-infection WHO 2015, Salazar-Austin et al. 2017, Mathad and Gupta 2012). Even with appropriate antiretroviral therapy (ART) and TB treatment, maternal and infant outcomes remain poor; both suffer higher mortality while infants are also burdened with higher rates of prematurity, low birth weight, and infant mortality (WHO 2015, Salazar-Austin et al. 2017, Mathad and Gupta 2012). Maternal TB disease may also increase mother to child transmission of HIV (Salazar-Austin et al. 2017, Gupta et al. 2011, Pillay et al. 2004).
Traditionally, a TB symptom screen is performed by a community health worker upon the patient’s arrival to clinic. Targeted TB symptom screening among high risk patients, including pregnant women, is not consistently documented. While the South African TB guidelines have recommended isoniazid preventive therapy (IPT) for all people living with HIV (PLHIV), including during pregnancy, for more than 10 years, implementation of these guidelines remains limited. Recent unpublished work from Matlosana suggests that only 1–2 percent of eligible HIV-positive individuals are initiated on IPT. Improving prevention and early detection of TB among pregnant women remains critical for both mothers and their babies.

Integration of HIV diagnosis and treatment into ANC services has greatly improved maternal health and infant health outcomes including reducing perinatal HIV transmission, improving postnatal maternal ART outcomes, and ensuring a high proportion of infants are immunized (Chasela et al. 2010, Shapiro et al. 2010, Coovadia et al. 2012, Abrams and Myer 2013, Barron et al. 2013, Myer et al. 2016, Myer et al. 2017). Learning from this success, Johns Hopkins University and the Perinatal HIV Research Unit in collaboration with local partners—under Project SOAR, funded by the United States Agency for International Development—aimed to implement and assess an integrated approach to TB screening, evaluation/diagnosis, and preventive treatment among pregnant women applicable to high-burden, low-resource settings. Because the sensitivity of symptom screening in HIV-positive pregnant women is so poor, the study also implemented enhanced TB screening for pregnant women living with HIV (PWLHIV). This enhanced screening included both a WHO TB symptom screen and a sputum sample for mycobacterial culture. In contrast, TB evaluation for symptomatic women included a sputum sample for Xpert MTB/RIF Ultra®, a PCR-based test with results in 24-48 hours for both the presence of *Mycobacterium tuberculosis* and rifampin resistance.

**METHODOLOGY**

This was a proof of concept model for the integration of TB and antenatal care (ANC) services in six ANC clinics in a real-world, high TB-incidence setting. It was therefore subject to real-world challenges including poor clinic staffing, political unrest, and commodity stockouts. TB evaluation and IPT were integrated into ANC services at the start of the study. Study duration was 10 months. Patients received care as per South African guidelines. No additional visits were required as a part of the research study. Nurse and mentor mother training was provided in all six clinics and built-in decision support tools for TB evaluation and IPT during pregnancy were added to all patient files. TB treatment remained separate; however, ANC and HIV treatment services were provided in the TB clinic for all pregnant women diagnosed with TB disease to minimize patient waiting. A poster campaign and patient education sessions were conducted in order to increase knowledge and demand for IPT among HIV-positive pregnant women visiting the clinics. Data were collected retrospectively from patient charts.
KEY FINDINGS

TB evaluation and prevention services can be integrated into ANC services in decentralized South African clinics.

ANC staff conducted a symptom screen in over 80 percent of ANC clients during the study period.

TB evaluation with sputum culture for asymptomatic PWLHIV is possible but full implementation of the protocol was slow to initiate.

The majority (80 percent) of asymptomatic pregnant women approached for a sputum sample were able to produce sputum. While only 30 percent of asymptomatic PWLHIV received a sputum culture, the number of cultures sent for screening increased three-fold from the first to the third and final study period.

