CARDIOVASCULAR RISK AMONG PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS AND HIV IN SOUTH AFRICA

By

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A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland
April, 2018

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Abstract

Problem Statement

South Africa has the highest incidence of drug resistant-tuberculosis (DR-TB) in sub-Saharan Africa and outcomes are poor. Only 54% of patients successfully complete treatment. The prevalence of HIV co-infection and cardiovascular (CVD) risk factors is also increasing. The purpose of this study was to describe cardiovascular risk in DR-TB patients with and without HIV co-infection and the impact of this risk on 6-month DR-TB negative treatment outcomes among patients co-infected with HIV.

Methods

This prospective cohort study was nested within an ongoing cluster randomized trial of nurse case management in 10 DR-TB hospitals in Eastern Cape and KwaZulu-Natal, South Africa. The data were collected between November 2014 and July 2016. The prevalence of CVD risk factors and a non-laboratory based risk score were estimated, compared by HIV status, and used to explore the impact on DR-TB negative treatment outcome among 443 HIV co-infected patients.

Results

Of 900 participants, 53.7% were male, 75.1% were HIV co-infected, and 52.3% had at least one CVD risk factor. Males were more likely to have ever smoked (52.5% vs 7.3%, $\chi^2=207.31$, $p<0.001$) and less likely to have an elevated body mass index (BMI) (8.3% vs 26.2% $\chi^2=50.97$, $p=<0.001$) compared with females. Compared with patients without HIV co-infection, HIV co-infected patients had significantly less risk of diabetes (aRR=0.45, 95% CI 0.28-0.72). Among HIV co-infected patients, BMI was the only
CVD risk factor that predicted an early DR-TB negative outcome; underweight BMI increased risk and overweight BMI was protective compared with normal BMI. Among 210 HIV co-infected patients >35 years old, patients with a high or moderate CVD risk score were 4.5 times more likely to have an early negative treatment outcome compared with those with low CVD risk.

Conclusions

Except for BMI, individual CVD risk factors did not impact early DR-TB outcomes, although an elevated CVD score did increase risk of negative outcome. Providers should screen and treat patients with CVD risk factors according to evidence-based guidelines. Health systems should provide comprehensive, patient-centered care to improve both DR-TB outcomes and CVD related morbidity and mortality in low- and middle-income countries like South Africa.

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Jason E. Farley, PhD, MPH, ANP-BC
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Naomi Levitt, MD, MBChB
Preface

Acknowledgments

This research was the result of many individuals providing encouragement, data analysis strategies, PhD jokes, and wisdom. My team of research advisors was critical in helping me to develop and refine my research questions and to maximize the quality of my science. This included: Dr. Jason Farley, Dr. Richard Chaisson, Dr. Nancy Perrin, Dr. Cheryl Dennison-Himmelfarb, Dr. David Dowdy, Dr. Martha Hill, and Dr. Naomi Levitt. I would especially like to acknowledge Dr. Martha Hill, Dean Emeritus at The Johns Hopkins University School of Nursing (JHUSON), who helped me to grow from a first-year student with “19 ideas for a research study” to a researcher who could navigate cross-disciplinary, cross-disease research in a global setting to complete this project. She is an inspirational nurse, leader and mentor and I am very grateful for her wisdom. In addition, there are numerous other faculty and staff at the School of Nursing and Bloomberg School of Public Health who provided excellent feedback that improved my scientific rigor, encouragement when I was in the weeds of data collection or analysis, and help in preparing grant submissions or submitting receipts for reimbursement! Thank you for your patience, kindness, and generosity with words and deeds.

Without Dr. Jason Farley this research would not have been completed. I am very grateful for his generosity in allowing me to participate in his National Institutes of Health (NIH) funded cluster randomized controlled trial to learn about how to conduct multi-site research in a South African context and to use the rich data to answer my own research questions. Thank you also to Kelly Lowens, Project Manager for this trial, for helping me to navigate paperwork, Institutional Review Board (IRB) approval, logistics
across two continents and of course finding great bottles of South African wine. The staff of the study in South Africa were patient and kind as I asked them to help me collect smoking data or find missing charts. Thank you for all that you taught me about how to care well for patients with MDR-TB and make the best of a sometimes challenging medical system! A final thank you to the participants in the research study. I thank you for sharing your stories through data and I hope that this research will contribute to the body of literature on improving MDR-TB care and outcomes.

Another huge thank you to my fellow PhD students at JHUSON. I would not have completed this program without your hugs, listening ears, and laughs. I am grateful for the memories of dissertation outlining with gin and tonics, carving the PhD student pumpkin, and organizing the PhD portal. To my friends across the globe and throughout the years: there are too many of you to mention, but thank you for rooting me in truth, love and encouragement so that I can face the next challenge and adventure. Finally, thank you to my parents, Peter and Catherine Whitehouse and siblings who instilled in me a love for life-longing learning and pursuit of social justice and care for the vulnerable. To quote lyrics from the musical Wicked, “I know I’m who I am today because I knew you. . .” Thank you to all who have influenced, encouraged, and inspired me.
Funding

I could not have completed this dissertation without significant financial support and I am very grateful to the numerous organizations that provided support for this research:

National Institute of Allergy and Infectious Disease, NIH R01 AI104488 (2014-2018)
Interdisciplinary Training Cardiovascular Health Research, National Institute of Nursing Research, National Institute of Health 5T32NR012704 (2014-2016)
Isabel Hampton Robb Scholarship, Nurses Educational Fund, Inc. (2015)
Global Health Established Field Placements Scholarship, Center for Global Health, Johns Hopkins University (2015)
Ellen Levi Zamoiski Doctoral Fellowship, Johns Hopkins University School of Nursing (2016)
Ruth L. Kirschstein National Research Service Award [NRSA] Individual Predoctoral Fellowship from National Institute of Nursing Research, NIH F31-NR016909 (2016-2018)
Jonas Nurse Scholars Program, Johns Hopkins University School of Nursing (2016-2018)
Dean’s Scholarship Fund, Center for Global Initiatives, Johns Hopkins School of Nursing (2017)
Sigma Theta Tau International Research Grant (2017-2018)
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Chapter 1: Introduction

Tuberculosis (TB) is the leading cause of death due to infectious diseases, recently surpassing Human Immunodeficiency Virus (HIV) as the number one global killer.\textsuperscript{1} While strides have been made, infectious diseases such as TB and HIV are leading causes of death among many low- and middle-income countries including South Africa.\textsuperscript{1,2} At the same time, rates of non-communicable diseases such as cardiovascular disease (CVD) and many risk factors for CVD including diabetes and hypertension are accelerating.\textsuperscript{2–4} This dual burden creates a unique pattern of multi-morbidity, the presence of two or more chronic conditions, where infectious and non-communicable diseases coexist. Such multi-morbidity often exists in countries such as South Africa where the health system is strained and where social determinants of health play a significant role in health outcomes.

HIV, TB, and CVD risk factors have complex intersecting relationships that are likely to exacerbate the prevalence and impact of multi-morbidity on health. Due to complex physiologic intersections, TB, HIV, and CVD risk factors have bidirectional relationships that increase prevalence of multi-morbidity and increase risk for mortality.\textsuperscript{5–7} Multi-morbidity not only impacts patients on a physiologic level, but also increases patient treatment burden. Multi-morbidity creates an additional strain on over-burdened and siloed health systems and may stress providers who have limited experience with treating multiple co-existing conditions.\textsuperscript{8}

South Africa has a high burden of HIV, TB, and co-occurring CVD risk factors including diabetes, hypertension, obesity, and smoking.\textsuperscript{3,9,10} TB and HIV are two of the leading causes of death and CVD accounts for nearly one quarter of mortality in South
Africa and is likely to increase. Drug-resistant-TB strains (DR-TB) increase mortality in TB-related deaths, a global public health concern. DR-TB, defined as TB resistant to at least the two most powerful drugs in the regimen, includes multi drug-resistant TB (MDR-TB), TB resistant to the first line regimen (i.e., isoniazid and rifampicin), and extensively drug-resistant TB (XDR-TB), TB resistant to the second line TB regimen (i.e., isoniazid, rifampicin, fluoroquinolones, and injectable aminoglycosides).\(^1\) DR-TB leads to dramatically higher mortality, requires a treatment regimen that has debilitating side effects, lasts up to 2 years, and costs more than 26 times as much as drug susceptible TB.\(^{11-13}\) In addition, rates of default and treatment failure are much higher in DR-TB, meaning that these patients are continuing to infect others in their community and intensifying the epidemic.\(^1,14\) While HIV is a primary driver of the TB epidemic, CVD risk factors also impact TB and DR-TB outcomes.\(^5-7,15-17\) Unfortunately, there are limited studies among HIV and DR-TB co-infected patients to understand the impact of CVD risk factors on DR-TB treatment outcomes particularly in a high HIV setting.

Like treatment for these conditions, research on non-communicable diseases (NCD) and infectious diseases has also been siloed, meaning that there is limited research that explores the intersection of these conditions and their impact on individuals, communities and health systems.\(^8,18,19\) One critical research priority in global health, and HIV research in particular, is a better understanding of the intersection with NCDs.\(^19\) It is impossible to stop excess mortality caused by this intersection without better understanding the prevalence of CVD risk factors and the impact of multi-morbidity including CVD risk factors on DR-TB treatment outcomes.
Background

TB and HIV are the leading causes of infectious disease in South Africa. South Africa has one of the highest incidence of TB and HIV in the world.\textsuperscript{1,20} In the past five years, South Africa has made tremendous strides in TB and HIV care including free access to anti-retroviral therapy (ART) and TB medications as well as decentralization of services.\textsuperscript{21} However, TB is still the leading cause of death among all South Africans and among people with HIV in particular, accounting for 9% of all deaths in South Africa.\textsuperscript{2} HIV is the fifth leading cause of death and as many as 70% of TB patients are co-infected with HIV.\textsuperscript{2,14} In addition, DR-TB including MDR-TB and XDR-TB is an increasing concern.\textsuperscript{1,12} According the most recent WHO data, South Africa has the highest incidence of MDR-TB in Sub-Saharan Africa.\textsuperscript{1} DR-TB treatment outcomes remain poor with approximately 54% of MDR-TB patients successfully treated.\textsuperscript{1,13,14} Mortality and loss to treatment follow-up in DR-TB patients are much higher than in drug susceptible TB patients.\textsuperscript{1,14} DR-TB is also very costly; in South Africa although only about 3% of TB cases are DR-TB, the cost for treatment is approximately 45% of the TB expenditures nationwide.\textsuperscript{11} Thus, improving DR-TB outcomes is critical to preventing further morbidity and mortality among HIV-positive patients.

DR-TB/HIV co-infection in South Africa exists within a population that is also experiencing increasing cardiovascular disease (CVD) multi-morbidity. One in three South Africans has elevated blood pressure, over 30% are obese, and approximately 7% have diabetes.\textsuperscript{3,9} As leading causes of death, diabetes and CVD account for 24% of deaths in South Africa.\textsuperscript{3} CVD is also costly; the World Health Organization (WHO) African region attributed 11.4 billion dollars (USD) to CVD disease in 2010 and this cost is increasing.\textsuperscript{22} Studies have consistently demonstrated under-diagnosis of CVD risk
factors particularly in Sub-Saharan Africa suggesting this burden could be even higher.\textsuperscript{7,23–26} In South Africa, this increases the risk for cardiovascular multi-morbidity, the presence of two or more chronic conditions including CVD and/or CVD risk factors, particularly among patients with HIV and TB. Cross-sectional studies of South African primary care centers suggest rates of multi-morbidity between 14 to 45%.\textsuperscript{27–29} While differences in the definition of multi-morbidity account for some of this variation, multi-morbidity is a significant clinical and public health concern. In addition, both TB and HIV can increase risk for the development of CVD risk factors. TB increases diabetes risk threefold and may contribute to CVD risk secondary to inflammatory processes.\textsuperscript{5,30} Further, HIV infection increases risk for hypertension, dyslipidemia, and CVD.\textsuperscript{31–34} While anti-retroviral therapy mitigates some CVD risk by decreasing inflammation, the long-term impacts of ART may increase CVD risk.\textsuperscript{31,35} Despite this, South African national DR-TB guidelines do not include provider guidelines for screening, treating or preventing CVD risk factors other than monitoring patients with diabetes.\textsuperscript{12} In addition, lack of health care integration among HIV, TB, and primary care clinics increases the imperative for all providers to monitor for co-morbidities.\textsuperscript{28,36,37}

Cardiovascular multi-morbidity appears to worsen MDR-TB treatment outcomes. HIV co-infected patients are already twice as likely to die from MDR-TB than HIV-negative patients and CVD multi-morbidity may increase this mortality risk.\textsuperscript{1,13} Diabetes and smoking, two common CVD risk factors, have well documented negative influences on TB and MDR-TB outcomes.\textsuperscript{6,7,17,38–41} Several studies have reported that multi-morbidity increases risk of death among MDR-TB patients.\textsuperscript{6,42} However, none of these studies have focused specifically on the role of CVD risk factors in countries with high
burdens of HIV co-infection where these risk factors may have a negative synergistic impact on MDR-TB treatment and overall health. Multi-morbidity may impact DR-TB treatment outcomes through several pathways. As noted above, CVD risk factors, TB, and HIV have intersecting physiologic influences that may decrease immune status and increase inflammation. In addition, CVD multi-morbidity adds to the already extensive patient and medication burden of MDR-TB and HIV treatment. In MDR-TB treatment the first phase, called the intensive phase, requires 5-7 times a week aminoglycoside antibiotic intermuscular injections along with oral medications and lasts 6 months or until the patient has two negative TB cultures. The second phase, called the continuation phase, requires an oral regimen of at least five antibiotics for a minimum of 18 months. South Africa has recently implemented a new 9-month regimen, but this still requires over 6 different antibiotics including an injectable intermuscular medication for at least four months. Importantly, newer agents are being integrated into DR-TB regimens, yet, unfortunately may impact cardiovascular associated outcomes in DR-TB treatment by directly prolonging QT interval. Case reports and clinical trial data demonstrate this to be a rare but possible event. Furthermore, multi-morbidity in South Africa is associated with lower education level and socioeconomic status, meaning that patients who have the highest disease burden may also be more vulnerable to the negative impact of social determinants of health.

Evaluating a patient’s cardiovascular risk using a CVD risk score may be one way to evaluate the potential for adverse events during MDR-TB treatment. One non-laboratory CVD risk score that predicts a person’s five-year risk of having a CVD related event or death is calculated based on body mass index (BMI), sex, age, smoking, the
presence of medication for hypertension, systolic blood pressure, and a history of diabetes. This score has been compared with other common CVD risk scores in South Africa and has been used in several low- and middle-income countries where community health workers have implemented it for screening purposes. Calculating this CVD risk score may be one way that clinicians can identify MDR-TB patients at higher risk for CVD related morbidity and mortality and potentially poor MDR-TB treatment outcomes.

**Purpose and Specific Aims**

This dissertation study was nested in an ongoing cluster randomized trial in a low resource setting investigating the effects of nurse case management (NCM) in improving treatment outcomes in individuals with MDR-TB with and without HIV co-infection in the Eastern Cape and KwaZulu-Natal provinces of South Africa [R01 AI104488-01A1, PI: J. Farley]. The parent study included DR-TB patients at baseline, but only followed patients who were determined to have MDR-TB for treatment outcomes. The purpose of this dissertation study was to describe the prevalence of cardiovascular disease risk and its impact on MDR-TB treatment outcomes in a population of DR-TB patients with and without HIV co-infection in South Africa.

The specific aims were:

1. To determine the prevalence of CVD risk factors (i.e. diabetes, elevated body mass index (BMI), smoking and hypertension) and calculate a non-laboratory CVD risk score among patients with DR-TB enrolled in the parent study

Among the sub-set of patients co-infected with MDR-TB and HIV:
2. To describe the impact of individual and combinations of CVD risk factors on 6-month negative MDR-TB treatment outcomes (i.e. death, loss to follow-up or treatment failure).

3. To describe the impact of a non-laboratory CVD risk score on 6-month MDR-TB negative treatment outcomes.

**Hypothesis:** *MDR-TB/HIV co-infected patients with higher CVD risk score will have a shorter time to MDR-TB negative treatment outcome.*

4. To explore if social determinants of health moderate the relationship between the non-laboratory CVD risk score and 6 months MDR-TB negative treatment outcome.

**Hypothesis:** *The impact of CVD risk on negative treatment outcomes will be greater for those receiving grant assistance, having no internet or phone access and being unemployed as compared to those not receiving grant assistance, having internet or phone access and being employed.*

**Parent Study**

The parent study, A Nurse Case Management Intervention to Improve MDR-TB/HIV Co-Infection Outcomes with and without HIV Co-Infection, is a NIAID-funded cluster randomized trial (R01 AI104488-01A1, PI: J. Farley). The primary aim is to determine the impact and cost effectiveness of the Nurse Case Management (NCM) plus health systems strengthening model on MDR-TB outcomes in patients with and without HIV co-infection in Eastern Cape and KwaZulu-Natal provinces, two provinces with the highest burden of MDR-TB and HIV in South Africa. Secondary aims are (1) to conduct sub-group analysis by sex/gender and age and (2) to compare the frequency and time to identification of adverse drug reactions between sites (NCM or control). Prior to
enrollment, 10 MDR-TB centers were stratified based on location (urban/rural) and program size and randomized to control or intervention group (NCM). Participants for this dissertation research were recruited into the parent study on initiation of MDR-TB treatment at the 10 study sites between November 2014 and July 2016 and were followed throughout the MDR-TB treatment course (approximately 2 years), although the parent study is ongoing and actively recruiting patients. While all racial groups have equal opportunity for participation, most patients receiving care at these public hospitals are Black/African.

The nurse case management intervention uses professional nurses as nurse case managers (NCMs) who have been trained for at least 3 years as a nurse and who received additional training for approximately one month on case management for the study. NCMs interact with patients and collect data on a weekly basis during the intensive phase of treatment and at least monthly during the continuation phase of treatment in person or by phone. NCMs ensure adherence to MDR-TB guidelines regarding medications, labs, and management of adverse drug reactions. In addition, they provide adherence counseling and address patients’ psychosocial needs including connecting them with resources such as government social grants. At the control sites, research assistants (RAs) do not intervene in the health system but record data at the same intervals based on chart reviews. After the initial consent and interview, RAs do not have further interaction with patients.

**Inclusion & Exclusion Criteria**

For inclusion in the parent study, MDR-TB centers must follow national SA MDR-TB treatment guidelines, have had a MDR-TB program for more than 6 months
and have access on-site to HIV/ART treatment. Patient level inclusion criteria include patients older than 13 years of age who have microbiologically confirmed MDR-TB and sign informed consent within 7 days of treatment initiation. Patients 13-17 years of age provide consent for the study team to contact a parent or legal guardian who is willing to provide approval for study participation. Patient level exclusion criteria include patients who have started MDR-TB treatment at a different facility or are enrolled in a clinical study that changes standard MDR-TB or HIV regimens.

**Data Collection**

Data for the parent study are collected by NCMs at intervention sites or RAs at control sites. At baseline, patients are interviewed for socio-demographic data. Data are also collected through medical chart review and the National Health Laboratory System (NHLS) online laboratory portal. Intervention sites conduct additional patient level assessments through face to face and phone interviews. All sites record weekly data from baseline to end of intensive phase of MDR-TB treatment (≈ 6 months) including patient vital signs, symptoms, medication changes, laboratory results and treatment outcomes based on medical chart review and patient interview (NCM sites only). Parent study data are collected on paper forms, scanned and then entered into the REDCap online data system. All study documents were developed in REDCap to facilitate data entry. Data queries are developed for each individual site and resolved with each site before the baseline record is complete.