CONCLUSION AND RECOMMENDATIONS

TB evaluation and preventive services can be integrated into ANC services in decentralized South African clinics. Lessons learned include the need for a larger lead time for full program integration as the team slowly incorporates all aspects of the integration into their daily routines. Recommendations include:

1. Integration of TB evaluation and prevention into ANC services is possible, but will require ongoing reinforcement of training over time.
2. More data are needed to show the benefit of sputum collection; this may improve nurse motivation and participation.
3. Nurses and other staff beyond the TB program should be trained and feel comfortable with sputum collection methods and its documentation. This cannot remain the sole responsibility of the TB program.
4. Task shifting of sputum collection and documentation to community health workers may improve implementation.
5. TB screening, including sputum collection, should become routine in ANC programs. Other facility-level challenges need to be considered, including patient flow upon return to clinic with sputum, sputum container storage, and sputum log books to enhance success of TB integration into ANC services.
6. Advocacy around TB prevention for pregnant women needs to be improved to increase demand for life-saving therapies including TB preventive therapy.
7. In the future, integration of IPT into postnatal services may serve as a safer way to integrate TB preventive therapy into pregnancy and postpartum care for PLHIV. Though the study primarily evaluated TB integration into ANC services, similar barriers would be expected for TB integration into postnatal care services.
INTRODUCTION

In 2015, the World Health Organization (WHO) estimated there were 10.4 million new tuberculosis (TB) cases worldwide affecting 3.5 million women and at least 1 million children (WHO 2018). TB remains a leading cause of death among women of childbearing age (20–49 years), killing 480,000 women in 2014 (WHO 2015). While the epidemiology of TB in pregnancy is unknown, estimates suggest that at least 216,500 TB cases occurred in pregnant women in 2010 (Sugarman et al. 2014). In sub-Saharan Africa, where women of childbearing age are disproportionately affected by HIV and TB, the WHO estimates HIV-positive pregnant women are 10 times more likely to develop TB disease than HIV-negative pregnant women WHO 2015).

The institutional maternal mortality rate in South Africa peaked in 2009 (~189 maternal deaths/100,000 live births) and has steadily decreased since that time (134 maternal deaths/100,000 live births in 2016) (Moodley, Fawcus and Pattinson 2018). This decline in mortality is largely attributed to a decrease in maternal deaths due to non-pregnancy-related infections that predominantly occur in HIV-infected women (>95 percent) and are due to tuberculosis, pneumonia, meningitis, and malaria. The proportion of these deaths attributable to tuberculosis is unknown. Studies have shown, however, substantial TB disease among pregnant women living with HIV in South Africa, with high rates of maternal and infant mortality (Gounder et al. 2011, Salazar-Austin et al. 2017). In 2017, TB incidence in South Africa was 567 per 100,000 population. Sixty percent of these cases had TB/HIV co-infection and nearly 25 percent died.

In Matlosana, the incidence of TB disease remains high (772/100,000 population) (Massyn et al. 2014). In sub-Saharan Africa, TB is driven by the HIV epidemic, which women of child-bearing age bear the brunt of. In Matlosana, nearly 30 percent of pregnant women are HIV-positive (Massyn et al. 2014). Currently, diagnosis of active TB disease among pregnant women in resource-limited settings relies on the presence of clinical symptoms, which often overlap with or are masked by the symptoms of pregnancy, resulting in low sensitivity of the WHO-recommended screening tool among HIV-positive pregnant women (Gounder et al. 2011, Getahun et al. 2011, Sheriff et al. 2010, Hoffmann et al. 2013). In our recently completed cluster randomized study in Matlosana, clinics performing universal screening of HIV-infected pregnant women using sputum uncovered 10 times more TB than clinics following the WHO-recommended symptom screen (unpublished data).

Early identification of maternal TB disease is important given the serious health consequences for both the mother and infant, particularly in the context of maternal HIV co-infection (WHO 2015, Salazar-Austin et al. 2017, Mathad and Gupta 2012). Even with appropriate antiretroviral therapy (ART) and TB treatment, maternal and infant outcomes remain poor; both suffer higher mortality while infants are also burdened with higher rates of prematurity and low birth weight WHO 2015, Salazar-Austin et al. 2017, Mathad and Gupta 2012). Maternal TB disease may also increase mother-to-child transmission of HIV (Salazar-Austin et al. 2017, Gupta et al. 2011, Pillay et al. 2004).
Traditionally TB screening is performed by a community health worker upon the patient’s arrival to clinic. Targeted TB screening among high risk patients, including pregnant women, is not consistently documented in Matlosana. And while the South African TB guidelines recommend isoniazid preventive therapy (IPT) during pregnancy for HIV-infected women, implementation of these guidelines remains limited. Recent unpublished work from Matlosana suggests only 1–2 percent of people living with HIV (PLHIV) are initiated on IPT, even though most are considered eligible for treatment. Improving prevention and early detection of TB among pregnant women, regardless of their HIV status, remains critical for both mothers and their babies.

Integration of HIV evaluation and treatment into antenatal care (ANC) services has greatly improved maternal health and prevention of mother-to-child transmission of HIV. Learning from this success, Johns Hopkins University and the Perinatal HIV Research Unit in collaboration with local partners—under Project SOAR, funded by the United States Agency for International Development—aimed to implement and assess an integrated approach to TB evaluation and prevention among pregnant women applicable to high-burden, low-resource settings. This may serve as an important platform from which to scale up TB prevention services among women of childbearing age living with HIV and may become an important component of Mycobacterium tuberculosis complex he United States President’s Emergency Plan for AIDS Relief’s (PEPFAR’s) aggressive plan to scale up TPT among PLHIV.
METHODOLOGY

OBJECTIVES

Implement and evaluate an integrated approach to TB screening, evaluation, and prevention within ANC services at six Matlosana clinics to improve identification of TB disease among all pregnant women and improve IPT uptake among pregnant women living with HIV.

STUDY DESIGN

This was a pragmatic study with a quasi-experimental design and no control group.

DESCRIPTION OF INTERVENTION

This was a proof of concept model for integration of TB and ANC services in a high TB-incidence setting. Clinics were integrated at the start of the study and followed for a 10-month period. Patients received antenatal, HIV and TB care as per South African guidelines. No additional study visits were required as a part of the research study.

TB screening, evaluation, and IPT were integrated into six ANC clinics. ANC care was already integrated into TB care meaning that women diagnosed with and/or treated for TB during pregnancy received TB, ANC, and HIV care from the same professional nurse. TB care was not integrated into ANC clinical care because wait times for pregnant women were shorter through the TB program than the ANC program. Pregnant women without TB were seen only in the ANC clinic where they received both their ANC and HIV care. Additional patient files with built-in support tools were created to follow patients through TB evaluation and diagnosis during pregnancy. These support tools focused on (1) type of sputum testing to send (Xpert versus mycobacterial culture) in symptomatic and asymptomatic women living with or without HIV, and (2) how to assess eligibility for IPT among HIV-positive pregnant women.

In South Africa, all PLHIV are eligible for IPT except those who are currently symptomatic of TB disease and require evaluation, those previously on IPT, those who have significant risk factors for the development of side effects while on isoniazid, those who have started ART within the past month, and those with a viral load >1,000 copies/mL (National Department of Health 2013).

Training was provided to all nurses within a clinic and all ANC support staff. TB and HIV guidelines were reviewed and common misunderstandings and misconceptions were addressed. Appropriate sputum collection techniques were reviewed with all ANC staff. Ongoing training and program assessment for each clinic was scheduled to be provided biweekly for 12 weeks and then monthly for the remainder of the study. Due to lapses in funding, sociopolitical unrest, holidays, and family emergencies, this proposed training schedule was significantly altered. For a period of four
months, beginning six weeks after study implementation, there was minimal face-to-face contact between the study team and clinic staff but full collaborative work was resumed in month six for the last three months of the study.

Poster campaigns and patient education talks were organized which aimed at increasing knowledge to create patient demand for TB preventive services (Kim et al. 2018). The information provided reinforced the high risk of TB during pregnancy, associated poor maternal and infant outcomes, and how diagnosis and treatment could reduce these risks.

The Matlosana sub-district health department provided support for compliance with the screening program by permitting the study, aiding in the training, reinforcing implementation through the collection of data for indicators, and conducting a quarterly review with associated appropriate action.

The TB evaluation algorithm was as follows:

**HIV-negative pregnant women:** All HIV-negative pregnant women were screened using the symptom screen recommended by the South African TB guidelines. Accordingly, any patient reporting at least one symptom had a single spontaneously expectorated sputum collected and sent for Xpert MTB/Rif Ultra®, a PCR-based test that measures both the presence of *Mycobacterium tuberculosis* (*M. tuberculosis*) and for rifampin resistance. Women who tested positive were initiated on TB treatment. Women who tested negative and whose symptoms resolved, resumed regular care and were symptom screened at all subsequent visits. Women who tested negative whose symptoms persisted were referred to the hospital for evaluation by a physician.