**Conceptual Framework**

The World Health Organization Innovative Care for Chronic Conditions model provided a framework for how patient, provider, and system level concepts relate to
This model has been specifically revised by South African researchers for the context of multi-morbidity, particularly for both chronic infectious and non-communicable diseases. This model suggests that multi-morbidity impacts the health of patients, families and communities through biologic, patient, provider, and system processes. Biologic interactions include the role of intersecting risk factors among HIV, TB and CVD; diagnosis of diseases and treatment outcomes for patients with multi-morbidity. In this study, this included variables such as age, kidney function and CD4 count. The patient perspective describes treatment burden and patient prioritization of multiple co-morbidities. In this study, patient perspective variables included co-morbidities, the number of medications a patient was taking at baseline, and social determinants of health. Healthcare provider perspective includes provider capacity and role delineation, which in this study is represented by the parent study nurse case management intervention. This intervention uses nurses at selected MDR-TB centers to provide individualized patient care and health systems strengthening compared to control sites where usual care by the existing health care team is provided. The parent study is based on the Chronic Care Model that, similarly to this framework, aims to understand the management of chronic conditions from a patient to health systems approach. In the context of this study, the NCM intervention is a provider level variable that may impact the relationship between CVD risk factors and 6-month MDR-TB negative treatment outcomes. Finally, the health system perspective explores the way multi-morbidity impacts policy (including SA national guidelines) and patient and provider engagement with the system. In this study, health system variables included characteristics of the
MDR-TB centers. Figure 1 shows the modified version of this framework with study aims.

Figure 1. Multi-Morbidity Conceptual Framework & Study Aims

**Innovation**

This study addresses the scientific gap in understanding the prevalence and impact of multi-morbidity on HIV/MDR-TB co-infected patients. This study is innovative for several reasons: (1) It is one of few studies to explore multi-morbidity among MDR-TB and HIV co-infected patients in South Africa including multiple CVD risk factors and a CVD risk score tool;46,48 (2) It is a nested study of one of the largest interventional cohorts assembled to assess the impact of nurse case management on MDR-TB outcomes in the world. Nurse case management may be one strategy to improve self-management and adherence in this complex patient population. The additional research questions proposed herein add richness to the understanding of HIV
and MDR-TB patients and treatment outcomes on top of the existing parent study aims;
(3) This study is the first to our knowledge to use a validated CVD risk score to explore
CVD morbidity and mortality risk in MDR-TB/HIV co-infected patients.\textsuperscript{46,48} Risk scores
are particularly useful in clinical decision-making and patient prioritization in low
resource settings such as South Africa.\textsuperscript{48} Additionally, this study will allow for
comparison of MDR-TB patients to other South African populations where the same risk
calculator has been applied.\textsuperscript{47,48}

\textbf{Dissertation Organization}

This dissertation is organized into five chapters. Chapter 1 includes introductory
and background materials, the purpose and specific aims, and the conceptual framework
that provided the foundation for this research. Chapter 2 and 3 are publication ready
data-based papers on the prevalence of cardiovascular risk factors in a DR-TB population
and the impact of these risk factors on 6-month MDR-TB outcomes. Chapter 2
specifically explores the prevalence of cardiovascular risk factors among a population of
DR-TB patients, comparing patients by HIV status. Chapter 3 explores the impact of
CVD risk factors and the non-laboratory CVD risk score on 6-month MDR-TB treatment
outcomes. As smoking was identified as an influential and common risk factor for
negative TB outcomes and further mortality and morbidity, chapter 4 is a review of
literature on smoking interventions implemented in TB clinics. Finally, chapter 5
provides a summary of findings, discusses further limitations of this study and suggests
implications for research, practice and policy.
Chapter 2: Prevalence of cardiovascular risk in South Africans with drug-resistant tuberculosis: a cross-sectional study

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Target Journal: The International Journal of Tuberculosis and Lung Disease (IJTLD)
Abstract

Introduction: South Africa has a high prevalence of drug-resistant tuberculosis (DR-TB), HIV, and cardiovascular disease (CVD) risk factors. The purpose of this study is to determine the prevalence of diabetes, smoking, hypertension, and elevated body mass index (BMI) and a summed non-laboratory CVD risk score and compare these by HIV status.

Study Population & Methods: This cross-sectional study is nested within an ongoing cluster-randomized trial in 10 DR-TB hospitals in South Africa. The data for this study were collected between November 2014 and July 2016.

Results: Of 900 participants ≥18 years of age, 75.1% were co-infected with HIV, 53.7% were men, the median age was 34.4, and 52.3% had one or more CVD risk factors. Males were more likely to smoke (52.2% vs 7.3%) and less likely to have an elevated BMI (8.3% vs 26.2%). HIV co-infected patients compared with HIV-negative patients were less likely to have diabetes (aRR=0.45, 95% CI 0.28-0.72). Of 398 participants over 35 years of age, 23.4% had a moderate or high calculated CVD risk score.

Conclusion: Some DR-TB patients are at risk for CVD related morbidity and mortality even during DR-TB treatment. TB providers should identify people at risk to initiate primary and secondary prevention to prevent future mortality.
Introduction

South Africa has the highest incidence of drug resistant tuberculosis (DR-TB) in sub-Saharan Africa and treatment outcomes remain poor; about 54% of patients successfully complete treatment.\(^1\) Approximately 70% of DR-TB in South African patients are co-infected with HIV, a leading cause of morbidity and mortality among DR-TB patients.\(^2\)–\(^4\) Non-communicable diseases (NCDs) such as diabetes also complicate treatment outcomes and are increasing in low- and middle-income countries.\(^5\),\(^6\) The four leading causes of adult death in South Africa are tuberculosis, diabetes, cerebrovascular disease and heart disease.\(^7\)

Cardiovascular disease (CVD) risk factors co-exist with HIV and DR-TB disease. TB has a complex relationship with CVD and risk factors; smoking and diabetes have known negative impacts on TB treatment outcomes.\(^8\)–\(^10\) HIV and long-term use of antiretroviral therapy (ART) may increase the risk of hypertension and CVD.\(^11\)–\(^15\) This co-morbidity may have an impact at a biologic level by increasing the inflammation and response to infection, at the patient level by increasing medication burden and at the health system level by stressing TB and HIV providers who may have limited experience with the diagnosis and treatment of CVD risk factors.\(^16\),\(^17\)

Cardiovascular risk can be assessed by calculating a CVD risk score that estimates the five or ten-year risk of having a cardiovascular related event or death. Such a risk score can guide clinicians to screen and recommend treatment in high-risk patients.\(^18\) Gaziano et al. developed a non-laboratory based CVD risk score and has been used in multiple countries.\(^19\),\(^20\)

Few studies have evaluated individual or combined CVD risk factors in patients with DR-TB in a high HIV prevalence setting\(^9\),\(^21\)–\(^23\) and to our knowledge no studies have
reported CVD risk scores among DR-TB patients. The purpose of this study was to
determine the prevalence of individual CVD risk factors (diabetes, smoking,
hypertension, elevated body mass index) among DR-TB patients and their summed CVD
risk score and compare by HIV status.

Methods
Study Design

This was a nested cross-sectional study of baseline data within an ongoing cluster
randomized controlled trial assessing nurse case management of patients with DR-TB
[R01-AI104488-01A1].24

Setting

The parent study is currently enrolling participants in 10 DR-TB hospitals in the
Eastern Cape and KwaZulu-Natal provinces in South Africa. For inclusion in the parent
study, DR-TB centers had to follow national DR-TB treatment guidelines, had a DR-TB
program for more than 6 months and have on-site access to HIV treatment. Hospitals
were stratified by location and center size and then randomized to nurse case
management or usual care; five hospitals were in urban/peri-urban settings and five were
in rural settings. Four of the centers treat <150 patients per year, while six treat >150
patients per year.

Sample

Enrollment into the parent study required the participant have a diagnosis of
rifampicin-resistant TB, the first criteria for DR-TB, and be 13 years of age or older.
Participants were excluded from the parent study if they had started DR-TB treatment at a
different facility or were enrolled in a clinical trial changing the standard DR-TB or HIV
regimen. For this study of CVD risk, all eligible participants ≥ 18 years of age who
enrolled in the parent study between November 2014 and July 2016 were included. This age cut-off was selected due to the low prevalence of CVD risk factors in people less than 18 years of age.

Study Procedures

Data collection was completed at each site either by a trained research assistant (i.e. control sites) or a nurse (i.e. intervention sites). At baseline, all participants were interviewed for socio-demographic data. Data such as medical history, medications, HIV status, ART, baseline vital signs and laboratory results were abstracted by medical chart review and from the Health Laboratory System online laboratory portal. After a comprehensive quality assurance process by senior research team members, case report forms were scanned and manually entered into the REDCap electronic data capture tools hosted by Johns Hopkins University.25

Measures

CVD risk factor data were obtained from chart review for baseline medical history, a review of medications, baseline laboratory tests and baseline vital signs. Height, weight, and blood pressure (BP) were abstracted from the medical record. All sites have automatic blood pressure machines used by clinicians for hypertension diagnosis and management. Hypertension was defined based on South African guidelines as systolic BP greater than 140mm/Hg or diastolic BP greater than 90mm/Hg, a prescription for blood pressure medication or medical history.26 Diabetes was defined based on baseline medical history, a prescription for medication for diabetes, or hemoglobin A1c (HbA1c) >6.5% according to South African guidelines.27 BMI categories were defined based on international and South African guidelines.28
laboratory based CVD risk score was calculated based on collected data for patients 35 years of age or greater. This risk score includes age, sex, current smoking status, diagnosis of diabetes, systolic blood pressure, whether on treatment for hypertension, and BMI and predicts 5-year CVD morbidity and mortality risk. 

Smoking was initially collected by the parent study as whether participant had a lifetime history of smoking more than 100 cigarettes, cigars or tobacco products and smoked for least 1 year. In July 2016, an additional questionnaire was added to collect whether the participant was a current smoker at the time of DR-TB treatment initiation based on the DR-TB medical record. However, 21.6% of participants (195 out of 900) did not have a documented smoking status from the DR-TB medical record. Thus, a history of ever smoking was used in this analysis. There was a very high correlation between the CVD risk score calculated based on ever smoking and current smoking that provided further support for this decision (p=0.9653, p<0.0001).

Ethics

The parent study was reviewed and approved by the Provincial Health Research Committee of the KwaZulu-Natal Provincial Department of Health, and the parent study and this sub-study were both approved by the Biomedical Research and Ethics Committee of the University of KwaZulu-Natal and the Institutional Review Board of the Johns Hopkins Medical Institutions.

Statistical Analysis

Statistical analysis included descriptive statistics and prevalence estimates expressed as a point prevalence and 95% confidence interval adjusting for clustering. The CVD risk score was calculated based on the algorithm of CVD risk equation and...
inputting appropriate variables.\textsuperscript{19} The CVD risk score was reported as a continuous percentage of risk and categorical risk (low <10%; moderate 10-20%; high >20% risk). CVD risk factors were compared across sex and HIV status using a chi-square test. As the CVD risk score was not normally distributed, the CVD risk score was compared across sex and HIV status using the Wilcoxon Rank Sum test. Poisson regression using generalized estimating equations to account for clustering was used to compare CVD risk factor prevalence by HIV status. The model compared participants with DR-TB only to participants with HIV co-infection, adjusting for age, sex, prior TB history, and other CVD risk factors. The models accounted for clustering of participants within healthcare centers using robust standard errors. Ordinal logistic regression was used to compare CVD risk score category (low, moderate, high) by HIV status adjusting for prior TB history and clustering. All statistical analyses were completed using STATA 14.0 (College Station, TX).

Missing data were evaluated and variables that were missing for more than 5% of the sample were height and baseline medical history for hypertension and diabetes. Height was imputed using the average height by sex and 5-year age categories for the 126 participants (14%) with no height. Baseline medical history was collected based on the medical record; 69 people (7.7%) were missing baseline medical history for hypertension and 38 (4.2%) were missing baseline medical history for diabetes. A higher percentage of participants with missing baseline history were HIV co-infected (85.1% vs 74.2%, p-value=0.037), had a lower BMI (19.5 vs. 20.97, p-value=0.017) and were all from control sites. These variables were adjusted for in the statistical models.
Results

The parent study enrolled 948 participants between November 2014 and July 2016. Of those, 900 participants were eligible for this study (Figure 1). The number of participants at each hospital varied from 23 to 163. There were slightly more males (53.7%) than females, the median age was 34.4 (IQR 28.6-42.1) and 75.1% of the sample were co-infected with HIV, see Table 1 for additional participant characteristics. Female participants had greater HIV co-infection, fewer CVD risk factors, and a lower mean CVD risk score.

CVD Risk Factors

Overall, 52.3% of participants had one or more CVD risk factors and 12.8% had two or more risk factors. Smoking data were available in 891 of 900 participants (99%) with 31.1% (n = 280) reporting a history of smoking for more than 1 year and at least 100 cigarettes in their lifetime (Table 2). Women reported smoking less frequently than men (7.3% vs 52.5%, p <0.001, n=891) but had a three times greater prevalence of elevated BMI (26.2% vs 8.3%, p<0.001, n=893).

Blood pressure data were available for 828 (92%) participants. Of these, 138 (16.7%) were classified as hypertensive based on medical history (n=63), elevated blood pressure (n=88) or a prescription for blood pressure medication (n=35). Of the 862 participants (95.7%) with complete data on diabetes status, 45 (5.2%) participants had diabetes (Table 2). Of those 45, 6 had an elevated HbA1c, 31 were on medications for diabetes, and 43 had a baseline history of diabetes. The prevalence of hypertension and diabetes did not differ by sex (hypertension: males 16.9% vs. females 16.5%, p=0.876, n=828; diabetes: males 5.2% vs females 5.3%, p=0.933, n=862).

CVD Risk Score
The non-laboratory CVD risk score was applied to the 398 participants (44.2%) who were 35 years of age or older and did not have missing data on CVD risk factors. Scores ranged from 0.92% to 49.0% with 76.6% having low risk (<10%), 15.8% had moderate risk (10-20%), and 7.5% had high risk (>20%) (Table 2). There was a statistically significant difference in the medians between males (median 5.36, IQR 3.30-9.81) and females (median 3.64, IQR 2.05-8.47) (p-value <0.001).

**Comparison by HIV Status**

When comparing individual risk factors by HIV status, HIV co-infected participants had a lower prevalence of smoking (29.4% vs 37.4%, p=0.027), hypertension (14.4% vs 23.2% p=0.003) and diabetes (3.3% vs 10.9%, p<0.001) compared with participants who were HIV-negative (Table 2). However, after adjusting for age, sex, other CVD risk factors and enrollment site, only the risk for diabetes was lower for participants with HIV co-infected participants compared with those without HIV infection (aRR 0.45, 95% CI 0.28-0.72) (Table 3). The prevalence of hypertension and smoking appeared lower for HIV co-infected patients but was due to difference in the distribution of sex, BMI, and diabetes not HIV status. HIV co-infected participants also had a lower systolic and diastolic blood pressure than HIV-negative participants although there was no difference in the number of patients with elevated blood pressure by HIV status (p=0.115)(Table 2). There was no difference in either mean BMI or BMI categories by HIV status (Table 2).

Among participants older than 35 years of age with a calculated CVD risk score, HIV-negative participants had double the CVD risk score (median 8.94, IQR 4.58-18.37) compared with co-infected participants (median 4.00, IQR 2.44-7.12) (p<0.001). There
was a higher proportion of HIV-negative participants in the high-CVD risk category (21.7% vs 3.6%). Ordinal regression was used to compare CVD risk score category by HIV status and the proportional risk assumption was met. After adjusting for prior TB history and clustering, participants with HIV co-infection had 81% reduced odds of being in the moderate- or high-CVD risk category compared with DR-TB only participants (aOR 0.19, 95% CI 0.10-0.38).

**Discussion**

This study of adults with DR-TB predominately under the age of 40 had several major findings. HIV-negative participants had almost four times the prevalence of diabetes than patients with HIV co-infection, but no differences in the risk for smoking, hypertension, and elevated BMI. Although the prevalence of diabetes and smoking were higher among HIV-negative patients in this study, the overall prevalence of the CVD risk factors was similar to SANHANES, a national survey including CVD risk factors in South Africa. The higher prevalence among HIV-negative patients may be because both smoking and diabetes increase susceptibility to TB disease. There are complex relationships between age, BMI, TB susceptibility, diabetes and HIV and further studies are needed to understand how this impacts diabetes prevalence among HIV/DR-TB co-infected patients.

Literature from high income countries suggests that people with HIV may have increased risk of hypertension, dyslipidemia, and cardiovascular related events. However, systematic reviews exploring the impact of HIV and ART on hypertension and blood pressure in sub-Saharan Africa, where people living with HIV are more likely to be female and younger than high income countries, have demonstrated mixed results and
significant heterogeneity across studies. Recent literature from sub-Saharan Africa and South Africa suggests that patients with HIV may have lower rates of hypertension and lower systolic blood pressure than patients without HIV-infection. In this study, the risk for hypertension and elevated CVD risk was not related to either HIV status or BMI, a pattern that may be similar to other sub-Saharan African context but also warrants further research. Importantly, this current analysis did not include data on how long patients had been living with HIV and did not compare by ART status. Future studies should explore how HIV infection contributes to hypertension risk in the context of other CVD risk factors and whether in this setting ART exposure increases CVD risk.

Among patients 35 years of age or greater, one in five HIV-negative patients was at high risk for having a CVD related event in the next five years. This group is potentially at very high risk for having a negative outcome given their burden of CVD risk and DR-TB disease. Thus, they are ripe for intervention both during and after DR-TB treatment. As these patients are being treated at specialty DR-TB hospitals, clinicians may not prioritize their CVD risk factors or co-morbidities even though they may have an impact on DR-TB outcomes. TB clinicians should ensure that patients with multiple co-morbidities receive appropriate treatment and management. Integration of HIV care into DR-TB care has been highly successful in South Africa; similar models to integrate non-communicable and infectious chronic care are needed to address patients’ needs from a holistic perspective.

Another finding from this study is that providers did not appear to follow South African MDR-TB National guidelines for evaluating HbA1c for all patients with diabetes, consistent with provider non-adherence to guidelines in other conditions and
settings. Only 11% of participants in this study with a reported history of diabetes had an HbA1c completed and all of them were elevated (>10%) suggesting uncontrolled diabetes. This finding suggests that providers are not ordering HbA1c for patients with diabetes putting them at risk not only for uncontrolled diabetes but also for poor TB treatment outcomes related to glycemic control. This may be because providers are concerned about the cost of the laboratory test, not aware of MDR-TB guidelines for monitoring patients with diabetics, not comfortable managing the care of diabetic patients or because patients are receiving care at another primary healthcare center. Some literature suggests that although HbA1c is a useful tool for evaluating diabetes status over a 3-month period, HbA1c may have limitations in a TB setting because HIV- or TB-related anemia may result in a lower HbA1c value. Additional research is needed to evaluate how patients with diabetes and TB should be assessed and monitored given the influence of TB and anemia on HbA1c.

In this sample of participants with DR-TB and HIV, half of participants with elevated blood pressure were not known to have hypertension, a finding similar to other studies in multiple settings. SANHANES survey in South Africa found that 15.9% of patients nationally with an elevated blood pressure had not been checked by a healthcare provider in the last year. This emphasizes the critical importance for all healthcare providers to evaluate blood pressure and risk for hypertension.

Both smoking and elevated BMI were strongly influenced by sex in this sample. Not surprisingly, men were more likely to smoke and women were more likely to be overweight or obese, a finding similar to other studies in South Africa. This points to the importance and interventions which are tailored to cultural and gender specific
messages. Smoking cessation messages given by nurses or community health workers during TB treatment may be an effective and simple method to help patients quit smoking.46

Limitations

As this is a nested study, data were limited to the variables the parent study collected. Baseline medical history addressed some potential co-morbidities and did not include history of pre-existing cardiovascular disease. In addition, one blood pressure was collected so there is no ability to validate if patients had consistently elevated blood pressure suggestive of a diagnosis of hypertension. As the parent study was a pragmatic study, vital signs were measured by hospital staff, so poor technique and measurement error may have occurred although all sites did have an automated machine. It is possible that patients with a single elevated blood pressure are over-represented in these data. However, pragmatic measures such as these are used by healthcare providers to make medical decisions including DR-TB treatment so they are clinically relevant.47 Under-diagnosis of CVD risk factors particularly hypertension and diabetes is high in sub-Saharan Africa meaning that the prevalence of CVD risk factors may be under-reported in this study.48,49 In particular, missing baseline medical history was more common among HIV co-infected participants, CVD risk factors among these patients may be more likely to be under-reported. In addition, the CVD risk score used in this study has not been specifically validated among patients living with HIV or TB, so it is unclear how sensitive it is in this population. It has been compared with other CVD risk scores in the general population in South Africa where there is a high prevalence of both HIV and TB, but further research should explore its specific use in patients with TB and HIV. Finally,
the cross-sectional design of this study precludes information on whether providers confirmed or treated any CVD risk factors.

Conclusions

Given that about 50% of patients diagnosed with DR-TB die, are lost to follow-up or develop additional resistance, it is imperative that the care of DR-TB improves.\textsuperscript{1} The treatment success rates for DR-TB will not improve unless providers and health systems address the multiple treatment and lifestyle behaviors that impact patients including CVD risk factors. The primary and secondary prevention of CVD risk factors is one component of quality patient-centered care that is paramount during and after DR-TB treatment, particularly for patients who are identified as high risk. Researchers and policy-makers need to collaborate to develop and evaluate evidence-based guidelines that providers including nurses can feasibly implement in low and middle-income countries like South Africa. Finally, additional studies are needed to better understand the trajectory of patients with DR-TB, HIV and CVD risk factors and high CVD risk to understand their treatment gaps and the impact on TB outcomes.

Acknowledgements

We would like to thank Dr. Richard Chaisson for his assistance developing and refining this research. We would also like to thank the parent study team including research assistants and nurses who assisted with data collection for this project and a huge thank you to the study participants. This research was supported by the National Institutes of Health under award number F31-NR016909 (NINR; EW), R01-AI104488 (NIAID; JF), and by Sigma Theta Tau International Research Grant (EW). The authors report no conflicts of interest.
Figure 1. Diagram for Study Flow

Assessed for eligibility (N=948)

Excluded (N=48)
- Withdrawals for minimal data (N=2)
- Ineligible for parent study (n=27)
- Patient withdrawal from study (n=2)
- Age <18 years of age (n=17)

Included in study (N=900)
Table 1. Participant Characteristics of DR-TB patients on treatment in 10 treatment hospitals in two provinces of South Africa

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=900)</th>
<th>HIV-negative (N=224)</th>
<th>HIV-positive (N=676)</th>
<th>(p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>483 (53.7)</td>
<td>148 (66.1)</td>
<td>335 (49.6)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Female</td>
<td>417 (46.3)</td>
<td>76 (33.9)</td>
<td>341 (50.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (sd)</td>
<td>36.2 (10.8)</td>
<td>36.1 (14.5)</td>
<td>36.3 (9.28)</td>
<td>(0.852)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>34.4 (28.7-42.1)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>HIV Co-infection Known ART exposure</td>
<td>676 (75.1)</td>
<td>-</td>
<td>676 (100%)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>410 (60.7)</td>
<td>-</td>
<td>410 (60.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Previous history of TB (N=884)</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>453 (51.2)</td>
<td>128 (57.7)</td>
<td>325 (49.7)</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>347 (39.3)</td>
<td>75 (33.8)</td>
<td>272 (41.7)</td>
<td>(0.101)</td>
</tr>
<tr>
<td>More than one</td>
<td>75 (8.5)</td>
<td>19 (8.6)</td>
<td>56 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Not documented # of episodes</td>
<td>9 (1.1)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Number of CVD Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>None</td>
<td>429 (47.7%)</td>
<td>92 (41.1)</td>
<td>337 (49.9)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>356 (39.6%)</td>
<td>84 (37.5)</td>
<td>272 (40.2)</td>
<td></td>
</tr>
<tr>
<td>2 +</td>
<td>115 (12.8%)</td>
<td>48 (21.4)</td>
<td>67 (9.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking History Among 280 Smokers</strong></td>
<td></td>
<td></td>
<td></td>
<td>(0.128)</td>
</tr>
<tr>
<td>Median cigarettes per day (IQR) (N=263)*</td>
<td>6 (4-10)</td>
<td>6 (4-10)</td>
<td>5 (4-10)</td>
<td></td>
</tr>
<tr>
<td>Median years smoking (IQR) (N=260)*</td>
<td>11 (6-20)</td>
<td>10 (5-18)</td>
<td>13 (6-20)</td>
<td>(0.238)</td>
</tr>
</tbody>
</table>

*Does not equal total because of missing data (cross symbol) Sample size for DR-TB/HIV co-infection for median cigarettes per days is n=183

Chi-square test for categorical variables; Students t-test for continuous variables; Wilcoxon Rank Sum test to compare median
ART: Anti-retroviral therapy; sd: standard deviation; IQR: inter-quartile range; CVD: Cardiovascular disease; DR-TB: drug-resistant tuberculosis
Table 2. CVD Risk Factor: Means/Medians & Population Prevalence Estimates by HIV Status among DR-TB patients in two provinces of South Africa

<table>
<thead>
<tr>
<th></th>
<th>Prevalence Estimate</th>
<th>Point Prevalence</th>
<th>Point Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>HIV-negative</td>
<td>HIV-positive</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>N=862</td>
<td>N=219</td>
<td>N=643</td>
</tr>
<tr>
<td></td>
<td>5.2% (3.4-8.0%)</td>
<td>10.9% (6.6-17.6%)</td>
<td>3.3% (1.8-5.9%)</td>
</tr>
<tr>
<td></td>
<td>χ²=19.540 (&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>N=828</td>
<td>N=211</td>
<td>N=617</td>
</tr>
<tr>
<td></td>
<td>16.7% (13.6-20.3%)</td>
<td>23.2% (16.3-31.9%)</td>
<td>14.4% (11.7-17.6%)</td>
</tr>
<tr>
<td></td>
<td>χ²=8.763 (0.003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood Pressure (BP)</strong></td>
<td>N=884</td>
<td>N=220</td>
<td>N=664</td>
</tr>
<tr>
<td>Systolic BP mean (sd)</td>
<td>113.60 (16.31)</td>
<td>117.20 (17.12)</td>
<td>112.41 (15.87)</td>
</tr>
<tr>
<td>Diastolic BP mean (sd)*</td>
<td>72.71 (11.73)</td>
<td>74.39 (12.83)</td>
<td>72.16 (11.30)</td>
</tr>
<tr>
<td></td>
<td>t=3.80 (&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t=2.46 (0.014)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body Mass Index (BMI)</strong></td>
<td>N=893</td>
<td>N=224</td>
<td>N=669</td>
</tr>
<tr>
<td>BMI Mean (sd)</td>
<td>20.85 (4.97)</td>
<td>20.53 (4.85)</td>
<td>20.96 (5.01)</td>
</tr>
<tr>
<td></td>
<td>t=−1.13 (0.261)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI Categories</td>
<td>N=893</td>
<td>N=224</td>
<td>N=669</td>
</tr>
<tr>
<td>Underweight (&lt;18.5kg/m²)</td>
<td>35.2% (27.0-44.3%)</td>
<td>39.7% (28.5-52.2%)</td>
<td>33.6% (26.1-42.0%)</td>
</tr>
<tr>
<td>Normal (18.5-24.9kg/m²)</td>
<td>48.3% (43.3-53.3%)</td>
<td>43.8% (34.0-54.0%)</td>
<td>49.8% (45.3-54.3%)</td>
</tr>
<tr>
<td>Overweight (25-29.9kg/m²)</td>
<td>10.1% (7.1-14.1%)</td>
<td>11.2% (6.9-17.6%)</td>
<td>9.7% (6.5-14.2%)</td>
</tr>
<tr>
<td>Obese (&gt;30kg/m²)</td>
<td>6.5% (3.9-10.6%)</td>
<td>5.4% (3.1-9.0%)</td>
<td>6.9% (3.9-11.8%)</td>
</tr>
<tr>
<td></td>
<td>χ²=3.982 (0.263)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ever Smoker</strong></td>
<td>N=891</td>
<td>N=222</td>
<td>N=669</td>
</tr>
<tr>
<td></td>
<td>31.4% (25.6-38.0%)</td>
<td>37.4% (28.7-47.0%)</td>
<td>29.4% (23.6-36.1%)</td>
</tr>
<tr>
<td></td>
<td>χ²=4.877 (0.027)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CVD Risk Score (among patients &gt;35 years of age)</strong></td>
<td>N=398</td>
<td>N=92</td>
<td>N=306</td>
</tr>
<tr>
<td>CVD Risk Score Mean (sd)</td>
<td>7.63 (7.90)</td>
<td>12.94 (10.7)</td>
<td>6.03 (6.0)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.62 (2.70, 9.47)</td>
<td>8.94 (4.58, 18.37)</td>
<td>4.00 (2.44, 7.12)</td>
</tr>
<tr>
<td></td>
<td>t=7.913 (&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>z=7.003 (&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CVD Risk Score Category</strong></td>
<td>N=398</td>
<td>N=92</td>
<td>N=306</td>
</tr>
<tr>
<td>Low (&lt;10%)</td>
<td>76.6% (69.3-82.6%)</td>
<td>52.2% (40.9-63.2%)</td>
<td>84.0% (74.2-90.5%)</td>
</tr>
<tr>
<td>Moderate (10-20%)</td>
<td>15.8% (11.7-21.0%)</td>
<td>27.2% (20.5-35.1%)</td>
<td>12.4% (7.2-20.7%)</td>
</tr>
<tr>
<td>High (&gt;20%)</td>
<td>7.5% (5.1-11.1%)</td>
<td>20.7% (12.8-31.7%)</td>
<td>3.6% (2.0-6.4%)</td>
</tr>
<tr>
<td></td>
<td>χ²=46.374 (&lt;0.001)</td>
<td></td>
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</tr>
</tbody>
</table>

Diabetes defined by medical history, prescription for diabetes medications, or elevated HbA1C; Hypertension defined by medical history, prescription for medications for hypertension, or elevated blood pressure (>140/90); Non-laboratory CVD risk score calculated based on ever smoking, age, sex, diabetes status, presence of hypertension medications, systolic blood pressure, and BMI. CVD: Cardiovascular disease

*Diastolic blood pressure was missing one additional value from the HIV-positive group so the overall n=883 and the HIV-negative n=663 (cross symbol) Chi-square test for categorical variables; Students t-test for continuous variables; Wilcoxon Rank Sum test to compare median
Table 3. Comparison of the Relative Risk of CVD Risk Factors by HIV Status among DR-TB patients in 2 provinces in South Africa

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted RR (95%CI)</th>
<th>Adjusted* aRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes (N=802)</strong></td>
<td></td>
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<tr>
<td>HIV negative (N=208)</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>HIV co-infection (N=594)</td>
<td>0.29 (0.16-0.51)</td>
<td>0.45 (0.28-0.72)</td>
</tr>
<tr>
<td><strong>Hypertension (N=802)</strong></td>
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<tr>
<td>HIV negative (N=208)</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>HIV co-infection (N=594)</td>
<td>0.62 (0.45-0.86)</td>
<td>0.86 (0.72-1.03)</td>
</tr>
<tr>
<td><strong>Elevated Body Mass Index (N=802)</strong></td>
<td></td>
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</tr>
<tr>
<td>HIV negative (N=208)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>HIV co-infection (N=594)</td>
<td>0.97 (0.66-1.40)</td>
<td>0.95 (0.69-1.31)</td>
</tr>
<tr>
<td><strong>Ever Smoker (N=802)</strong></td>
<td></td>
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<tr>
<td>HIV negative (N=208)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>HIV co-infection (N=594)</td>
<td>0.78 (0.63-0.97)</td>
<td>0.93 (0.78-1.12)</td>
</tr>
</tbody>
</table>

*Adjusted for sex, age, prior history of TB, enrollment site, and other CVD risk factors (diabetes, ever smoking, hypertension, and elevated body mass index)

Diabetes defined by medical history, prescription for diabetes medications, or elevated HbA1C; Hypertension defined by medical history, prescription for medications for hypertension, or elevated blood pressure (>140/90mmHg); Elevated BMI defined ≥25kg/m²; Ever smoking defined as >100 cigarettes in a lifetime and >1 year of smoking. CVD: Cardiovascular disease
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increased mortality during tuberculosis treatment: A prospective cohort study


Burden of undiagnosed hypertension in sub-saharan Africa: a systematic review
Chapter 3: Cardiovascular Disease risk burden as a predictor of early treatment outcome of patients co-infected with HIV and multi drug-resistant tuberculosis: a nested prospective cohort study

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Total words: 4660

Key Words: Diabetes, Smoking, Cardiovascular Disease Risk Score, MDR-TB
Abstract

Setting: South Africa has the highest incidence of multi-drug resistant tuberculosis (MDR-TB) and HIV co-infection in sub-Saharan Africa. As only 54% of patients successfully complete MDR-TB treatment, it is critical to identify risk factors for poor treatment outcome. Cardiovascular disease (CVD) risk factors are common in South Africa and CVD risk factors such as diabetes and smoking have known negative impacts on MDR-TB treatment outcomes.

Objective: The purpose of this study is to explore the impact of individual CVD risk factors (i.e. diabetes, smoking, body mass index [BMI] and hypertension) and a calculated CVD risk score on early MDR-TB negative treatment outcomes (i.e. death, lost to follow-up and treatment failure) among patients co-infected with HIV.

Design: This prospective cohort study is nested within an ongoing cluster randomized trial of nurse case management at 10 MDR-TB hospitals in Eastern Cape and KwaZulu-Natal provinces of South Africa. The parent study enrolled 948 patients between November 2014 and July 2016; 443 were eligible for this cohort study.

Results: Participants had a median age of 35.1 years, 52.7% were male, 62% had exposure to anti-retroviral therapy, 52.4% had a prior history of TB, and the median CD4 count was 188 cells/µL. The prevalence of CVD risk factors was 2.4% for diabetes, 13.5% for hypertension, 16.4% for elevated BMI and 28.8% for ever smoking. Elevated BMI was protective for early negative MDR-TB treatment outcome (aHR=0.42, 95% CI 0.23-0.75) and underweight BMI increased the risk of poor outcome (aHR=1.51, 95% CI 1.24-1.82). Of the 210 patients over 35 years of age, a high or moderate CVD risk score
was predictive of MDR-TB negative treatment outcome compared with a low CVD risk score (aHR=4.52, 95% CI 1.91-10.70).

**Conclusion:** In this sample, patients with a moderate or high CVD risk score had greater risk of a negative MDR-TB treatment outcome. Providers and researchers should better understand the role of CVD risk factors in poor MDR-TB outcomes to improve MDR-TB treatment outcomes.
Introduction

South Africa, like many low and middle-income countries, experiences a trifecta of tuberculosis (TB), HIV and cardiovascular disease (CVD) along with related risk factors increasing morbidity and mortality.\textsuperscript{1,2} Tuberculosis remains the leading cause of death in South Africa, but diabetes, cerebrovascular disease and other cardiovascular diseases follow closely in succession; among women, diabetes has overtaken tuberculosis as the leading cause of death.\textsuperscript{2} Multi-morbidity, the prevalence of two or more chronic conditions, has been described most extensively in relation to CVD risk factors, while this conceptualization of disease burden is less frequently identified in the HIV and TB literature.\textsuperscript{3}

The influence of cardiovascular risk and the potential impact in patients with TB and multi drug-resistant tuberculosis (MDR-TB), a form of tuberculosis resistant to first line medications, is not well described. Given the duration, associated adverse drug reactions and poor treatment outcomes with treatment for MDR-TB, it is imperative that all comorbid conditions that worsen the patient experience be identified and managed. MDR-TB treatment regimens in South Africa are evolving; newer short course regimens may require only 9 months of treatment, while longer 18 to 20-month regimens are still used for some patients.\textsuperscript{1,4} Approximately 54% of patients complete treatment and treatment outcomes remain poor.\textsuperscript{1,5} Seventy percent of patients with MDR-TB are also co-infected with HIV and those patients are twice as likely to have a poor treatment outcome.\textsuperscript{1,5,6} Studies have demonstrated that diabetes, smoking and HIV individually increase risk of negative MDR-TB & TB treatment outcomes.\textsuperscript{7–9} However, it is unknown whether cardiovascular multi-morbidity may have a multiplicative effect on treatment outcomes given the intersection of these conditions.
Evaluating a patient’s cardiovascular risk may be one tool to assess the complexity and potential for adverse events during MDR-TB treatment. Gaziano et al. developed a non-laboratory based CVD risk score that assess a person’s five-year risk of having a CVD related event or death that has been validated in a South Africa population.\textsuperscript{10,11} This score has been used in several low and middle income countries where community health workers have implemented it for screening purposes.\textsuperscript{12} Calculating this CVD risk score may be one way that clinicians can identify MDR-TB and HIV co-infected patients at higher risk for CVD related morbidity and mortality and potentially poor MDR-TB treatment outcomes.

To our knowledge, there have been no studies which explore the impact of cardiovascular risk in an MDR-TB population co-infected with HIV. The purpose of this study was to explore the impact of CVD risk factors and elevated CVD risk score on short-term MDR-TB treatment outcomes by describing (1) the impact of individual and a combination of CVD risk factors on 6-month MDR-TB negative treatment outcomes: death, lost to follow-up or treatment failure; (2) the impact of a non-laboratory CVD risk score on 6-month MDR-TB negative treatment outcomes; and (3) if social determinants of health moderate the relationship between the non-laboratory CVD risk score and 6-month MDR-TB negative treatment outcome.

**Methods**

*Study design*

This prospective cohort study was nested within a larger cluster randomized trial of nurse case management to improve MDR-TB treatment outcomes in Eastern Cape and KwaZulu-Natal provinces of South Africa (i.e., parent study).\textsuperscript{13} Meanwhile, this study
was guided by the World Health Organization (WHO) Innovative Care for Chronic Conditions model as modified by Oni et al.\textsuperscript{14,15} This model posits that multi-morbidity, in the context of non-communicable and infectious chronic conditions, impacts the health of patients, families, and communities through biologic, patient, provider, and system processes.\textsuperscript{14}

\textit{Parent Study Setting and Enrollment}

The parent study enrolled participants in 10 public MDR-TB hospitals chosen because they followed national MDR-TB treatment guidelines, had an established MDR-TB program for more than 6 months and had access to HIV treatment on-site. These hospitals were randomized by location and size to a nurse case management intervention, described by Farley et al.\textsuperscript{13} Four hospitals were small, treating less than 150 patients per year and six were large, treating more than 150 patients per year. Five were urban/peri-urban and five were rural. Participants in the parent study include individuals 13 years of age and older, receiving care at a participating center and who was willing to provide informed consent. Participants were excluded from the parent study if they started MDR-TB treatment at a different facility or were enrolled in another clinical trial that impacted their HIV or MDR-TB treatment regimen.

\textit{Prospective Cohort Sample}

For this prospective cohort, we selected participants who were at least 18 years of age and enrolled in the parent study between November 2014 and July 2016. Patients also had to have microbacterially confirmed MDR-TB, HIV co-infection and remained in the parent study for follow-up. Participants who transferred to another MDR-TB facility
during treatment, had baseline drug sensitive TB or additional resistant patterns demonstrating fluoroquinolone and/or aminoglycoside resistance were excluded from the parent study follow-up and thus this analysis. This study focused on participants co-infected with HIV and MDR-TB as HIV is a strong predictor of negative MDR-TB treatment outcome and the purposes of this study was to explore the additional impact of CVD risk factors.

**Study Procedures**

All data were collected and confirmed from the parent study database except current smoking status which was a single question abstracted from the medical record. At parent study baseline, all patients were interviewed to obtain socio-demographic data. Data were also collected through medical chart review and the National Health Laboratory System online laboratory portal. Outcome information was recorded by study staff and confirmed by the authors. Parent study data were collected on paper-based case report forms. After a comprehensive quality assurance process by senior research team members, case report forms were scanned and manually entered into the REDCap online data system. Data queries were developed for each site and resolved before the baseline record was complete.