**HIV-positive pregnant women:** In the baseline antenatal clinic visit, all women with a confirmed HIV-positive status were screened using both the WHO TB symptom screen and an expectorated sputum sample that was sent for mycobacterial culture. If a woman was symptomatic, she underwent “TB evaluation” including a sputum sample for Xpert MTB/Rif Ultra® and a clinician visit at either the clinic or the local hospital. Asymptomatic women with a negative sputum culture continued to have symptom screens at all subsequent visits. Women whose symptoms persisted with a negative sputum test were referred to the hospital for evaluation by a physician. Asymptomatic women with a positive sputum culture were evaluated by a nurse or physician and initiated on TB therapy. HIV-positive pregnant women without TB disease were eligible for IPT. Contraindications included recent ART initiation (<1 month), viral load >1000 copies/mL, liver disease, excessive alcohol use, peripheral neuropathy, current TB treatment, a history of IPT, or a history of an adverse reaction to isoniazid (National Department of Health 2013, National Department of Health 2009).

**Screening vs TB evaluation:** TB screening refers to both the WHO TB symptom screen (all pregnant women), and a sputum sample for mycobacterial culture for all PWLHIV whether symptomatic or asymptomatic. Therefore, these sputum cultures will be referred to as a part of TB screening. Symptomatic women should have undergone a “TB evaluation” which may have included expectorated sputum for Xpert MTB/RIF Ultra®, a PCR-based test that results in 24–48 hours for both the presence of *M. tuberculosis* and rifampin resistance, and a clinician visit.
DATA COLLECTION METHODS

While the intervention was prospective, data were abstracted from clinical charts onto clinical research forms retrospectively. Abstracted data included demographic details, pregnancy history and outcomes, TB screening, IPT, and TB treatment. These data were mainly abstracted from the newly implemented adult female chart that includes ANC, TB, and HIV care. Additional information was taken from the TB register and from the newly implemented patient files with built-in TB prevention support tools.

ETHICAL REVIEW

The study team shared evidence that universal screening of HIV-positive pregnant women with sputum sent for liquid culture identified 10 times the amount of TB without significant risk. This was found to be so compelling that informed consent was waived and randomization to a placebo group was considered not ethical.

The study received a waiver of informed consent for study participants from the University of Witwatersrand Human Ethics Research Committee and the Johns Hopkins Institutional Review Board. North West Province Department of Health also provided programmatic permission to conduct this study.

DATA ANALYSIS

The study used descriptive statistics, including proportions, means, and medians with interquartile range, to describe the characteristics of the pregnant women with and without HIV.
KEY FINDINGS

CHARACTERISTICS OF THE PARTICIPANTS

Six clinics were included in this study, each for a total of 10 months. Thirty-nine professional nurses and 39 other staff were trained on study procedures and integration services within the six study clinics. During the 10-month study period, 1,130 pregnant women aged 15 years and above were newly admitted to the ANC and/or TB programs at those clinics (Table 1). The median number of pregnant women attending each clinic during the study period was 164 (range 149–311). The median age was 26 (IQR 21,31) years. Women first presented to the clinic at a median 17 (IQR 11,24) weeks gestation. A total of 252 (22 percent) women presenting at these six ANC clinics were documented as living with HIV; 177 of these women (70 percent) already knew their HIV-positive status at their first antenatal visit and 75 (30 percent) women were newly diagnosed with HIV. PWLHIV were almost entirely on Efavirenz-based combined antiretroviral therapy (cART; 96 percent).

Seventy-four of the 1,130 newly admitted pregnant women delivered during the 10-month time period including 71 live born infants and 3 birth outcomes were not recorded. Sixty-three women were documented as having a normal spontaneous vaginal delivery. The remaining 11 women did not have recorded method of delivery. The median birth weight was 2.9kg (IQR 2.6, 3.3).