**Measures**

CVD risk factor data were obtained from the parent study data based on medical chart review. Diabetes was determined based on baseline medical history, prescription of medications for diabetes or Hemoglobin A1C (HbA1c) >6.5% according to South African guidelines. Hypertension was defined based on South African guidelines as baseline
systolic pressure greater than 140 mm/Hg or diastolic pressure greater than 90 mm/Hg, prescription of blood pressure medications or baseline medical history.\textsuperscript{18} BMI categories were based on International and South African guidelines: underweight < 18.5 kg/m\textsuperscript{2}, normal 18.5-24.99kg/m\textsuperscript{2}, overweight 25-29.99kg/m\textsuperscript{2}, obese >30 kg/m\textsuperscript{2}.\textsuperscript{19,20} Smoking status was collected based on lifetime smoking so an additional question was added to the parent study to assess current smoking status, based on medical record review. However, because 19.2\% of “current smoking” status data were missing the decision was made to use “ever smoked” in this analysis. The non-laboratory based CVD risk score was calculated based on age, sex, smoking status, diagnosis of diabetes, systolic blood pressure, whether on treatment for hypertension and BMI, and predicts 5-year CVD morbidity and mortality.\textsuperscript{10}

Alcohol use was asked based on the Audit-C which has been validated in patients with HIV in South Africa and sub-Saharan Africa.\textsuperscript{21-23} HIV related variables included anti-retroviral therapy (ART) status and baseline CD4 count, a measure of immune status. Creatinine clearance was estimated using the Cockcroft-Gault formula which has been validated in South Africa and was used by the parent study.\textsuperscript{24} Measures of the social determinants of health included access to government grant assistance, employment, and access to mobile phones and internet. Treatment burden was measured with the number of medications (poly-pharmacy) on the day of treatment initiation. Health system variables included the province where the MDR-TB center was located and whether the hospital was an intervention or control site, as the intervention’s goal was to improve patient outcomes.
The outcome variable was time to any MDR-TB negative treatment outcome (i.e. death, lost to follow-up or treatment failure) censored at 6-months because this is the period of greatest death in MDR-TB treatment. A negative treatment outcome was defined as death, loss to follow-up, or treatment failure as defined by the South African and WHO guidelines. Treatment failure also included development of additional resistance patterns after baseline as defined by the parent study. The date of loss to follow-up was counted as the day after the date that the patient was last seen at a MDR-TB clinic.

_Ethics_

The parent study was reviewed and approved by the Provincial Health Research Committee of the KwaZulu-Natal Provincial Department of Health, and the parent study and this sub-study were both approved by the Biomedical Research and Ethics Committee of the University of KwaZulu-Natal and the Institutional Review Board of the Johns Hopkins Medical Institutions.

_Power analysis_

The study was powered based on the proposed analysis for exploring the impact of the non-laboratory CVD risk score on 6-month MDR-TB negative treatment outcomes. A power analysis was conducted with PASS (v.14, Kaysville, TN) by varying the inter-class correlation (ICC) to account for clustered data, effect size and sample size. The proportion of people with a negative outcome was estimated at 40% for the low CVD risk group based MDR-TB outcomes in South Africa. The prevalence of elevated CVD risk was set at 20% based on previous literature of the prevalence of elevated CVD risk using this risk score in South Africa; the ICC varied from 0.02 to 0.04 based on other
cluster randomized controlled trials of TB patients in South Africa. Based on power of 0.80, a sample size of 450 was sufficient to detect an OR of 1.50 when the ICC is 0.04.

**Statistical analysis**

Statistical analysis included descriptive statistics including the prevalence of CVD risk factors and the non-laboratory CVD risk score. Cox Proportional Hazard modeling was used with robust standard errors to account for clustering to explore the impact of CVD risk on time to negative outcome. Initially, bivariate analysis was conducted to examine the impact of each individual CVD risk factor on time to negative treatment outcome and estimate effect size. Next, all CVD variables were entered into a multi-variable model, to account for the multicollinearity of the individual risk factors and to understand the unique contribution of each risk factor to negative outcomes. Bivariate analysis was conducted on potential confounders including age, baseline CD4 count, antiretroviral therapy (ART) status, alcohol use, non-CVD related co-morbidities such as epilepsy and intervention group assignment to assess their relationship with MDR-TB negative treatment outcome. A final model included all CVD risk factors and covariates that were statistically significant (p<0.05) in bivariate analysis. Cox Proportional hazard with robust standard errors was also used to explore hazard ratios for the time to negative outcome with CVD risk score as a primary predictor both as a continuous and dichotomous variable (low vs. mod/high risk) adjusting for co-variates significant with a p-value <0.05 in bivariate analysis. As smoking is a significant and modifiable CVD risk factor, one aim of this study was to test whether smoking impacted the relationship between the individual CVD risk factors and MDR-TB negative treatment outcome using interaction terms between smoking and individual CVD risk factors. However, the low
prevalence of CVD risk factors and a low prevalence of negative outcome (19%) lead to an insufficient sample size to perform this analysis.

The final aim of this study was to explore if social determinants of health moderated the relationship between elevated CVD risk score and treatment outcomes. For this analysis, social determinants of health included: receipt of governmental grant assistance, access to mobile phone or internet at home and employment status. As multimorbidity is associated with lower socioeconomic status in South Africa, it was hypothesized that the impact of CVD risk score on time to negative treatment outcome would be greater for patients receiving grant assistance, having no access to internet or mobile phone access, and who were unemployed compared with patients who did not have these characteristics.\textsuperscript{31,32} However, the low prevalence of moderate or high CVD risk and few negative outcomes contributed to an insufficient sample size to be able to complete this interaction analysis.

Significant data on diabetes and hypertension were missing in the baseline medical history. To assess whether there were systematic differences between those who had missing data and those who did not, a comparison was done on key baseline variables between patients with and without missing data. Missing baseline medical history (n=41) to those with complete baseline medical history for diabetes and hypertension (n=401). There were no differences based on sex, age, ART status, smoking status and blood pressure. Patients with missing baseline history data had a lower BMI (19.5kg/m\textsuperscript{2} vs 21.2kg/m\textsuperscript{2}, t=1.97, p=0.0493, n=435). All missing data were from control sites (N=41) and the majority were from control sites with smaller enrollments (92.7% vs 7.3%, $\chi^2=53.3$, p<0.0001). In addition, creatinine and CD4 was not checked at baseline on 37
(8.4%) and 55 (12.4%) participants respectively. There were differences in age, sex, ART status, and enrollment site among patients who had a CD4 completed at baseline compared with those without a baseline CD4. Patients who did not have a creatinine done at baseline were more often from control sites and the Eastern Cape Province and had a higher percentage of prior TB, higher systolic blood pressure and higher BMI compared with those who had a creatinine done at baseline. To understand the impact of this systematic missingness, a sensitivity analysis was conducted comparing models adjusting for all co-variates related to missingness. There was no difference in the interpretation of results, so the final model only included variables significant in the bivariate analysis.

**Results**

Between November 2014 and July 2016, the parent study enrolled 948 participants across 10 MDR-TB hospitals. Of those, 900 were eligible to be assessed for additional inclusion criteria for this analysis; 442 patients were included, see Figure 1. The number of participants from each hospital ranged from 11 to 80. There were slightly more males than females, 52.5% to 47.5%, and the median age was 35.1 years of age, see Table 1 for participant characteristics. All patients were co-infected with HIV and 62.0% had known exposure to anti-retroviral therapy (ART). Of the 387 patients with a CD4 count available within one week of treatment initiation, over 50% of patients had a CD4 count below 200 cells/µL (Median=188.0) and 30% had a CD4 count of 100 cells/µL or below. Most of the sample, 67.6%, had a normal creatinine clearance (>90 ml/min/1.73m²) and 47.6% had no previous history of TB. 52.8% were unemployed at the time of MDR-TB treatment initiation. While 90.5% of participants had access to a
mobile phone at home, only 17.2% had internet access at home and most of those (91.7%) had access through their mobile phone. Out of 442 participants, 84 (19.0%) had a negative outcome before 6 months: 43 (9.7%) died, 35 (7.9%) were lost to follow-up, and 6 (1.4%) developed additional resistance patterns (treatment failure). The median time to negative outcome was 84 days (IQR 36.5-116.5).

[Table 1. Participant characteristics]

Smoking was the most common CVD risk factor with 126 (28.8%) patients ever smoking out of 437 patients with available smoking data, see Table 2. Smoking was significantly more common in males than females, 48.7% and 6.8% respectively ($\chi^2=93.36$, p= <0.0001). Among patients with available data, the prevalence of diabetes was 2.4%, hypertension was 13.5% and elevated BMI was 16.4%, see Table 2. Overall, the non-laboratory CVD risk score was low with 86.2% of patients having a score <10% indicating low risk of a CVD related event in 5 years.

[Table 2. CVD Risk factor prevalence]

The impact of individual CVD risk factors on the risk for negative outcome was evaluated using Cox Proportional Hazard models. Due to a low prevalence of diabetes and negative outcomes, diabetes was not included in the final model. Patients with an underweight BMI had a 51% greater risk of MDR-TB negative treatment outcome compared to those with a normal BMI (aHR=1.51, 95% CI 1.24-1.83). However, patients with an elevated BMI (overweight or obese) had a 58% reduced risk of MDR-TB negative treatment outcome compared to those with a normal BMI (aHR=0.42, 95% CI 0.23-0.75), see Table 3 and Figure 2. Having a prior history of TB, lower creatinine clearance, CD4 count below 200 cells/µL, being unemployed and obtaining treatment in
the Eastern Cape all increased the risk of negative outcome in bivariate analysis, see
Table 3. After adjusting for other covariates, CD4 count below 200 cell/µL (aHR=1.82,
95% CI 1.24-2.68) and creatinine clearance below 30 m/min/1.73 m² (aHR=8.75, 95% CI
3.75-20.34) were still statistically significant. Having access to a mobile phone and
receiving government assistance decreased the risk of a negative MDR-TB treatment
outcome but these relationships did not remain statistically significant after adjusting for
other variables. Alcohol use followed a U-shaped curve so that light drinking was
associated with a decrease risk in negative outcome compared to no alcohol use
(aHR=0.25, 95% CI 0.09-0.71) while heavy alcohol use was associated with an increased
risk of negative outcome compared to no alcohol use although this was not statistically
significant (HR=1.16, 95% CI 0.69-1.95).

[Table 3. CVD Risk Factors & MDR-TB Negative Treatment Outcome]

[Figure 2. KM Cumulative Proportion & BMI Category]

As the non-laboratory CVD risk score is only valid for patients 35-74 years of
age, it was applied to the 210 patients 35 years of age or older for whom complete data
were available for all variables needed to compute the score. The relationship between
MDR-TB negative treatment outcome and the CVD risk score was explored with CVD
risk as a continuous score and dichotomized as low risk compared to moderate and high
risk as there were only 7 people in the high-risk category. Age and sex were not included
in this model as they were accounted for in the calculation of the CVD risk score. As a
continuous score, there was a 5% increased risk of MDR-TB negative treatment outcome
for a one-point increase in the CVD risk score (aHR=1.05, 95% CI 1.01-1.09) after
adjusting for CD4 count, unemployment, mobile phone access, and receipt of government
grant assistance, see Table 4. When comparing participants with high or moderate CVD risk scores to low CVD risk scores, participants with moderate/high risk were 4.5 times more likely to have an MDR-TB negative treatment outcome (aHR=4.52, 95% CI 1.91-10.70) compared with those at low risk for a CVD related event after adjusting for CD4 count, unemployment, mobile phone access, grant assistance and clustering, see Table 4 and Figure 3. In the final model, having a low CD4 <200cells/µL and being unemployed increased the risk of MDR-TB negative treatment outcome, while having a mobile phone access (CVD risk as a continuous variable only) and receiving government grant assistance reduced the risk of MDR-TB negative treatment outcome.

[Table 4. CVD Risk Score & MDR-TB Negative Treatment Outcome]

[Fig 3. KM for CVD Risk Category]

**Discussion**

In this study of patients with MDR-TB and co-infection with HIV, patients who were underweight (BMI <18.5kg/m²) had a 51% increased risk of MDR-TB negative treatment outcome at 6-months, a well-known phenomenon for MDR-TB and TB patients. Elevated BMI was protective, reducing the risk of a MDR-TB negative treatment outcome by 58%, a finding similar to a study in South Africa of TB outcomes by Hanrahan et al. In this analysis, diabetes, smoking, and hypertension were not associated with MDR-TB negative treatment outcome although smoking and diabetes are known risk factors for poor MDR-TB/TB outcomes. There are several possible explanations for these findings. First the prevalence of diabetes was very low in this sample, so this study was not powered to explore the impact of diabetes on MDR-TB negative treatment outcome. Smoking was related to BMI so that patients who smoked
were more likely to be underweight than non-smokers (42.1% vs 27.3%). It may be that the impact of smoking was muted by the stronger effect of BMI on early MDR-TB negative treatment outcomes. In addition, smoking was measured by a history of smoking not current smoking which may have reduced the impact of smoking on early MDR-TB negative treatment outcome. This study only explored MDR-TB treatment outcomes at 6-months so the impact of risk factors such as diabetes may be stronger on more distal outcomes. In addition, as this was a composite outcome, this may have muted some of the impact of risk factors on specific negative outcomes. For example, diabetes increases the risk of death through inflammatory pathways, but it may be that hypertension could increase the risk of lost to follow-up because of the increased burden of disease management for these patients. Future studies are needed to follow patients beyond 6-month outcomes and to explore the impact of CVD risk factors on specific negative outcomes.

Among patients 35 years of age or greater, the non-laboratory CVD risk score suggested that being in a moderate or high CVD risk category predicted poorer MDR-TB treatment outcome at 6-months. Patients with a moderate or high CVD risk score were older, had more smoking, had more diabetes and a high systolic blood pressure, but there was no difference in BMI, ART status or sex between patients with low CVD risk score and moderate/high CVD risk score. It may be that while age, smoking, diabetes, and hypertension individually did not contribute significantly to the risk of MDR-TB negative treatment outcome, that the combination of these risk factors led to an increased CVD risk score had an overall effect on poor outcome.
Both low CD4 count (below 200 cells/µL) and low creatinine clearance were strong predictors of MDR-TB negative treatment outcome at 6-months in this sample. Patients with creatinine clearance values suggestive of severe renal impairment (<30 mL/min/1.73m²) were almost nine times more likely to have a negative outcome, but even moderately low creatinine clearance led to an increased risk of negative outcome. Lower creatinine clearance was also associated with CVD risk category; 6.6% of patients with moderate or high CVD risk had a normal creatinine clearance (>90mL/min/1,73m²) compared with 93.4% in the low CVD risk group ($\chi^2(1)=17.625, p=0.001$). Although this study did not differentiate between chronic and acute kidney failure, poor renal function increases CVD risk, reinforcing the complexity of these relationships on negative outcome. Patients with a low CD4 count were almost twice as likely to have a negative outcome than those with a CD4 count greater than 200 cells/µL, a finding very similar to other literature.27,35 Interestingly, patients with elevated CVD risk were more likely to have a higher CD4 count even though there was no difference by ART status. This could be because patients with elevated CVD risk were older and had been on ART for longer and have improved viral suppression. In this sample, 10% of patients did not have a creatinine or creatinine clearance drawn at baseline and 14% did not have a CD4 count available at baseline or up to 6-months prior to the start of MDR-TB treatment. Given this strong relationship to negative outcome, it is critical that providers order baseline labs to identify high risk patients and to prescribe correct dosing of MDR-TB treatment as doses must be adjusted for poor renal function.

ART exposure did not influence the risk of MDR-TB negative treatment outcome at 6-months. Previous studies have also demonstrated mixed results about the
relationship between ART and MDR-TB negative treatment outcomes among HIV co-infected patients.\textsuperscript{27,38} However, a recent study by Brust et al. suggested that concurrent ART and MDR-TB treatment could improve treatment success among HIV co-infected patients, most of whom were on ART at MDR-TB treatment initiation.\textsuperscript{39} In this sample, 62\% of patients had exposure to ART but this does not reflect whether a patient was actively taking ART at MDR-TB treatment initiation, how long they had been taking ART, nor which ART regimen. Future studies should explore whether the total time of ART exposure may impact the risk of MDR-TB negative treatment outcome.

Previous literature suggests that patients with multi-morbidity may have increased risk for poor socio-economic status which could impact MDR-TB negative treatment outcomes.\textsuperscript{40} In this study, patients in the moderate or high CVD risk category were more likely to be employed compared with those in the low risk group. This may be because these patients are older so have more economic stability or it could be a spurious finding due to low sample size. Among patients 35 years of age or greater, social factors such as unemployment or having grant assistance influenced the risk for having a negative outcome. Patients are eligible for this grant based on HIV and MDR-TB diagnosis in addition to low income so obtaining grant assistance prior to MDR-TB treatment initiation may reflect a person’s access to social services. This study was underpowered to explore whether these risk factors would influence the relationship between CVD risk factors and CVD risk score on MDR-TB negative treatment outcome. Future studies are needed to explore why and how social factors influence outcomes and whether they might mediate the relationship between risk factors such as diabetes or low CD4 count and negative MDR-TB treatment outcomes.
Limitations

There were four major limitations for this analysis: sample size, missing and pragmatic data, limited follow-up time and the lack of validation for the CVD risk score. Based on the power analysis, this study was largely underpowered. Although there were 676 HIV co-infected patients, 233 (33%) were ineligible for this study because they were a withdrawal from the parent study because the participant was determined to have baseline drug-sensitive TB, fluoroquinolone and/or aminoglycoside resistance, or transferred facilities. Low prevalence of CVD risk factors and a 20% prevalence of negative outcome also contributed to an underpowered analysis. There were also significant missing data of baseline measures which limited the sample size for analysis. Some of this missing data such as creatinine clearance and CD4 count reflects a lack of adherence to MDR-TB guidelines for ensuring that patients have baseline labs, an important finding. For baseline medical history, patients with and without missing data were compared to adjust for possible difference in the analysis. Current smoking was not used in this analysis because of significant missing data. The non-laboratory CVD risk score was calculated using current smoking and ever smoking for a sub-set with both variables and there was a high correlation between the two scores (rho=0.958, p<0.0001). In addition, patients with TB are known to stop smoking at the onset of symptoms, so ever smoking may be a more accurate measure of smoking status and risk. However, this may have weakened the effect of smoking on MDR-TB negative treatment outcome in this sample.

CVD risk factor data were collected based on pragmatic measures collected in the clinic so there may be error in these measurements. However, treatment decisions such as MDR-TB treatment dosing are made based on these measurements, so they are
important clinical results and contribute to the generalizability of these findings. In addition, this analysis only followed patients for negative outcome within the first 6-months of MDR-TB treatment. While this is the period of greatest death, a short follow-up time may be too short to see the impact of cardiovascular risk on patients with HIV co-infection. Finally, the non-laboratory CVD risk score has not been validated specifically in patients with TB and/or HIV, so this score may incorrectly categorize patients with these conditions. However, the score was compared with other CVD risk equations in a large South African population where TB and HIV are prevalent.

**Conclusion**

While the overall prevalence of individual CVD risk factors was low, this study presents preliminary yet intriguing data about the role of CVD risk factors and elevated CVD risk score on MDR-TB negative treatment outcome within the first 6-months. The non-laboratory based CVD risk tools may help providers identify patients at higher risk for MDR-TB negative treatment outcomes. However, the results of this study need confirmation in a study where the impact of CVD risk factors on negative outcome are adequately powered and can explore the intersecting relationship between CVD risk, renal function, and social factors. The risk of MDR-TB negative treatment outcome remains as high as 54% and typically higher among patients co-infected with HIV. Providers and health systems will not improve treatment outcome for MDR-TB unless the influence of CVD risk factors are better understood and managed. Future studies should continue to explore CVD risk factors and multi-morbidity among patients with infectious diseases such as TB and HIV. As the prevalence of CVD risk factors is increasing in South Africa and globally alongside chronic infectious diseases, it is critical
that researchers and clinicians approach patients as central to their care and in the context of their daily lives.

Acknowledgements

We would like to thank Dr. Richard Chaisson for his assistance developing and refining this research. We would also like to thank the parent study team including research assistants and nurses who assisted with data collection for this project and a huge thank you to the study participants. This research was supported by the National Institutes of Health under award number F31-NR016909 (NINR; EW), R01-AI104488 (NIAID; JF), and by Sigma Theta Tau International Research Grant (EW). The authors report no conflicts of interest.
Assessed for eligibility at baseline (N=948)

Assess for eligibility for follow-up (N=900)

Followed for 6-month MDR-TB negative outcome: death, lost to follow-up or treatment failure (N=442)

Excluded (n=48)
- Withdrawals for minimal data (n=2)
- Ineligible for parent study (n=27)
- Patient withdrawal from study (n=2)
- Age <18 years (n=17)

Excluded (n=458)
- HIV-negative (n=224)
- Not followed in parent study (n=234)

Figure 1. CONSORT Study Flow Diagram
Table 1. MDR-TB/HIV Co-infected Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristics (n=442)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>232 (52.5)</td>
</tr>
<tr>
<td>Female</td>
<td>210 (47.5)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (sd)</td>
<td>36.5 (9.0)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>35.1 (30.1-41.5)</td>
</tr>
<tr>
<td><strong>HIV Co-infection</strong></td>
<td></td>
</tr>
<tr>
<td>Known ART exposure</td>
<td>442 (100)</td>
</tr>
<tr>
<td><strong>Previous history of TB Disease (n=429)</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>204 (47.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>225 (52.5)</td>
</tr>
<tr>
<td><strong>Number of CVD Risk Factors</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>224 (50.7)</td>
</tr>
<tr>
<td>1</td>
<td>181 (41.0)</td>
</tr>
<tr>
<td>2 +</td>
<td>37 (8.4)</td>
</tr>
<tr>
<td><strong>CD4 Count (n=387)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (sd)</td>
<td>241.6 (213.9)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>188.0 (78-329)</td>
</tr>
<tr>
<td><strong>Creatinine Clearance (n=405)</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;90mL/min/1.73m²</td>
<td>274 (67.6)</td>
</tr>
<tr>
<td>60-90mL/min/1.73m²</td>
<td>90 (22.2)</td>
</tr>
<tr>
<td>30-60mL/min/1.73m²</td>
<td>34 (8.4)</td>
</tr>
<tr>
<td>&lt;30mL/min/1.73m²</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td><strong>Alcohol Use (n=438)</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>256 (58.5)</td>
</tr>
<tr>
<td>Low/Moderate Use</td>
<td>41 (9.4)</td>
</tr>
<tr>
<td>High Use</td>
<td>141 (32.2)</td>
</tr>
<tr>
<td><strong>Poly-pharmacy (n=439)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (sd)</td>
<td>10.4 (2.9)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>10 (8-12)</td>
</tr>
<tr>
<td><strong>Internet available at home (n=425)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>73 (17.2)</td>
</tr>
<tr>
<td><strong>Mobile phone available at home (n=440)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>398 (90.5)</td>
</tr>
<tr>
<td><strong>Unemployment (n=441)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>233 (52.8)</td>
</tr>
<tr>
<td><strong>Receipt of government grant assistance (n=441)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>104 (23.6)</td>
</tr>
</tbody>
</table>

*Does not equal 442 due to missing data
^Does not equal 442 because some patients did not have CD4 or creatinine done at baseline
Sd: standard deviation; IQR: inter-quartile range; ART: anti-retroviral therapy; CVD: cardiovascular disease; polypharmacy defined as the number of medications given to the patient on the date of MDR-TB treatment initiation
Table 2. Cardiovascular risk factor prevalence among patients with MDR-TB and HIV co-infection

<table>
<thead>
<tr>
<th>Prevalence (n=442)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (n=419)</td>
<td>10 (2.4)</td>
</tr>
<tr>
<td>Hypertension (n=401)</td>
<td>54 (13.5)</td>
</tr>
<tr>
<td>Elevated Body Mass Index (n=435)</td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5kg/m^2)</td>
<td>137 (31.5)</td>
</tr>
<tr>
<td>Normal (18.5-24.99 kg/m^2)</td>
<td>227 (52.2)</td>
</tr>
<tr>
<td>Overweight (&gt;25-29.99kg/m^2)</td>
<td>39 (9.0)</td>
</tr>
<tr>
<td>Obese (&gt;30kg/m^2)</td>
<td>32 (7.4)</td>
</tr>
<tr>
<td>Ever Smoker (n=437)</td>
<td>126 (28.8)</td>
</tr>
<tr>
<td>Smoking History among smokers (n=126)</td>
<td></td>
</tr>
<tr>
<td>Median cigarettes per day (IQR) (n=118)</td>
<td>5 (4-9)</td>
</tr>
<tr>
<td>Median years smoking (IQR) (n=115)</td>
<td>13 (6-20)</td>
</tr>
<tr>
<td>CVD Risk Score Categories (n=210)</td>
<td></td>
</tr>
<tr>
<td>Low Risk (&lt;10%)</td>
<td>181 (86.2)</td>
</tr>
<tr>
<td>Moderate/High Risk (&gt;10%)</td>
<td>29 (13.8)</td>
</tr>
<tr>
<td>CVD Risk Score (n=210)</td>
<td></td>
</tr>
<tr>
<td>Mean (sd)</td>
<td>5.8 (5.9)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3.9 (2.3-6.8)</td>
</tr>
</tbody>
</table>

~ Does not equal 442 because of missing data;  
^ Does not equal 126 because of missing data;  
* Among patients >35 years of age  
Diabetes defined by medical history, prescriptions, or HbA1C>6.5; Hypertension defined by medical history, prescriptions, or elevated blood pressure >140/90 mm/Hg; Ever smoked defined as >100 cigarettes/lifetime and >1 year of smoking at least daily. BMI categorized as underweight <18.5 kg/m^2, normal 18.5-24.99 kg/m^2, overweight 25-29.99 kg/m^2 and obese >30kg/m^2. CVD: cardiovascular disease.
<table>
<thead>
<tr>
<th>Variable (n)</th>
<th>Bivariate models HR (95%CI)</th>
<th>Model with only CVD Risk Factors aHR (95% CI) (N=394)</th>
<th>Adjusted Model aHR* (95% CI) (N=324)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (n=401)</td>
<td>1.26 (0.62-2.55)</td>
<td>1.61 (0.74-3.47)</td>
<td>1.07 (0.54-2.17)</td>
</tr>
<tr>
<td>BMI (n=435)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n=227)</td>
<td>1.00</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Underweight (n=137)</td>
<td>1.86 (1.45-2.38)</td>
<td>1.86 (1.46-2.35)</td>
<td>1.51 (1.24-1.83)</td>
</tr>
<tr>
<td>Elevated (n=71)</td>
<td>0.51 (0.25-1.04)</td>
<td>0.33 (0.16-0.70)</td>
<td>0.42 (0.23-0.75)</td>
</tr>
<tr>
<td>Ever Smoker (n=437)</td>
<td>1.27 (0.83-1.96)</td>
<td>1.07 (0.68-1.69)</td>
<td>0.75 (0.55-1.03)</td>
</tr>
<tr>
<td><strong>Covariates</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (n=442)</td>
<td>1.01 (0.98-1.03)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ART exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown/None (n=168)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Known (n=274)</td>
<td>1.03 (0.64-1.65)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex (n=442)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=232)</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female (n=210)</td>
<td>0.62 (0.33-1.16)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD4 Count (n=387)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=200 cells/µL (n=181)</td>
<td>1.00</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;200 cells/µL (n=206)</td>
<td>2.16 (1.44-3.25)</td>
<td>-</td>
<td>1.82 (1.24-2.68)</td>
</tr>
<tr>
<td>Prior history of TB (n=429)</td>
<td>1.41 (1.01-1.96)</td>
<td>-</td>
<td>0.83 (0.54-1.26)</td>
</tr>
<tr>
<td>Co-morbidities (n=442)</td>
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<td></td>
</tr>
<tr>
<td>None (n=406)</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1 or more (n=36)</td>
<td>1.51 (0.81-2.82)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Polypharmacy (n=439)</td>
<td>1.08 (0.98-1.20)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Creatinine Clearance (n=405)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90 (n=274)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>60-90 (n=90)</td>
<td>1.23 (0.66-2.26)</td>
<td>0.86 (0.42-1.78)</td>
<td>0.64 (0.27-1.50)</td>
</tr>
<tr>
<td>30-59 (n=34)</td>
<td>2.35 (1.06-5.19)</td>
<td>1.54 (0.70-3.39)</td>
<td>-</td>
</tr>
<tr>
<td>&lt;30 (n=7)</td>
<td>8.69 (3.38-22.37)</td>
<td>8.75 (3.75-20.34)</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol Use (n=438)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (n=256)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Light (n=41)</td>
<td>0.35 (0.15-0.80)</td>
<td>0.25 (0.09-0.71)</td>
<td>-</td>
</tr>
<tr>
<td>Heavy (n=141)</td>
<td>1.15 (0.68-1.95)</td>
<td>0.93 (0.43-2.05)</td>
<td>-</td>
</tr>
<tr>
<td>Unemployed (n=441)</td>
<td>1.62 (1.13-2.30)</td>
<td>1.63 (0.90-2.93)</td>
<td>-</td>
</tr>
<tr>
<td>Mobile phone access at home (n=440)</td>
<td>0.47 (0.29-0.78)</td>
<td>-</td>
<td>0.80 (0.38-1.69)</td>
</tr>
<tr>
<td>Receives government grant assistance (n=441)</td>
<td>0.41 (0.20-0.82)</td>
<td>0.48 (0.22-1.05)</td>
<td>-</td>
</tr>
<tr>
<td>Internet access at home (n=425)</td>
<td>0.83 (0.48-1.44)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Province (n=442)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KZN (n=310)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Eastern Cape (n=132)</td>
<td>1.74 (1.03-2.95)</td>
<td>-</td>
<td>1.31 (0.62-2.76)</td>
</tr>
<tr>
<td>Center Size (n=442)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small (n=175)</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Large (n=267)</td>
<td>1.01 (0.49-2.07)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intervention (n=442)</td>
<td>0.64 (0.27-1.50)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
*Adjusted for CD4 count, prior history of TB, creatinine clearance, alcohol use, employment status, mobile phone access, grant assistance, province, and enrollment site.

Hypertension defined by medical history, prescriptions, or elevated blood pressure >140/90 mm/Hg; Ever smoked defined as >100 cigarettes/lifetime and >1 year of smoking at least daily. Diabetes not included due to sample size. BMI categorized as underweight <18.5 kg/m², normal 18.5-24.99 kg/m², elevated >25 kg/m². Creatinine clearance measured in mL/min/1.73m².

BMI: body mass index; ART: anti-retroviral therapy; KZN: Kwa-Zulu Natal
Table 4. Cox Proportional Hazard Modeling of CVD Risk Score on MDR-TB Negative Treatment Outcome

<table>
<thead>
<tr>
<th>Variable (N)</th>
<th>Bivariate model HR (95% CI)</th>
<th>Adjusted model* aHR (95% CI)</th>
<th>Adjusted model* aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CVD Risk Continuous N=190</td>
<td>CVD Risk Continuous N=190</td>
<td>CVD Risk Categorical N=190</td>
</tr>
<tr>
<td>CVD Risk Score (n=210)</td>
<td>1.00 (0.96-1.04)</td>
<td>1.05 (1.01-1.09)</td>
<td>-</td>
</tr>
<tr>
<td>Low Risk</td>
<td>1.0</td>
<td>-</td>
<td>1.0</td>
</tr>
<tr>
<td>Mod/High Risk</td>
<td>2.03 (1.01-4.09)</td>
<td>-</td>
<td>4.52 (1.91-10.70)</td>
</tr>
<tr>
<td>Covariates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (n=210)</td>
<td>1.02 (0.97-1.07)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex (n=210)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>0.45 (0.22-0.92)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ART exposure (n=210)</td>
<td>1.30 (0.72-2.35)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD4 Count (n=191)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=200 cells/µL</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;200 cells/µL</td>
<td>2.47 (1.34-4.56)</td>
<td>2.97 (1.65-5.36)</td>
<td>3.13 (2.02-4.85)</td>
</tr>
<tr>
<td>Prior history of TB (n=209)</td>
<td>1.05 (0.63-1.76)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of Co-morbidities (n=210)</td>
<td>1.58 (0.57-4.33)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Polypharmacy (n=210)</td>
<td>1.01 (0.86-1.18)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Creatinine Clearance (n=196)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90 mL/min/1.73m²</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>60-90 mL/min/1.73m²</td>
<td>1.78 (0.83-3.81)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&lt;60 mL/min/1.73m²</td>
<td>2.36 (0.92-6.02)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol Use (n=208)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Light</td>
<td>0.80 (0.17-3.82)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heavy</td>
<td>1.43 (0.80-2.55)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Unemployed (n=209)</td>
<td>2.17 (1.59-2.97)</td>
<td>1.96 (1.52-2.53)</td>
<td>2.21 (1.60-3.06)</td>
</tr>
<tr>
<td>Mobile phone access at home (n=209)</td>
<td>0.41 (0.18-0.93)</td>
<td>0.52 (0.26-1.05)</td>
<td>0.47 (0.23-0.95)</td>
</tr>
<tr>
<td>Receives government grant assistance (n=210)</td>
<td>0.32 (0.13-0.78)</td>
<td>0.28 (0.11-0.71)</td>
<td>0.25 (0.10-0.64)</td>
</tr>
<tr>
<td>Internet access at home (n=200)</td>
<td>0.80 (0.30-2.12)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Province (n=210)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KZN</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eastern Cape</td>
<td>2.01 (0.83-4.83)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Center Size (n=210)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small &lt;150 enroll/year</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Large &gt;150 enroll/year</td>
<td>0.81 (0.29-2.30)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intervention (n=210)</td>
<td>0.54 (0.16-1.84)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Adjusted for CD4 count, unemployment, grant assistance, mobile phone access, and enrollment site.
CVD: cardiovascular disease; ART: anti-retroviral therapy; KZN: KwaZulu-Natal Province;
Figure 2. Kaplan-Meier Cumulative Proportion of Negative Outcome by Body Mass Index Category

Figure 3. Kaplan-Meier Cumulative Proportion of Negative Outcome by CVD Risk Category


Chapter 4: A Systematic Review of the Effectiveness of Smoking Cessation Interventions among Patients with Tuberculosis

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Running Head: Smoking Cessation Interventions

Key Words: Tobacco Use; Tobacco Use Cessation; Smoking Cessation Products; TB

Accepted to Public Health Action: April 2018
Abstract

Smoking is a significant risk factor for morbidity and mortality particularly for patients with tuberculosis. Smoking cessation has been recommended by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease; however, there has been no published evaluation of smoking cessation interventions among people with tuberculosis. The purpose of this review was to synthesize the evidence on interventions and suggest practice, research and policy implications. A systematic review of the literature identified 14 peer reviewed studies describing 13 smoking cessation interventions between 2007 and 2017. There were five randomized controlled trials, three non-randomized interventions, and five prospective cohort studies. The primary types of interventions were brief advice (n=9), behavioral counseling (n=4), medication (n=3), and community based care (n=3). A variety of healthcare workers implemented interventions from physicians, nurses, clinic staff, community healthcare workers and family members. There was significant heterogeneity of design, definition of smoking and smoking abstinence and implementation making comparison across studies difficult. Overall, all smoking interventions increased smoking cessation between 15% and 82%, but many studies had a high risk for bias including six without a control group. The implementing personnel did not make a large difference in cessation results, suggesting that national TB programs may customize to their needs and limitations. Family members may be an important supporter/advocate for cessation. Future research should standardize definitions of smoking and cessation to allow comparisons across studies. Policy-makers should encourage collaborations between tobacco and TB initiatives and develop smoking cessation measures to maximize results in low resource settings.
Introduction

Tuberculosis (TB) is the leading cause of death from infectious disease, globally.\textsuperscript{1} Smoking is a significant driver of the TB epidemic, accounting for 8% of TB cases among the 30 countries with the highest TB burden.\textsuperscript{1,2} Smokers have increased risk for developing TB and negative treatment outcomes.\textsuperscript{3,4} This may be due to biologic processes that impact lung health as well as social factors associated with tobacco use such as alcohol use.\textsuperscript{3,5} Ongoing tobacco use increases the risk for negative TB outcomes, primarily TB relapse or recurrence.\textsuperscript{4,6}

Eighty percent of the one billion smokers globally reside in low and middle-income countries (LMIC); many of these countries also have a high burden of TB.\textsuperscript{7} Provision of smoking cessation services during TB treatment is critical to reduce negative effects of smoking on TB treatment and life-long health and patients are more likely to change their smoking behavior during the TB treatment period, underscoring this as a critical intervention period for cessation.\textsuperscript{8–10} The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (The Union) recommended smoking cessation interventions be added to national TB programs in 2007 using the 5 “A’s” approach of (1) Ask the patient about smoking; (2) Advise about the risk of smoking; (3) Assess willingness to stop smoking; (4) Assist patient to stop smoking; and (5) Arrange for follow-up or a modified format of this ABC: (A) Ask about smoking, (B) Provide brief advice and (C) Provide cessation support.\textsuperscript{9,11} These frameworks provide a foundation for national TB programs to integrate smoking cessation interventions within TB care.

Smoking interventions have been implemented as part of TB programs since 2007
in LMICs such as Sudan, Pakistan, and South Africa, but no systematic review has explored the impact of these programs on smoking cessation among TB patients. The purpose of this systematic review was to consolidate existing evidence on smoking cessation interventions among TB patients in LMICs and summarize the practice, policy and research implications of these findings to improve smoking cessation efforts.

Methods

Search strategy

A systematic review of peer-reviewed literature on smoking cessation interventions among TB patients was conducted using PRISMA guidelines in May 2017. The following databases were used: PubMed, Cumulative index to Nursing and Allied Health Literature, SCOPUS, Web of Science, Cochrane, and Embase. Search criteria were developed using Medical Subject Headings (MeSH) and non-Mesh terms which were adapted to the specific database as follows:

TB: tuberculosis[Mesh] OR tuberculo* OR "TB"


Inclusion criteria

Peer reviewed journal articles were included if they evaluated any smoking cessation intervention among patients with suspected or confirmed TB. Any studies that did not report on smoking cessation outcomes were excluded. The search included publications written in English, French, Spanish, Portuguese, and Korean.

Procedure

All retrieved citations were imported into Covidence® and duplicates removed. Two reviewers (EW, JL) independently reviewed titles and abstracts. Difference in full-text inclusion were resolved through consensus. Reviewers then independently extracted data on participant characteristics, intervention characteristics, smoking cessation outcome, and other qualitative or quantitative information about implementation of the intervention. Risk of bias was assessed using the Cochrane Risk of Bias tool for intervention studies. Results were compared and discrepancies were resolved through discussion. Due to the heterogeneity of comparison groups among the randomized controlled trials, results were synthesized but a meta-analysis was not conducted.
Ethics

Institutional Board of Review approval was not required for this review of literature.

Results

After removing duplicates, the search resulted in 1,645 articles for review (Figure 1). A total of 14 articles were included based on the inclusion/exclusion criteria for this review. Although there were no country-based exclusion criteria, all studies took place in LMICs. Two of the articles were based on the same intervention but compared outcomes for different groups. Thus, there were a total of 13 different interventions.

Study characteristics

Included studies were conducted across 11 different countries and published between 2007 and 2016. Study designs included three randomized controlled trials,\textsuperscript{14–16}, two cluster randomized controlled trials,\textsuperscript{17,18}, five prospective cohort studies,\textsuperscript{19–23}, and three non-randomized interventions studies,\textsuperscript{24–26} (Table 1). Three of the studies were intended as feasibility or pilot studies focused on initial implementation of smoking cessation.\textsuperscript{19,24,25}

Settings for the studies varied, with the majority (n=7) being conducted in primary health centers. All but one (Kumar et al.) were conducted as multi-site studies and most (n=11) included patients with TB on treatment. Only Kumar et al. included some patients living with HIV without TB in addition to TB patients. Siddiqi et al. included patients with presumptive but not confirmed TB. Study sample sizes ranged from 28 to 1,955. Mean age of participants, where reported, ranged from 38 to 47 years.
of age. Most participants 60.7% to 100% were male; five studies included only male participants. Only two studies included TB outcome measures. Awaisu et al. found higher rates of successful TB treatment outcomes in the intervention group (79.5% vs 78.3%, p=0.0031) while El Sony et al. found no differences.24,26

The operational definition of smoking varied from any self-reported smoking to those who smoked at least 20 packs in their lifetime (Table 2). The majority (n=11) included patients who smoked cigarettes or tobacco only, while three23,27,28 included hookah as well. The outcome definition of smoking cessation was highly variable (Table 2). Six of 14 studies used exhaled carbon monoxide (CO) to define smoking cessation, some in addition to self-report and cotinine. Two studies used cotinine measurement, one in saliva and the other urine to confirm self-reported smoking status. The remaining seven studies used patient self-report of smoking cessation with two of those studies asking for family member confirmation of smoking status when possible.