Table 1. Baseline maternal characteristics at presentation to the ANC clinic

<table>
<thead>
<tr>
<th>Maternal characteristic</th>
<th>n=1,130 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>26 years (21,31)</td>
</tr>
<tr>
<td>Weeks gestation at first visit</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>17 weeks (11,24)</td>
</tr>
<tr>
<td>Number of previous pregnancies</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>310 (34%)</td>
</tr>
<tr>
<td>1</td>
<td>304 (33%)</td>
</tr>
<tr>
<td>2</td>
<td>191 (21%)</td>
</tr>
<tr>
<td>≥3</td>
<td>113 (12%)</td>
</tr>
<tr>
<td>HIV positive</td>
<td></td>
</tr>
<tr>
<td>Previously known HIV</td>
<td>177</td>
</tr>
<tr>
<td>On cART at first visit</td>
<td>93 (53%)</td>
</tr>
<tr>
<td>Previously on cART</td>
<td>22 (12%)</td>
</tr>
<tr>
<td>Never on cART</td>
<td>11 (6%)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>41 (23%)</td>
</tr>
</tbody>
</table>
PROPORTION OF PREGNANT WOMEN APPROPRIATELY SCREENED FOR TB

Among the 1,130 newly pregnant women attending the ANC clinic, nurses used the newly designed TB evaluation/prevention file designed for pregnant women with 873 of them (77 percent).

Of the 878 pregnant women without HIV, 634 (72 percent) received a symptom screen at their first antenatal visit and 44 (5 percent) were symptomatic. None of these women was diagnosed with TB disease or started anti-tuberculous treatment during pregnancy. Two women who were asymptomatic at their first ANC visit were diagnosed with TB disease later in pregnancy and started on anti-tuberculous therapy.

Of the 252 pregnant women living with HIV (PWLHIV), 205 (81 percent) received a symptom screen at their first antenatal visit and 22 (9 percent) were symptomatic. One of these symptomatic women was diagnosed with TB disease and initiated on anti-tuberculous therapy. Two additional women who were asymptomatic at their first ANC visit were diagnosed with TB disease after they became symptomatic later in pregnancy and initiated on anti-tuberculous therapy. One additional woman living with HIV was diagnosed with TB disease and was initiated on anti-tuberculous therapy; she did not have a documented symptom screen at her initial ANC visit. It remains unclear when suspicion for TB disease began.

Of the 183 asymptomatic HIV-positive pregnant women, 61 (30 percent) were documented as having provided a sputum sample for mycobacterial culture at their first visit (Table 2). An additional 14 (7 percent) PWLHIV were reportedly unable to produce sputum and only 1 (0.5 percent) refused to produce sputum. Over half (107; 52 percent) PWLHIV had no sputum recorded in the medical record. Thirteen sputum cultures were received and worked up in the laboratory; one of these cultures was positive. The only positive culture occurred in an asymptomatic pregnant woman with HIV. The TB Prevention Care Cascade among PWLHIV is shown in Figure 1. Only 76 (37 percent) PWLHIV had appropriate TB screening as defined by the protocol.

Table 2 Proportions of PWLHIV who had sputum taken or attempted to be taken

<table>
<thead>
<tr>
<th>Sputum for PWLHIV</th>
<th>Asymptomatic PWLHIV</th>
<th>Symptomatic PWLHIV</th>
<th>PWLHIV unrecorded symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provided</td>
<td>61</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Unable to provide</td>
<td>14</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Refused to provide</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not recorded</td>
<td>107</td>
<td>14</td>
<td>45</td>
</tr>
</tbody>
</table>
Implementation improved over time. For women who had their first ANC visit in the first third period of the study, only nine asymptomatic PWLHIV had a culture performed (Figure 2). During the next three months, 22 (29 percent) asymptomatic PWLHIV had a culture performed. For women whose first ANC visit was in the final three months of the study, 29 (38 percent) asymptomatic PWLHIV had a culture performed.

**Figure 1** TB prevention care cascade among PWLHIV

**Figure 2** TB cultures sent over time

Dark green columns represent the number of identified pregnant women who were asymptomatic for TB at their initial ANC visit. The light green column represents the number of sputum cultures taken from those women. Proportions indicate the proportion of asymptomatic PWLHIV who had a sputum culture reported. Asymptomatic pregnant women without dates for their initial visit are excluded from this analysis.
TREATMENT AND PREVENTION OF TB AMONG PWLHIV

Four (0.5 percent) PWLHIV were diagnosed with TB and started on TB treatment. Two HIV-negative pregnant women were diagnosed with TB during this study. Four of these six pregnant women diagnosed with TB, whether HIV positive or not, were asymptomatic at their first ANC visit, and only one had a positive Xpert or culture. All six (100 percent) women who had initiated TB treatment remained on treatment at study completion.