Intervention characteristics

All interventions were based generally on the WHO or The Union smoking cessation guidelines; what varied across studies was the interventionist, method and frequency. Only El Sony et al. and Nichter et al. followed patients beyond TB treatment, 12-months in total.14,24 The other studies followed patients for 1-month (n=1)17, 3-months (n=1)19, and 6-months or end of TB treatment (n=10).15,16,20–23,25–28 Awaisu et al. and Siddiqi et al. were the only published protocol papers which described the process of developing smoking cessation tools to the local training context and implementing a training program for staff.29,30 A variety of healthcare workers delivered the interventions, many of which were Directly Observed Therapy (DOT) providers.
Physicians most often prescribed smoking cessation medication in intervention studies\textsuperscript{16,26,27}, but two studies specifically evaluated the added effect of brief advice provided by a physician\textsuperscript{14,17}. Of the remaining studies, interventionists were nurses \textsuperscript{(n=2)}\textsuperscript{19,26}, trained TB staff/DOTs facilitators \textsuperscript{(n=6)}\textsuperscript{20,21,23-25,31}, community health workers (CHW) \textsuperscript{(n=2)}\textsuperscript{15,22}, and one included trained family member supporters\textsuperscript{14}.

There were four general categories of interventions: brief advice, behavioral counseling, medication and community-based care/family support. Many of the smoking cessation services combined a number of these interventions, as summarized in Table 3. Brief advice was the common intervention \textsuperscript{(n=9)}. This was typically 5-10 minutes of advice on harms of smoking, asking the person if they want to quit and promoting cessation strategies with a possible referral to smoking cessation services outside the TB clinic. The number of sessions ranged from one at the beginning of TB treatment to expected brief advice sessions at every visit. Of brief advice interventions occurring with every TB visit, only Sereno et al. reported on adherence with 12 out of 33 patients receiving any brief counseling\textsuperscript{19}. Behavioral counseling was the second most common intervention \textsuperscript{(n=4)}. What differentiated behavioral counseling from brief advice was not well described, but included behavioral change training for staff, additional questions to elicit stronger patient involvement in behavior change and longer but fewer sessions (15-30 minutes for typically 1-2 sessions). Awaisu et al. was the exception with 11 behavioral counseling sessions across 6-months of TB treatment\textsuperscript{26}. There did not appear to be any correlation between the number of sessions and the success of smoking cessation although this was difficult to evaluate given the varied study designs. Two studies prescribed medication (bupropion) for seven or nine weeks as a specific
intervention arm in addition to counseling; Awaisu et al. allowed providers to prescribe nicotine replacement therapy (NRT), only 60% of participants received NRT. Finally, three studies involved community based care, either family members or CHWs providing cessation support in the community. Community based care did not demonstrate any significant improvement in smoking cessation above routine provider advice; however, qualitative interviews suggest that family members provided sustained counseling beyond TB treatment which may have led to unmeasured improvements in quit rates.

Implementation

There was a significant component of clinician training involved in the implementation of interventions (Table 1). Most of the training sessions were one to two days although five of the studies did not include the duration of the training. Kaur et al. and Lin et al. used train the trainer models to enable more staff to be trained at local TB clinics. For example, Kaur et al. trained over 1,400 staff total in smoking cessation messaging by this model. Trainings which involved more hands-on components such as role-playing appeared to last longer. However, since many of the studies did not detail how knowledge and skills regarding smoking cessation messages were taught in the trainings, it is difficult to draw any conclusions. Only Louwagie et al. provided specific follow-up training for staff to reinforce smoking cessation messages; Nichter et al. provided follow-up training for family members. Few studies provided evidence on the effectiveness or acceptability of the training by staff. El Sony et al. noted an increase in the use of smoking abstinence messaging after the training, but this was not statistically significant between the control and intervention staff. Lin et al. and Sereno
et al. noted challenges in implementation due to busy clinical schedules or clinicians that smoked and did not believe smoking cessation was important.\textsuperscript{19,20} However, three other studies reported on positive response by staff including that staff and families were not always aware of the connection between smoking and TB and appreciated the training.\textsuperscript{14,19,21}

Effectiveness of interventions

One of the challenges for evaluating effectiveness is that six of the studies did not use a control group. In addition, studies with a control group varied greatly about the standard of care provided to the control group. The standard of care ranged from asking about smoking status\textsuperscript{24,25}, to receiving standard DOT care that may or may not have included smoking cessation messages\textsuperscript{16,26}, brochures\textsuperscript{17,31} or even brief advice or counseling by a smoking cessation counselor.\textsuperscript{15,17} This made comparison across different types of intervention very difficult.

*Randomized controlled trials*

Among the five randomized controlled trials both advice by a healthcare provider and advice plus medication improved smoking cessation. Among the studies (n=3) that reported a relative risk (RR), the relative risk for smoking abstinence ranged from 2.3 to 8.5 at the end of the follow-up period for counseling (n=3 studies)\textsuperscript{15,16,31} and from 9.3 to 35.3 (odds ratio) for the combination of counseling and medication (n=2 studies).\textsuperscript{16,31} In both studies where bupropion was added to counseling, there was an increase in cessation but it was either not evaluated statistically or was statistically not significant. In the additional comparison of hookah smokers with cigarette smokers (n=1 study), smoking
cessation interventions had less impact on hookah smokers but still doubled their risk for smoking abstinence (2.2 to 2.5 RR). Both Kumar and Nichter did not have standard of care control groups, but compared counseling or trained family support to only physician advice, respectively. In these two studies, the quit rates were comparable between the groups, suggesting that advice given specifically by a non-physician, including a family member, may be as effective as provider advice. Kumar et al. reported quit rates of 40.5-44%, among TB patients while Nichter et al. reported 71-73% quit rates. Nichter et al. may have been more successful because the intervention continued for the entire treatment period whereas Kumar et al. only had one advice session.

Non-randomized interventions

Three of the 14 interventions were non-randomized but included a control group receiving standard of care. All three studies reported that more participants receiving intervention quit compared with the control group, with a quit rate ranging from 39 to 82.5% compared with 0 to 14.3%, respectively. Awaisu et al. reported the highest level of smoking cessation (78%) compared with the control (9%). However, the study recruited patients into the intervention who were already motivated to quit based on the trans-theoretical model stages of change whereas the control group was made up of smokers unwilling to quit. Awaisu et al. was the only study to use NRT along with counseling but did not analyze differences between patients who received NRT and those that did not. Campbell et al. and El Sony et al. both reported on pilot/feasibility studies taking place within the existing national TB program structures where TB treatment staff received training on brief smoking advice.

Prospective cohort studies
Five studies were based on implementation of smoking cessation interventions for all smokers within existing TB programs with no control group comparison.\textsuperscript{19-23} The percentage of smokers who quit at the end of follow up ranged from 66.8\% to 82\%. Most of these interventions were 5-10 minutes of brief advice by TB center staff at initiation with follow-up sessions intended for each return TB visit. The highest quit rate was 82\% in a study where community volunteers where trained in smoking cessation brief advice and provided weekly or bimonthly follow-up advice in the community.\textsuperscript{22}

Quality of articles

All the studies were evaluated using the Cochrane Risk for Bias for Interventional Studies tool (Figure 2).\textsuperscript{13} Most of studies have significant risk for bias as they did not have a control group or participants were not randomized to the intervention. Many studies did not have blinding of study participants or study personnel both in assignment of intervention and for data collection, leading to a higher risk of bias in the outcome. However, the nature of this behavioral intervention makes it difficult to blind participants and clinicians from the intervention.

Discussion

The addition of smoking cessation interventions to routine TB case management is feasible and effective in reducing smoking rates among patients during TB treatment. While all the studies in this review reported at least some level of decrease in smoking, there remains a need for clearer evidence to guide the operationalization and scale up of smoking cessation strategies within TB programs.

Practice implications
This review suggests that TB programs can implement smoking cessation interventions using existing staff for advice or counseling.\textsuperscript{19,24} However, clinicians in LMICs often have high demands for providing clinical care and thus limited time.\textsuperscript{19,32} This review suggests that in addition to physicians and nurses, lay counselors and healthcare workers (HCW) can provide ongoing smoking cessation counseling.\textsuperscript{15,17} There is some evidence that physicians may have an important role in smoking cessation messaging.\textsuperscript{33} Physicians and nurses could incorporate short cessation messages that would be followed up with ongoing support provided by CHWs or HCWs. A combination of HCWs reinforcing smoking cessation messaging could complement a more holistic approach to health messaging around smoking and other related topics in TB care. Standardized patient education materials could make it more feasible for this messaging to be provided consistently.

Furthermore, family members are a critical component of smoking cessation that could be more systematically included during smoking cessation interventions. Given that smoking may resume after TB treatment has completed, this is particularly important follow-up for preventing relapse.\textsuperscript{14,20,34} This review found that family members enjoyed learning more about TB and smoking cessation messages and requested additional topics for training in the future.\textsuperscript{14} When considering who participates in the family, an intergenerational approach to engaging older and younger generations could facilitate stronger messaging.\textsuperscript{35,36} Research on smoking cessation in non-TB specific contexts has demonstrated the influence of both social networks and family members on smoking habits and cessation efforts.\textsuperscript{37–39} Despite this, a review of smoking cessation interventions involving family members found few studies that directly compared
individual vs family based intervention limiting conclusions on whether family member involvement has an additive effect. In addition, all of these studies were from Europe and North America and family dynamics may vary across countries. This review suggests that family members may have a positive influence for TB patients, but additional research is needed to identify how to maximize family support. In addition, second-hand smoke is a serious health concern not only for TB patients but their families so counseling TB patients and any other family members within the household that smoke may help to reduce the risk of second-hand smoke exposure and the risk of development of TB for household members.41,42

Training and supervision is a key input required for integrating smoking cessation messaging into routine TB programs.43,44 Healthcare workers themselves may smoke and not recognize the importance of smoking cessation messages particularly for TB patients.32,43 In addition, even if healthcare workers agree with smoking cessation they may not have adequate knowledge to provide tailored advice for patients with TB.32,43,44 For example, one study noted that TB nurses asked about smoking habits and gave advice 87% of the time, but they did not provide TB specific messaging that could increase the likelihood of quitting.15 Most interventions required a one-day training of providers, with some utilizing a training of trainer’s approach to increase reach. More in-depth techniques such as motivation interviewing could be incorporated into the training as time and resources allow. Motivational interviewing has been found to be effective on counseling on a variety of topics from medication adherence to chronic disease management to smoking cessation.45 These techniques may help TB providers target
Cessation counseling may be accompanied by medications such as NRT or antidepressants used to reduce cravings such as bupropion. Of the three studies that included medications, only one compared the effect of advice with advice plus medication and found no difference. A systematic review by Cochrane suggested that antidepressants such as bupropion may not be any more effective than NRTs. In addition, a separate review found that combined behavioral interventions with medication (NRTs or bupropion) worked better than usual care in the general population, but they did not explore the separate impacts of medication and intensive behavioral therapy on smoking cessation. However, given that NRT and other pharmaceuticals can be costly and add additional pill and side effect burden, providers may try other methods for promoting smoking cessation before routinely prescribing medications. Further studies are needed to determine which patients may have the most benefit from medications to guide prescribers. In addition, it is important for TB and tobacco control programs to be able to evaluate whether it would be beneficial to include medications in their programming choices or whether there is more benefit to other smoking cessation methods which could have a larger impact on community smoking norms and behaviors.

None of the studies in this review used technology to promote smoking cessation. As more people have mobile and smartphones, this may be a way to provide additional information and smoking cessation messages to smokers and their families. There is some evidence that mobile phone use in HIV care improved treatment adherence and mixed results about whether text reminders could also improve TB treatment.
In general populations, mobile technology including short message service (SMS) text reminders has been effective in promoting and sustaining smoking cessation for up to 6-months, although most studies have been in high income countries. However, as mobile phone use increases in low and middle-income countries, technology will continue to be a possible source of cessation or medication adherence messaging.

Research implications

This review provides initial evidence that smoking cessation interventions can reduce smoking rates in TB patients. However, there are few randomized trials and most studies did not have a control group for comparison. Thus, the risk for bias is high and there is a need for additional studies such as adaptive clinical trials that evaluate the effectiveness of smoking cessation interventions in this population. Both qualitative and quantitative studies of TB patients who have and have not successfully quit smoking would further elucidate what was most helpful about specific interventions, how interventions impact patients beyond just smoking cessation such as improving overall quality of life, and other factors that contribute to smoking cessation such as self-efficacy. Nichter et al. included qualitative interviews for patients who continued smoking after the six months TB treatment and intervention. These interviews suggested that these smokers did not see low level smoking as harmful and they resumed smoking to demonstrate that they were healthy enough to smoke. This also suggests a critical need for studies that follow patients after TB treatment ends because patients who quit may resume smoking once they have completed treatment and have been shown to be at greater risk of recurrent TB. In this review, only two studies assessed smoking adherence.
cessation after the end of TB treatment. Thus, studies with longer follow-up and using more qualitative research methods are critical to facilitating and maintaining smoking abstinence.

While the recommendations for integrating smoking cessation messages into TB care are clear, the most cost-effective methods for improving cessation are not known. Only two of the studies in this review mentioned cost and none did a cost analysis.\textsuperscript{23,31} Siddiqui et al. reported that the behavioral support cost 2.50 USD per person while adding the medication cost 20.90 USD per person. Kaur et al. reported that the entire program, training 1436 staff and counseling 1333 smokers out of 2879 registered TB patients, was conducted between October 2010 and June 2011 for 7000 USD and could be incorporated into the national TB program and smoking cessation budget. Future studies should focus on the direct and indirect costs of smoking cessation interventions to assist programs decide how to effectively use scarce resources.

Policy implications

Both the WHO and The Union have recommended the integration of smoking cessation messages into TB care for over a decade. However, this review points to the challenges of implementation of effective smoking cessation interventions in resource limited TB care programs. While the WHO and The Union guidelines provide broad overviews of smoking cessation techniques and messaging, additional resources based on empirical research which can be adaptable to different settings are needed. In addition, encouraging the standardization of tools and definitions in research and practice will allow for better comparison of different smoking cessation interventions. This review also points to the richness of data from studies outside of randomized controlled trials.
Although randomized controlled trials are the standard particularly in biomedical research, they may not be the most useful for developing effective pragmatic behavioral interventions and programming, particularly when smoking cessation messaging should be the standard of care.\textsuperscript{56,57}

National and local TB programs should look for ways to integrate smoking cessation training and messaging into existing programs. While smoking cessation interventions can feasibly be introduced in TB clinics, these programs do require resources including smoking cessation materials, training of personnel, changing TB protocols and forms to include ongoing smoking screening. Incorporating smoking indicators into TB clinical documentation tools as recommended by the WHO could increase the accountability for providers to implement smoking cessation interventions. These indicators also provide important feedback on the programs’ success. In addition, as demonstrated with Kaur et al., integration of national tobacco control programming with TB programming can be successful especially when TB clinics are located within primary health clinics.\textsuperscript{23} National and international policy should encourage collaboration between chronic disease prevention and health promotion with TB programming to maximize the impact of messaging.

Strength and limitations of the studies

Most of the studies reviewed were non-randomized or observational without control groups. As noted in Figure 2, there was a high risk for bias among many of the studies. Additional limitations were small sample size, high rates of attrition among participants, and measurement error related to self-reporting of smoking status. Furthermore, most studies followed patients only through the end of TB treatment which
does not capture longer term relapse and intervention impact. In addition, differing
definitions of smokers and smoking cessation made it difficult to compare results across
studies.

A major strength of these studies is that they were largely pragmatic interventions
situated in existing TB programs. They all demonstrate that it is feasible to integrate
smoking cessation into TB care and that it can successfully increase the number of
patients who quit smoking. In addition, half of the studies used biometric methods
(exhaled CO or cotinine) to validate self-reported smoking status, increasing the validity
of the results.

Strength and limitations of this review

This review was limited by only including peer-reviewed journal articles and
excluding program reports and grey literature such as WHO or national reports. National
TB programs implementing smoking cessation interventions may have important findings
that have not been published in peer reviewed journals. This review specifically included
a variety of study designs making comparison of outcomes difficult. The strength of this
method was to include more interventions beyond randomized controlled trials to
understand the qualitative aspects of interventions that may have otherwise been
excluded.

Conclusion

Smoking cessation interventions can be incorporated into TB treatment and care
programs across hospitals and clinics. Increased access to smoking intervention services
within TB programs can play a critical role in reducing rates of tobacco use among
patients, which could improve TB cure rates and decrease risk of subsequent morbidity and mortality. However, to facilitate the integration of behavioral smoking cessation interventions within TB programs as standard practice, greater policy and program guidance is still needed. In addition to research assessing the effectiveness of smoking cessation strategies on TB patients, a greater focus on the feasibility and cost requirements of various intervention approaches are critically needed to guide implementation.