Forty-five (4 percent) PWLHIV were started on IPT in accordance with South African guidelines. None of the women who had initiated IPT had completed their 6-, 12-, or 36-month course of therapy at study completion. Among women who delivered, IPT eligibility was determined for only 7 percent, all of whom were considered IPT eligible; 93 percent of women failed to be deemed eligible or ineligible, indicating poor uptake of the designed IPT eligibility tool.
DISCUSSION

The study team successfully implemented nurse-driven TB screening among pregnant women with and without HIV in six ANC clinics. Our protocol included TB screening, evaluation, and prevention services. TB screening included not only the WHO symptom screen for all pregnant women, but also a sputum culture for PWLHIV. TB prevention programming at the time included IPT for all PWLHIV. Integration of TB prevention into antenatal and postnatal care services, including preventive therapy, may assist PEPFAR in their efforts to aggressively scale up TPT among PLHIV. This intervention addresses women of childbearing age, a highly-vulnerable population. Implementation of the program occurred more slowly than expected over the 10-month study period. For example, by the end of the study period, there was finally significant momentum for sputum collection. This is evidenced by sputum collection that continued after study cessation, requiring several post-study visits to stop sputum collection.

Though 80 percent (61/76) of the PWLHIV approached for sputum reportedly provided sputum, only 13 of 61 sputa arrived in the laboratory. Either women failed to produce sputum, the transport system failed to deliver them to the laboratory, or they were not labeled as asymptomatic pregnant woman. It was discovered that nurses were providing sputum containers to PWLHIV to bring home and return the following morning. Unfortunately, the security guards guided all women with sputum to the TB office instead of the ANC office when they returned with sputum the following morning. The initial training was reinforced and the ANC staff were requested to obtain on-the-spot sputum, meaning women would go outside and cough prior to the completion of their visit. The team was unsuccessful in changing habits in most cases. If these women had had a positive sputum and were started on TB treatment, record review would have demonstrated these findings. Moving forward, it will be necessary to assist nurses in getting out of their comfort zones to improve sputum collection. This cannot remain the responsibility of the TB nurse and TB clinic staff alone if true integration of services is to occur. Other important facility-based challenges that were more easily overcome during the study period were placement of sputum containers and sputum log books within ANC services.

Due to the low number of sputa collected, only four cases of active TB among PWLHIV were identified; more women with active TB may have been identified if more sputa were taken. The median gestational age at the first ANC visit in this study was 17 weeks. The national program has been promoting earlier registration upon first suspecting pregnancy with the hope of improving maternal and infant outcomes for all pregnant women in South Africa. This is important, as the median gestational age at presentation was much later in the universal sputum screening study. Women presenting earlier in pregnancy may not have TB disease or a positive culture. The timing of universal sputum screening for asymptomatic PWLHIV may therefore need to be reconsidered. Due to the duration of the study, women were not followed post-delivery to identify additional TB cases presenting in the postpartum period. More data are needed to show the benefit of sputum collection. These data may contribute to improving nurse motivation and participation.
For asymptomatic PWLHIV, all ANC staff were trained on the importance of IPT for TB prevention to improve both maternal and infant outcomes. Nurses and mentor mothers were trained to emphasize these maternal and infant benefits, as prior studies highlighted this lack of awareness as a reason why PWLHIV would be less likely to accept IPT. An IPT eligibility tool was requested by the nursing staff and placed in the TB evaluation/prevention file, but was poorly utilized by nurses. This was an anticipated challenge that was planned to be addressed with ongoing audits with feedback and targeted ongoing training that could not be performed due to funding delays and political unrest. This was a critical aspect of the training and implementation plan. Unfortunately, also due to funding constraints, informal qualitative assessments could not be performed to assess reasons for poor uptake of the nurse-designed study tools.

Only 45 PWLHIV initiated IPT. Unfortunately, due to poor use of the IPT eligibility tool, the proportion of eligible PWLHIV who were initiated on therapy cannot be calculated. Data from IMPAACT P1078 TB Apprise showed IPT during pregnancy had a higher risk of adverse pregnancy outcomes than IPT given in the postpartum period (Gupta et al. 2019). While these data did not result in a change in National South African HIV or TB guidelines during this study, it may have influenced key providers within the Matlosana community to stop providing IPT to pregnant women. It is important to note that throughout the study, national guidelines were followed except for obtaining sputum for mycobacterial culture in all PWLHIV. It remains unclear what effect these findings may or may not have had in these Matlosana clinics as concurrent controls were not included in the study design. In the future, integration of IPT into postnatal services may serve as a safer way to integrate TB preventive therapy into pregnancy and postpartum care for PLHIV.

Anecdotally, implementation in clinics with stable ANC staff, where nurses did not rotate through different programming every one to two months, had higher proportions of PWLHIV initiated on IPT. Clinics with established mentor mothers, a group of community-health workers focused on maternal and infant care, were better able to delegate and successfully complete tasks than clinics where mentor mothers had been newly hired near the same time as study implementation. Task sharing specific roles within TB evaluation and prevention with community health workers may also improve implementation.

Overall, the implementation activities were largely helpful, but more work is needed to define successful implementation models for screening and preventing TB among pregnant women living with HIV in high burden settings.

**LIMITATIONS**

This was a pragmatic study where the clinic nurses and staff recorded the data on newly implemented TB evaluation and prevention files. With local government support, the study team instructed and reminded the nursing staff that non-recorded tasks were considered “not performed.” It is possible that tasks were indeed performed and that the number of integration events and either the number of attempted sputum cultures and/or the number of cultures sent were underestimated. High nurse turnover in the clinics in the study and low overall staffing rates resulted in poor continuity of care and the need for frequent retraining during the 10-month study period.
Finally, several implementation barriers at critical time points early on likely resulted in poor initial implementation of the study procedures and subsequent slow uptake of study programming that likely resulted in limited efficacy in program integration. Implementation was slow for a number of reasons. First, two months after the study began there was an interruption in study funding that prevented ongoing training and implementation activities, when reinforcement was most critical. Second, shortly after study funding resumed, there was unexpected political unrest with focused demonstrations at the district hospital, where PHRU headquarters are located, and the individual clinics, both of which hampered implementation for an additional two months once study funding was in place. Third, PHRU devised a series of interventions to improve sputum collection in clinics including sputum collection reminders and additional training. Unfortunately, these interventions required additional approval from the Matlosana government. There were no isoniazid stock outs in the study clinics for the duration of the study.
CONCLUSION AND RECOMMENDATIONS

CONCLUSIONS

TB screening, evaluation and preventive services can be integrated into ANC services in decentralized South African clinics. Utilizing antenatal and postnatal care services to improve TB prevention and TPT uptake among PLHIV may assist PEPFAR in their efforts to aggressively scale up TPT. This intervention addresses women of child-bearing age living with HIV, a highly-vulnerable population. Lessons learned include providing for a larger lead time for full program integration so that all members of the team can slowly incorporate all aspects of the program into their daily routines. This study also showed that a majority (80 percent) of asymptomatic women approached for a sputum sample were able to produce sputum for mycobacterial culture.

RECOMMENDATIONS

1. Integration of TB evaluation and prevention into ANC services is possible, but will require ongoing reinforcement of training over time.

2. More data are needed to show the benefit of sputum collection; this may improve nurse motivation and participation.

3. Nurses and other staff beyond the TB program should be trained and feel comfortable with sputum collection methods and its documentation. This cannot remain the sole responsibility of the TB program.

4. Task shifting of sputum collection and documentation to community health workers may improve implementation.

5. TB screening, including sputum collection, should become routine in ANC programs. Other facility-level challenges need to be considered including patient flow upon return to clinic with sputum, sputum container storage, and sputum log books to enhance the success of TB integration into ANC services.

6. Advocacy around TB prevention for pregnant women needs to be improved to increase demand for life-saving therapies including TB preventive therapy.

7. In the future, integration of IPT into postnatal services may serve as a safer way to integrate TB preventive therapy into pregnancy and postpartum care for PLHIV. Though we primarily evaluated TB integration into ANC services, similar barriers would be expected for TB integration into postnatal care services.

These findings and recommendations were discussed with the Matlosana sub-district managers in March 2019. Discussions with district and provincial managers are scheduled.
REFERENCES