Acknowledgements

The authors would like to thank Maria Truskey, an information specialist at the Welch Medical Library, for her assistance developing and implementing the search strategy. EW and JL performed the search, article extraction and the primary synthesis. JG and JF assisted with the development of the research question and provided input into the results and implications. All authors reviewed and agreed with the final submission. This manuscript was supported by the National Institutes of Health under award number F31-NR016909 (NINR; EW), R01-AI104488 (NIAID; JF), and R01-DA030276 (NIDA; JG). The authors report no conflicts of interest.
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<th>First Author, Year, Setting, Sample Size, Guiding Framework</th>
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<td>Aryanpur et al., 2016, Iran, N=210 WHO 5As</td>
<td>Sex (% male)</td>
<td>CG: 90.2%; BSS: 90.3%; BSS+: 90.0%; Age (M &amp; SD)</td>
<td>CG: SOC; BSS: Behavioral Counseling</td>
<td>4 sessions over 2 weeks; 9 weeks of medication</td>
<td>6 health centers &amp; 1 hospital; Physician</td>
<td>Exhaled CO</td>
<td>Not described</td>
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<td>Smoking abstinence at 6 months was 71.7% BSS+, 33.9% BSS and 9.8% CG (p&lt;0.001). Behavioral counseling increased smoking cessation (OR=7.1, 95% CI 2.7-18.7) and medication increased the effect (OR=35.3, 95% 13.8-90.3).</td>
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<td>Dogar et al., 2014, Pakistan, N=1955 WHO 5As</td>
<td>Sex (% male)</td>
<td>Cigarette =98.3%; Hookah= 79%; Both =95%</td>
<td>CG: SOC (self-help leaflet); BSS: individual counseling; BSS+: Counseling plus 7 weeks of bupropion</td>
<td>2 sessions and 7 weeks of medication for BSS+</td>
<td>33 health centers; DOT facilitator &amp; Physician</td>
<td>Physician</td>
<td>Exhaled CO</td>
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<tr>
<td>Kumar et al, 2017, India, N=160 WHO 5As</td>
<td>Sex (% male)</td>
<td>100%</td>
<td>56.3% 30-40, 27.5% 41-50, 5% &gt;50</td>
<td>CG: Brochure plus counseling by a counselor</td>
<td>Use of WHO 5A's;</td>
<td></td>
<td>Physician advice is feasible and acceptable in people living with HIV and TB. There was no difference between MD and counselor (RR=1.2, 95% CI 0.8-1.8). Among TB patients, 40.5% quit from CG and 44.4% from IG (p=0.735).</td>
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<td>Louwagie et al., 2014, South Africa, N=409</td>
<td>Sex (% male)</td>
<td>CG: Brief advice by TB nurse</td>
<td>CG: 1 session with 3 follow-up surveys</td>
<td>6 TB Clinics; CHW &amp; Nurse</td>
<td>Exhaled CO</td>
<td>CG: Training on brief advice using motivational interviewing, one-page MI guide form, video-taped role play with feedback; IG: 1-day training</td>
<td>Self-reported 6 months sustained abstinence was 21.5% for IG and 9.3% for CG (RR=2.29, 95% CI 1.4-3.92). This was similar to the results for 3-month self-report abstinence and biochemically confirmed abstinence.</td>
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<td>Niechter et al., 2016, Indonesia, N=101 WHO 5As</td>
<td>Sex (% male)</td>
<td>IG-MD: MD advise every visit to TB clinic (~6 months)</td>
<td>IG-MD: MD advise every visit during TB treatment (6 months) plus family support</td>
<td>5 TB centers; Physician &amp; Family</td>
<td>Self-report confirmed by family member</td>
<td>Physicians: Use of modified WHO 5As and educational handout; evidence based articles on smoking and TB; Family members: Educational session on TB, adherence, and smoking cessation messages; role play to teach cessation related to communication; Physicians 1-day training; Family: 3-4 hours plus 1 booster training</td>
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<td>Siddiqi et al., 2013, Pakistan, N=1955 WHO5As</td>
<td>Sex (% male)</td>
<td>CG: SOC (self-help leaflet)</td>
<td>CG: Brief advice by TB nurse plus MI</td>
<td>33 health centers; DOT facilitator &amp; Physician</td>
<td>Exhaled CO</td>
<td>BSS/BSS+: Behavior change techniques; educational flipbook of 25 slides detailing smoking harms, developing a plan, triggers for smoking, and coping strategies; 1-day training</td>
<td>Behavioral support with and without medications reduced smoking (BSS RR=8.5, 95% CI 3.7-19.6; BSS+ RR=9.3 95% CI 4.0-21.6). 6-month smoking abstinence was 8.5% CG, 41.0% BSS, &amp; 41.5% BSS+. There was no added benefit to medications for quit rates (RR=1.1 95% CI 0.5-2.3).</td>
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<tr>
<td>First Author, Year, Setting, Sample Size, Guiding Framework</td>
<td>Participant Characteristics: Sex, Age</td>
<td>Intervention Components</td>
<td>Dosing</td>
<td>Service Point &amp; Provider</td>
<td>Measurement of Smoking Cessation</td>
<td>Provider Training: Content &amp; Duration</td>
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<tr>
<td>Awaisu et al., 2011, Malaysia N=120 TTM &amp; WHO 5As</td>
<td>Sex (% male): CG: 97.8% IG: 100%</td>
<td>CG: SOC IG: Individual behavioral counseling with or without NRT</td>
<td>IG: 11 sessions of counseling over 6 months; 60% of IG patients received NRT</td>
<td>5 health centers; Nurse (counseling) &amp; Physician (medication)</td>
<td>Saliva cotinine, Exhaled CO</td>
<td>IG-Nurse: Experiential learning of smoking cessation messaging; mentor relationship with quit smoking clinic; didactic lectures, role-plays and video shows; 3-day training</td>
<td>Patients were enrolled into IG based on motivation to quit which may avoid ethical challenges to not offer an intervention. The intervention increased smoking abstinence and linearly increased until month 5 (4-week abstinence at month 6: 77.5% IG vs 8.7% CG, p&lt;0.001).</td>
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<tr>
<td>Sex (% male)</td>
<td>CG: 69% IG: 82%</td>
<td>Age (% by group) CG: 37% &lt;40, 55% 41-70, 4% &gt;70</td>
<td>IG: 11 sessions of counseling over 6 months; 60% of IG patients received NRT</td>
<td>5 health centers; Nurse (counseling) &amp; Physician (medication)</td>
<td>Saliva cotinine, Exhaled CO</td>
<td>IG: Training on giving brief advice and use of expired air CO machine; 1 training initially (length not specified) and 1 refresher after 2 years</td>
<td>Simple brief advice lead to 39% quit rate compared with 0% in the control group (p&lt;0.0001) over 6 months within the NTP program using existing staff.</td>
</tr>
<tr>
<td>Campbell et al., 2014, Nepal, N=246 No framework</td>
<td>Sex (% male) 4% &gt;70</td>
<td>CG: SOC IG: Brief advice by HCW</td>
<td>3 sessions total over TB treatment (5-10 minutes each)</td>
<td>2 TB treatment centers; TB HCW Self-report</td>
<td>IG: Training on smoking and TB, use of protocol and questionnaires, and use of open-ended questions to increase motivation to quit; 2-day training</td>
<td>Implementation of smoking cessation intervention did not negatively impact TB outcomes across the centers. It was feasible to implement and increased the quit rate to 56.3% compared with 14.3% at the control centers.</td>
<td></td>
</tr>
<tr>
<td>El Sony et al., 2007, Sudan, N=513 (356 smokers) No framework</td>
<td>Sex (% males) 100%</td>
<td>CG: SOC/pamphlet IG: Brief advice by MA</td>
<td>4 sessions total over 8 months of TB treatment</td>
<td>16 health centers; MA Self-report</td>
<td>IG: Training on smoking and TB, use of protocol and questionnaires, and use of open-ended questions to increase motivation to quit; 2-day training</td>
<td>Implementation of smoking cessation intervention did not negatively impact TB outcomes across the centers. It was feasible to implement and increased the quit rate to 56.3% compared with 14.3% at the control centers.</td>
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<tr>
<td>First Author, Year, Setting, Sample Size, Guiding Framework</td>
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<tr>
<td>Bam et al., 2015, Indonesia, N=750 (525 smokers)</td>
<td>Among smokers (N=525)</td>
<td>Sex (% male) 96.7%</td>
<td>Establishing a smoker-free environment at health care facilities; brief advice from DOTs worker at TB visits</td>
<td>5-10 minutes at every TB visit (approximately monthly)</td>
<td>17 health centers; TB HCW</td>
<td>Self-report confirmed by family member</td>
<td>Use of ABC Guidelines; length not described</td>
</tr>
<tr>
<td>Kaur et al., 2013, India, N=2879 (1333 smokers)</td>
<td>Among smokers (N=1333)</td>
<td>Sex (% male) 89.6%</td>
<td>Initial session and then follow-ups at TB visits</td>
<td>All DOT centers in the district; TB HCW</td>
<td>Self-report</td>
<td>Basic counseling skills for brief advice to stop smoking based on WHO 5 A’s; 2-day train the trainer leading to other local workshops</td>
<td>The intervention was feasible in existing programming with minimal financial resources and infrastructure. Among smokers, 67.3% quit tobacco, 18.2% relapsed and 14.5% were lost to follow-up at the end of treatment.</td>
</tr>
<tr>
<td>Lin et al., 2015, China, N=800 (244 smokers)</td>
<td>Among smokers (N=244)</td>
<td>Sex (% male) 100%</td>
<td>One session at treatment initiation on the harm of smoking; education reinforced</td>
<td>2 TB clinics; TB HCW</td>
<td>Self-report</td>
<td>Integration of smoking cessation into TB care and brief advice; 1-day train the trainer leading to other local workshops</td>
<td>Smokers with TB were willing to quit (96%) with a 66.7% cessation rate at 6 months. Only 3% of patients (n=7) relapsed at 6 months.</td>
</tr>
<tr>
<td>First Author, Year, Setting, Sample Size, Guiding Framework</td>
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<tr>
<td>Sereno et al., 2012, Brazil, N=28 WHO 5As</td>
<td>Sex (% male)</td>
<td>Unspecified; 12 out of 33 patients received the intervention</td>
<td>Nurse</td>
<td>Self-report, Urine Cotinine</td>
<td>Use of WHO 5As; Not described</td>
<td>Smoking cessation was feasible but modified from 5As to AAR (ask, advise, refer) by providers to help with intervention adherence</td>
<td>15% (3 out of 28 smokers) reported quitting after 3 months.</td>
</tr>
<tr>
<td>Siddiquea et al., 2013, Bangladesh, N=3134 Union ABCs</td>
<td>Among smokers (N=3134)</td>
<td>One counseling session at TB treatment initiation</td>
<td>17 TB centers; Self-report confirmed by community volunteers</td>
<td>TB HCW: ABC method of smoking cessation intervention including harm of smoking, impact on TB, and cessation support techniques. Training on counseling methods and documentation. Community volunteers: Brief advice on cessation and DOT support. Community volunteers may have contributed to high quit rates.</td>
<td>Modified ABC's for brief advice is feasible and effective, with 82% smoking reduction by month 6. High nicotine dependence and extra-pulmonary TB decreased likelihood of cessation.</td>
<td></td>
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</tbody>
</table>

Notes: WHO 5As; Union 2008\(^\text{a}\); Union 2010\(^\text{b}\); BSS = behavioral support intervention; BSS+ = behavioral support intervention plus medication; CG = control group; CHW = community healthcare worker; CI = confidence interval; DOT = direct observed therapy; HCW = healthcare worker; IG = interventional group; M = mean; MA = medical assistant; MI = motivational interviewing; NRT = nicotine-replacement therapy; OR = odds ratio; PHC = primary healthcare clinic; RR = relative risk; SD = standard deviation; SOC = standard of care; TTM = trans theoretical model of change;
Table 2. Definition of current smoker and smoking abstinence by study

<table>
<thead>
<tr>
<th>First Author</th>
<th>Definition of current smoker</th>
<th>Definition of smoking cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aryanpur16</td>
<td>Self-reported smoking based on guidelines of WHO and Union (cited) but not specifically mentioned</td>
<td>Exhaled CO of &lt;7ppm at each measurement</td>
</tr>
<tr>
<td>Awaisu26</td>
<td>Self-reported cigarette use during TB diagnosis before enrollment in study</td>
<td>Urine cotinine between 0-10 (negative result); Exhaled CO negative result (did not include cut-off)</td>
</tr>
<tr>
<td>Bam21</td>
<td>Self-reported smoking (even a puff) in the last 3 months</td>
<td>Self-reported abstinence from smoking for 3 months</td>
</tr>
<tr>
<td>Campbell25</td>
<td>Self-reported cigarette smoking at time of enrollment</td>
<td>Self-reported abstinence for 6 months confirmed with exhaled CO</td>
</tr>
<tr>
<td>Dogar/Siddiqi28,31</td>
<td>&gt;1 cigarette/hookah session a day</td>
<td>Exhaled CO &lt;9 ppm</td>
</tr>
<tr>
<td>El Sony24</td>
<td>Not specified</td>
<td>Self-reported abstinence for &lt;3 months, 3-6 months or &gt;6 months</td>
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<tr>
<td>Kaur23</td>
<td>Self-reported use of any type of tobacco (includes smokeless tobacco)</td>
<td>Self-reported abstinence at the end of 6 months</td>
</tr>
<tr>
<td>Kumar17</td>
<td>Self-report of smoking at least 1 cigarette in past week</td>
<td>Self-reported not currently smoking and exhaled CO &lt;10 ppm</td>
</tr>
<tr>
<td>Lin20</td>
<td>Self-reported smoked at least 20 packs of cigarettes in a lifetime or one cigarette/day for at least 1 year and was, at the time of the study, smoking daily or occasionally.</td>
<td>Sustained abstinence: Self-reported abstinence in the last 3 months (even a puff) Recent abstinence: Self-reported abstinence for &gt;= 7 days but &lt;3 months</td>
</tr>
<tr>
<td>Louwagie15</td>
<td>Not specified</td>
<td>Self-reported ongoing abstinence ignoring the first two weeks since enrollment. Verified in some patients exhaled CO&lt;10 ppm</td>
</tr>
<tr>
<td>Nichter14</td>
<td>Self-reported any smoking at time of TB diagnosis or enrollment in study (up to 10 weeks into treatment)</td>
<td>Self-reported abstinence of cigarettes; not clearly defined.</td>
</tr>
<tr>
<td>Sereno19</td>
<td>Self-reported daily smoking at time of enrollment</td>
<td>Saliva cotinine at follow-ups; specific cut off points not mentioned</td>
</tr>
<tr>
<td>Siddiquea22</td>
<td>Self-reported smoking in the last 2 weeks (even a puff)</td>
<td>Self-reported abstinence from tobacco for 2 weeks at each follow-up</td>
</tr>
<tr>
<td>Type of intervention</td>
<td>Possible components</td>
<td>Who delivered intervention</td>
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</table>
| Brief advice         | - Open ended questions  
                        - Information on the benefits and risk of smoking  
                        - Refer to smoking cessation counselor within facility (TB or Primary Healthcare Center)  
                        - Advice on making homes smoke-free  
                        - Encouragement to speak with their families for understanding and support of quitting  
                        - No smoking sign for home | Nurse, CHW, Physician, DOT provider | - Typically 5-10 minutes (up to 20 minutes)  
                        - Treatment initiation  
                        - Follow-up visits varied from none to every TB visit |
| Behavioral counseling| - Motivational interview assessment and solution development  
                        - Behavioral change technique based on 5 A’s such as envisioning person as non-smoker  
                        - Identify specific situations likely to be difficult and develop coping strategies  
                        - Follow-up on the set quit date to review progress | CHW, DOT provider | - 15-30 minute initial session  
                        - Shorter follow-up sessions |
| Medication           | - Nicotine replacement therapy  
                        - Bupropion (7-9 weeks) | Physician | Consult for initial prescription and follow-up to monitor for side effects |
| Community based care | - Information on the benefits and risk of smoking  
                        - Proactive support to quit and maintain abstinence including smoke-free home | CHW, Family members | - With community health visits weekly or monthly  
                        - Ongoing with family member including post-TB treatment |
Figure 2. Literature Review Flowchart based on PRISMA Guidelines\textsuperscript{12}
<table>
<thead>
<tr>
<th>First Author</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other Bias</th>
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Figure 3. Cochrane Risk of Bias Assessment Tool\(^{13}\)

L represents low risk for bias, H represents high risk of bias, and U represents unclear bias due to insufficient information to permit judgement.
Chapter 5: Discussion

To our knowledge, this was the first study to use a non-laboratory based CVD risk score along with individual CVD risk factors to evaluate the CVD risk in a population of patients with drug-resistant tuberculosis (DR-TB) in South Africa. Overall, the study identified that CVD risk factors were common with over 50% of the sample having at least one CVD risk factor. In addition, the study had preliminary but intriguing results that a moderate or elevated CVD risk score increased the risk of early negative outcomes in MDR-TB treatment. This has important implications for patients, providers, and health systems in low- and middle-income countries that are facing a dual burden of chronic infectious diseases such as TB and HIV and non-communicable diseases such as diabetes and hypertension.

Summary of Findings

Manuscript one of this dissertation described the CVD risk in the overall population of DR-TB patients enrolled in the parent study between November 2014 and July 2016, a total of 900 participants. In this sample, there were more males than females (53.7% vs 46.3%), a median age of 34.4 (IQR 28.7-42.1), 48.8% had a prior history of TB, and 75.1% were co-infected with HIV. Of those co-infected with HIV, 62.1% had known antiretroviral therapy (ART) exposure. The overall prevalence of CVD risk factors was: diabetes (5.2%), hypertension (16.7%), elevated body mass index [BMI] (16.6%) and ever smoking (31.4%). Both smoking and elevated BMI were sex-specific so that women were much more likely to have an elevated BMI (26.2% vs 8.3%, \( X^2=50.97, p<0.001 \)) but men were more likely to have a history of ever smoking (52.2%)
vs 7.3% X^2=207.31, p<0.001). This suggests that gender specific, culturally appropriate interventions may be required to address these risk factors.

When comparing patients with and without HIV co-infections, HIV-negative patients had a greater prevalence of diabetes (10.9% vs 3.3%), hypertension (23.2% vs 14.4%), and ever smoking (37.4% vs 29.4%). However, in regression analysis adjusting for potential confounders, other CVD risk factors and clustering, diabetes was the only risk factor that was significantly lower in HIV-negative patients (aRR=0.45, 95% CI 0.28-0.72). This finding adds to the increasing body of literature on the complex relationship between TB, HIV and CVD risk. Large cohort studies in the US and European populations have demonstrated that HIV-infection increases risk for CVD including hypertension, dyslipidemia, diabetes and CVD related morbidity and mortality.\textsuperscript{52–54} Many of these studies also suggest that ART increases CVD risk, although the evidence on the direct effect of ART is mixed.\textsuperscript{55–57} In sub-Saharan Africa, the evidence is sparser. Some literature suggests that patients living with HIV have a lower risk of hypertension than those without HIV infection, in part because of lower BMI. \textsuperscript{58,59} A systematic review by Nduka et al. found an increase in hypertension and systolic blood pressure with ART exposure, but there was significant heterogeneity among studies making it difficult to draw strong conclusions.\textsuperscript{32} One study based in KwaZulu-Natal province found that BMI and systolic blood pressure decreased on the population level after ART was introduced and found that there were significant differences in the impact by gender.\textsuperscript{60} In addition, by exploring this in a population with DR-TB, the prevalence of CVD risk factors is also impacted by factors that increase TB susceptibility including smoking, HIV, and diabetes.\textsuperscript{1}
As the non-laboratory CVD risk score has only been validated among patients older than 35 years of age, it was applied to 398 patients in this sample. Overall, the median score was 4.62% (IRQ 2.70-9.47) but HIV-negative patients had double the CVD risk score compared with patients with HIV co-infection (8.94 vs 4.00, z=7.003, p-value <0.0001). In addition, 20.7% of HIV-negative patients had a high risk (>20%) of a CVD related event in five years and a few patients had a CVD risk as high as 40%. This suggests that some high-risk patients have a risk of CVD morbidity or mortality during the two years of MDR-TB treatment. Providers should seek to screen, counsel, and treat CVD risk factors including obesity, smoking, diabetes, and hypertension. In addition, non-laboratory CVD risk scores, like the one used in this analysis, may identify high risk patients that require additional follow-up such as monitoring for dyslipidemia.

Given the high prevalence of CVD risk factors in the general population in South Africa and even among DR-TB patients, the second manuscript of this dissertation explored the impact of these risk factors on early MDR-TB treatment outcomes among patients co-infected with HIV. Of the 900 participants in the original cohort, 442 were co-infected with HIV, diagnosed with culture confirmed multidrug-resistant TB (MDR-TB) and remained in the parent study. Among these 442 participants, there were more males (52.5%), the mean age was 36.5 years (sd 9.0), 62% had known ART exposure, the median CD4 count was 188 (IQR 78-329), and 49.3% had at least one CVD risk factor. Smoking was the most common CVD risk factor (28.8%); the prevalence of other risk factors included: diabetes (2.4%), hypertension (13.5%) and elevated BMI (16.4%). There were 84 patients (19%) with a MDR-TB negative outcome at 6-months (i.e. death, lost to follow-up or treatment failure). BMI was the only CVD risk factor that impacted
early MDR-TB negative treatment outcome. Being underweight increased the risk of negative outcome (aHR=1.51, 95% CI 1.24-1.83) and being overweight decreased the risk of an early negative outcome compared with normal BMI (aHR=0.42, 95% CI 0.23-0.75). Smoking is a common risk factor that was hypothesized to moderate the relationship between the other CVD risk factors and outcome, but this hypothesis was unable to be explored because of insufficient sample size.

Among the 210 participants who were 35 years of age and older and did not have missing data on CVD risk factors, a non-laboratory CVD risk score was calculated and 86.4% of patients had a low CVD risk (<10% on the calculated score). Interestingly, a moderate or high CVD risk score increased the risk of MDR-TB negative treatment outcome compared with patients with a low CVD risk score (aHR=5.52, 95% CI 1.91-10.70) even after adjusting for other co-variates such as CD4 count. This appears to be driven by increased age, higher prevalence of smoking and diabetes and higher systolic blood pressure, even though these factors did not impact MDR-TB negative outcome individually. Further research with a larger sample is needed to explore why this combination score might have a greater impact than individual CVD risk factors.

Finally, as smoking was identified as a common risk factor for DR-TB patients with and without HIV co-infection, the third manuscript of this dissertation is a review of literature on smoking cessation interventions among TB patients. The review identified 13 intervention studies across 11 countries that were published between 2007 and 2017. All smoking interventions increased smoking cessation rates, ranging from 15% to 82% across the studies, although most of the studies had significant bias due to the study design (prospective cohort [n=5] or non-randomized intervention [n=3]) or lack of a
control group (n=6). The primary types of interventions were brief advice (n=9), behavioral counseling (n=4), medication (n=3), and community-based care with family members or community health volunteers (n=3). There was significant heterogeneity of definition of smoking and smoking abstinence and implementation that made it difficult to compare the results across studies. Louwagie et al. implemented a behavioral counseling intervention informed by motivational interviewing and found that smoking cessation increased by two-fold compared with patients who received brief advice by a TB nurse (RR=2.29, 95%CI 1.4-3.92). This suggests that more intensive counseling may provide an added benefit but needs to be weighed against the increased training and staff required, particularly in high prevalence TB settings where healthcare workers have limited time and resources.

A variety of healthcare workers implemented the smoking cessation interventions including nurses, physicians, clinic staff, community health workers and family members. Kumar et al. was the only study to compare the impact of physician brief advice compared with advice by a smoking cessation counselor and found no difference in smoking cessation rates (RR=1.2, 95% CI 0.9-1.8). Overall, it appeared that whomever provided the intervention was not very important suggesting that TB programs may use a variety of personnel including family members to promote smoking cessation. Several of the studies (n=4) successfully integrated smoking cessation into the existing TB programming even across several districts. Health policy makers and TB program managers should encourage collaboration between tobacco control and TB programming on a national and local level to better integrate care and potentially share resources.
Limitations & Strengths

This dissertation study had several limitations including the limitations of a secondary data analysis, missing data, low sample size, CVD risk score and outcome.

Secondary Data Analysis

As this study is primarily a secondary data analysis, this study has several limitations including (1) limitations of the parent study, (2) pragmatic data collection, (3) additional unmeasured variables and (4) use of only baseline data.

Limitations of the parent study: The parent study is a rigorously designed cluster randomized study with stringent quality assurance and control measure including site auditing and data monitoring. Patients at the nurse case management (NCM) sites may have had better quality data collection since NCMs are involved in baseline data collection, for example, part of their intervention was to ensure that vital signs were collected. However, research assistants and NCMs received the same training on rigorous data collection and accuracy of patient interviewing, minimizing this potential bias. NCM sites may have been more likely to initiate screening and treatment for CVD risk factors since nurses are more involved in patient care. The parent study intervention was evaluated as a potential contributor to negative outcome to account for differences between the NCM and control sites.

Pragmatic data collection: Vital sign measures were collected by hospital staff who have not been trained by the study. However, as all sites use the MDR-TB hospital equipment and no additional equipment is provided by the study, measurement error may occur at all sites. However, these pragmatic measurements are used by health care providers to make medical decisions including TB medication dosing, so they are
clinically relevant. Pragmatic designs focus on creating research that is more clinically relevant and thus externally valid, at the potential cost of internal validity related to measurement error or bias.\(^67,68\) Particularly, in low resource and “real world” settings like MDR-TB clinics, pragmatic research has greater potential to capture knowledge about participants and outcomes that are reproducible and clinically meaningful compared with tightly controlled “gold-standard” randomized controlled trials.

*Additional unmeasured variables:* As a secondary analysis, the study was limited in the variables that were available. Current smoking was added to the parent study but was not able to be used because of significant missing data. Baseline medical history included some possible medical conditions but did not include a history of cardiovascular disease specifically. In addition, only one blood pressure was measured so there was no ability to validate if patients had consistently elevated blood pressure suggestive of a diagnosis of hypertension.

*Use of baseline data:* This secondary analysis only used variables collected at baseline including CVD risk factors, HIV status, and other covariates such as CD4 count or creatinine clearance. Thus, the study did not capture patients who are later found to have HIV or CVD risk factors which may impact subsequent outcome. Rates of under-diagnosis of CVD risk factors are high in South Africa meaning that the number of CVD risk factors may be under-reported on baseline data before a provider can provide risk factor screening or follow-up. Thus, CVD risk factors may be under-represented in this study and the effect size for their impact on outcomes may be reduced. In addition, this study did not capture any changes in regimen or clinical status (i.e. renal function) longitudinally that might have influenced patient outcomes.
Missing Data

As the parent study was designed to programmatically support the MDR-TB program in a low resource setting, there were missing data on some key variables. Height was missing for 126 out of the 900 participants (14%) and this was concentrated at two hospitals, one of which did not routinely collect height. For this study, missing height was imputed using the mean height for those with a height by sex and 5-year age categories. In addition, baseline medical history and current smoking status were abstracted from the medical record and >10% of the sample was missing these variables. Given that smoking and diabetes are two common risk factors for negative MDR-TB treatment outcome, this is an important finding that medical providers are not completing or fully documenting patient medical histories. Finally, among patients co-infected with HIV who were followed for short term treatment outcome, creatinine and CD4 were not done at baseline for 37 (8.4%) and 55 (12.4%) participants respectively. This again suggests that providers may not be adhering to MDR-TB guidelines particularly for laboratory assessments that may be predictive of poor outcome. Among the 37 patients missing a CD4 count at baseline, 23 did have a viral load at baseline, another important measure of HIV immunologic status. However, overall, 34% of patients did not have a viral load so that variable could not be included in this analysis. To understand systematic bias resulting from patterns of missingness, differences between participants with and without missing baseline medical history, CD4 and creatinine clearance were evaluated. A sensitivity analysis was done on models adjusting for variables related to missingness.

Sample Size
A power analysis was conducted *a priori* that determined approximately 450 participants were required to evaluate the difference between patients with moderate/high CVD risk compared with low CVD risk on MDR-TB negative treatment outcome at 6-months. Of the 667 participants who were co-infected with HIV and eligible for the outcome analysis, 234 (35%) were eventually excluded from the parent study because the participant was determined to have baseline drug-sensitive TB, fluoroquinolone and/or aminoglycoside resistance or transferred facilities. In addition, missing data as described above, reduced the overall sample available for analysis to 322 participants. Thus, this study was underpowered to see differences in MDR-TB negative treatment outcome by individual CVD risk factors. In addition, two additional analyses exploring the interaction of smoking and other CVD risk factors and social determinants of health and CVD risk score on MDR-TB negative outcome could not be completed due to inadequate sample size.

**CVD Risk Score**

The CVD risk score used in this study has not been specifically validated in a population of patients with TB or HIV. The CVD risk score was compared with Framingham and six other laboratory based CVD risk scores and had comparable results, although these other CVD risk scores are not based on populations with a high prevalence of TB and HIV. It is possible because of the dyslipidemia associated with HIV and the weight loss associated with TB that this risk score misclassified patients. One of the challenges of any risk score is how to best calibrate and use risk scores across different populations. Even the DAD CVD risk score which was created based on a large cohort study of patients living with HIV and includes HIV specific variables was found to have
poorer discrimination than the Framingham CVD risk score in other samples of patients living with HIV.\textsuperscript{69–71} This points to the importance of recognizing the limitations of using risk scores based on even similar but not the same samples. However, at the same time, these risk scores including the non-laboratory based CVD risk score used in this dissertation, are important tools to identify patients at potentially higher CVD risk who may require additional screening such as lipid levels. Particularly in a low resource setting where laboratory tests are expensive, a non-laboratory based risk score can provide an initial screening for CVD risk and can be implemented by physicians, nurses or community health care workers in hospital or community settings.\textsuperscript{47} However, future research studies should look to validate CVD risk scores such as this non-laboratory based version, in population from low- and middle-income countries where HIV and TB are more prevalent.

\textit{Outcome}

The outcome variable for Aims 2 through 4 for this study was early negative treatment outcome (i.e. death, lost to follow-up or treatment failure) at 6-months of MDR-TB treatment. While these three outcomes are different, they all ultimately lead patients down a path towards death and thus are indicative of a non-successful outcome at the end of 6-months.\textsuperscript{1} Although studies have demonstrated that 6-months is the period with the greatest risk for death, this may not have been enough time for patients to become lost to follow-up or develop treatment failure.\textsuperscript{13,72–74} In addition, non-communicable diseases such as cardiovascular risk factors may not lead to immediate health consequences or negative outcomes but develop over time. Measuring outcomes at 6-months may not have allowed sufficient time for CVD risk factors to influence the
outcome. Future studies should be conducted to explore the impact of CVD risk on MDR-TB treatment outcomes at completion of therapy and to explore changes in CVD risk because of MDR-TB and HIV treatment.

**Implications: Practice**

This study found that over 50% of patients diagnosed with DR-TB had at least one CVD risk factor, with the most common being smoking, a known risk factor for negative TB outcomes. Although the prevalence of CVD risk factors among HIV co-infected patients were low in this sample, the relationship between TB, HIV, ART and CVD risk factors is complex so providers should not assume that CVD risk factors are not important to screen, monitor and treat among patients with HIV co-infection. Indeed, among patients over 35 with HIV co-infection, a moderate or high CVD risk score may increase the risk of early MDR-TB negative treatment outcome compared with patients with a low CVD risk score, highlighting a possible relationship between CVD risk factors for patients with HIV co-infection. Regardless of HIV status, if providers want to improve MDR-TB treatment outcomes, they need to address other co-morbidities including CVD risk factors. In addition, undiagnosed diabetes and hypertension are common in sub-Saharan Africa, so engagement with the health care system through a DR-TB diagnosis is an opportunity for providers to ensure that patients are screened, counseled and referred to the appropriate follow-up care. A non-laboratory based CVD risk score, such as the one used in this study, may be a simple way for providers or other clinic staff to evaluate a patients’ CVD risk and refer them for additional laboratory or clinical evaluation. This CVD risk score has been implemented in multiple countries in community based settings so it does not require extensive training or sophisticated
tools to use.\textsuperscript{47} Most importantly, a holistic patient centered perspective is needed for all healthcare providers as they are caring for patients with increasing complex disease profiles and medication regimens.

Providers also should seek to follow MDR-TB guidelines regarding medical history and laboratory evaluation. South African Department of Health MDR-TB medical records include screening for CVD risk factors and other co-morbidities and this information is being integrated into the electronic medical reference.\textsuperscript{75} Completing this information will assist providers in identifying at risk patients and provide more information for researchers and policy makers on the prevalence of co-morbidities among DR-TB patients. In addition, 11\% of patients with a reported history of diabetes had a HbA1c to evaluate their diabetes status and all those patients had an HbA1c greater than 10\% suggesting poorly controlled diabetes. South African MDR-TB guidelines suggest that providers evaluate HbA1c at baseline for known diabetes, every 3-months during treatment if the HbA1c does not meet the target of <7, and every 6-months if the patient is stable. This study did not evaluate monitoring of HbA1c over time, but this suggests that at baseline providers are not monitoring these at-risk patients per guidelines. Finally, as mentioned above, creatinine and CD4 counts were not available for all patients co-infected with HIV, 8.4\% and 12.4\% of the sample respectively. As patients with HIV are at greater risk for immune suppression and poor kidney function from anti-retroviral therapy, these are critically important baseline measures. TB clinic staff including nurses and clinical officers should monitor compliance to guidelines and could implement check-lists or other tools to ensure that guideline laboratory assessment and clinical evaluation are being completed.
Implications: Research

This study contributes to the body of literature supporting the importance of integrating research on non-communicable diseases such as CVD risk factors with infectious diseases such as TB and HIV.\textsuperscript{8,19} Primarily, this requires that infectious disease researchers incorporate other co-morbidities including CVD risk factors into their data collection to understand MDR-TB, TB and HIV treatment trajectories. In addition, national databases such as the MDR-TB National Register could incorporate some of that data to be able to explore population level prevalence and impact. In addition, while some risk factors such as smoking and diabetes are commonly explored with TB, other risk factors and the combination of risk factors are less understood. This study found that an elevated CVD risk score increases the risk of short term MDR-TB negative outcomes among patients with HIV co-infection. This suggests that the combination of age, sex and CVD risk factors may have a different impact than individual CVD risk factors on MDR-TB outcomes and patients. Further research is needed to better understand how specifically CVD risk factors impact MDR-TB treatment and explore the potential additive effects of multiple CVD risk factors.

This study also found that CVD risk factors were more common among patients with DR-TB only compared with patients co-infected with HIV. This adds to the body of evidence that CVD risk factors may be influenced by other factors including but not limited to HIV and ART use in sub-Saharan Africa. Further research is needed to explore the impact of the convergence of TB, HIV and CVD risk factors on HIV and TB outcomes and non-communicable disease morbidity and mortality, particularly in a sub-Saharan African context. In addition, this study did not examine how CVD risk factors
might impact negative outcomes in DR-TB without HIV co-infection. As diabetes and smoking are common risk factors for developing active TB, these risk factors and an elevated CVD risk score may be stronger predictors of negative outcome among patients with DR-TB only. It may also be that medications used to treat CVD risk factors influence TB treatment outcomes. For example, a recent study by Degner et al. found that diabetics treated with metformin during TB treatment had reduced mortality, similar to those of non-diabetics, compared with diabetics not treated with Metformin. 76 As CVD risk factors such as hypertension, obesity, and diabetes increase in prevalence in low- and middle-income countries like South Africa, ongoing integration of CVD risk factors into infectious disease care and research is needed.

Finally, research is needed to be understand how to integrate CVD risk factor prevention into TB care as demonstrated by the review of literature on smoking cessation interventions. Health promotion and prevention messages like smoking cessation can halt the further development of CVD risk factors and prevent morbidity and mortality during DR-TB treatment and beyond. However, the best way to integrate this messaging into TB care is not well documented. Researchers can facilitate this by working closely with local and national governments to help develop standardized definitions and tools to assess existing programming and develop additional intervention studies. Adaptive randomized controlled trials could be an effective tool for comparing multiple types of interventions to understand what strategies work best for which types of patients and settings. 77
Implications: Policy

Building health care systems that are integrative and promote holistic care are critical for the integration of non-communicable and chronic infectious disease. South Africa like many other low- and middle-income countries with high HIV prevalence has made tremendous strides in integrating TB and HIV care. Similarly, health care systems need to consider how to integrate non-communicable diseases into their care models. This can be a challenge as practice is often siloed, but health policy makers can influence and support providers in holistic care by providing adequate resources and training to manage these complex patients. Developing easy screening tools for TB and HIV providers to use for CVD screening, such as using a non-laboratory CVD risk score could be one step forward. In addition, sufficient personnel and training are needed to ensure that TB clinics are adequately staffed to manage these complex patients and that individual staff have sufficient expertise to screen, manage and refer patients with CVD co-morbidities. TB managers could work with other programs such as tobacco control to share resources and improve all programming.

Successfully implementing electronic health records and national MDR-TB databases could also provide data to better understand the intersection of non-communicable and infectious diseases particularly among TB and HIV patients. In addition, data from these systems could also be used to evaluate hospital and provider adherence to national guidelines. Again, this requires collaboration with local TB clinics including assuring resources for sufficient personnel and training to ensure that data is adequately collected.
It is also critical to understand the role that poverty and other social determinants of health play in negative outcomes from DR-TB and other chronic diseases. In this study, access to grant assistance from the government and employment was protective against MDR-TB negative treatment outcomes at 6-months. Most patients with MDR-TB experience some level of poverty so patients who already have grant access may already have social networks which connected them to this resource. It is critical for policy-makers to design government support systems that are accessible for patients. TB program managers at the national and local level should encourage patients to maintain their connection in community and could provide life skill training opportunities during TB treatment to facilitate employment after treatment completion.

**Conclusion**

This dissertation study suggests that that many DR-TB patients come for DR-TB treatment with at least one or more CVD risk factors and that these risk factors may complicate DR-TB treatment and impact early DR-TB outcomes. South Africa has made tremendous strides in improving DR-TB treatment including decentralization care and introducing new regimens such as the 9-month regimen or injection-sparing regimens. However, as the prevalence of CVD risk factors continues to increase, more patients will enter care for DR-TB with increasingly complex conditions and risk. It is critical for providers, researchers and policy-makers to continue to integrate non-communicable chronic care into infectious disease care. A patient-centered not disease-specific perspective to health will improve the morbidity and mortality in DR-TB outcomes and subsequent CVD related events.
References for Chapters 1 and 5


75. Manesen R. Introduction of a National DR-TB Register and how it has improved the DR-TB programme management within the South African context. 2017.


Appendix: Study Instrument

Additional Smoking Questions: *If patient already enrolled*

Patient Study Number: _______________________

Date of interview: ___________________________

For RA sites: Check MDR-TB chart and fill out based on medical chart
For NCM sites: Ask the patient at the next phone call/visit

1. When you initiated MDR-TB treatment did you smoke at that time?  
   ○ Yes  
   ○ No  
   ○ Not Documented

Additional Smoking Questions: For *newly enrolled patients*

Patient Study Number: _______________________

Date of interview: ___________________________

For RA & NCM sites: Ask patient on enrollment

1. Do you currently smoke?  
   ○ Yes  
   ○ No
Curriculum Vitae

PERSONAL DATA
Erin Rachel Whitehouse, MPH, RN
Telephone: 443-721-0425
ewhiteh3@jhmi.edu
Born September 26, 1981
Baltimore, Maryland, USA

EDUCATION

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<tr>
<th>Year</th>
<th>Degree</th>
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<tr>
<td>2018</td>
<td>Doctorate of Philosophy (expected)</td>
<td>Johns Hopkins University School of Nursing, Baltimore, MD</td>
</tr>
<tr>
<td>2011</td>
<td>Masters of Public Health</td>
<td>University of North Carolina, Gillings School of Public Health, Chapel Hill, NC</td>
</tr>
<tr>
<td>2003</td>
<td>Bachelor of Science in Nursing</td>
<td>University of Maryland School of Nursing, Baltimore, MD</td>
</tr>
<tr>
<td>2002</td>
<td>Bachelor of Arts (Biology)</td>
<td>Mount Holyoke College, South Hadley, MA</td>
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Fellowships

- 2016-2018: Jonas Nurse Leader Scholars Program, Johns Hopkins University School of Nursing
- 2016: Ellen Levi Zamoiski Doctoral Fellowship, Johns Hopkins University School of Nursing
- 2014-2016: Interdisciplinary Training in Cardiovascular Health Research (T32NR012704), Johns Hopkins University School of Nursing

CURRENT LICENSE AND CERTIFICATION

- 2014-: District of Columbia Board of Nursing, Registered Nurse
- 2004-: Maryland Board of Nursing, Registered Nurse
- 2002-: BLS Health Professionals Certification (AHA)

PROFESSIONAL EXPERIENCE

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<th>Years</th>
<th>Position</th>
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<tr>
<td>2014-2018</td>
<td>Pediatric Nurse Case Manager</td>
<td>Johns Hopkins Pediatrics at Home, Baltimore MD</td>
</tr>
<tr>
<td>2014, 2016</td>
<td>Research Assistant</td>
<td>Johns Hopkins University School of Nursing, Baltimore, MD; A Nurse Case Management Intervention to Improve MDR-TB/HIV Co-infection Outcomes. (PI: Dr. Jason Farley)</td>
</tr>
<tr>
<td>2014</td>
<td>Research Assistant</td>
<td>Johns Hopkins University School of Nursing, Baltimore, MD; Symptom Prevention and Management in African American Women With Breast Cancer (PI: Dr. Fannie Gaston-Johansson)</td>
</tr>
<tr>
<td>2013</td>
<td>Interim Nutrition Program Manager</td>
<td>Samaritan’s Purse, Yida Refugee Camp, South Sudan</td>
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<tr>
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<tr>
<td>2012-2013</td>
<td>Nutrition Program Coordinator</td>
<td>Samaritan’s Purse Yida Refugee Camp, South Sudan</td>
</tr>
<tr>
<td>2010-2012</td>
<td>Project Manager</td>
<td>Frances Payne Bolton School of Nursing Case Western Reserve University, Cleveland, OH; Addressing Childhood Obesity: BP and BMI Screening in the Cleveland Municipal School District (PI: Dr. Lynn Lotis, Dr. Donna Dowling)</td>
</tr>
<tr>
<td>2010-2012</td>
<td>School Nurse</td>
<td>The International School &amp; Near West Intergenerational School Cleveland, OH</td>
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<td>2010-2012</td>
<td>Registered Nurse</td>
<td>Hillcrest Hospital, Cleveland Clinic Mayfield Heights, OH</td>
</tr>
<tr>
<td>2009-2010</td>
<td>Registered Nurse</td>
<td>Family Developmental Center San Francisco, CA</td>
</tr>
<tr>
<td>2008-2009</td>
<td>HIV Case Manager</td>
<td>Zimpeto Children’s Center, Iris Ministries Maputo, Mozambique</td>
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<td>2006-2008</td>
<td>Pediatric Nurse Case Manager</td>
<td>Johns Hopkins Pediatrics at Home Baltimore, MD</td>
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<td>2005</td>
<td>Registered Nurse</td>
<td>Camp Boggy Creek Eustis, FL</td>
</tr>
<tr>
<td>2004-2005</td>
<td>Registered Nurse</td>
<td>Pediatric Intensive Care Unit Johns Hopkins Hospital, Baltimore, MD</td>
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**HONORS AND AWARDS**

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<tr>
<td>2016</td>
<td>Public Health Nursing Scholarship, American Public Health Association</td>
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<td>2016</td>
<td>Honorable Mention, Poster Presentation, Global Health Day</td>
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<td>2015</td>
<td>Isabel Hampton Robb Scholarship, Nurses Educational Fund, Inc.</td>
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<tr>
<td>2011</td>
<td>Delta Omega Honor Society Theta Chapter, University of North Carolina Chapel Hill</td>
</tr>
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<td>2011</td>
<td>Margaret Blee-Ruth Warwick Hay Public Health Nursing Leadership Award, University of North Carolina Chapel Hill</td>
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<tr>
<td>2003</td>
<td>Sigma Theta Tau International Inductee, University of Maryland-Baltimore</td>
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<td>2002-2003</td>
<td>John Whitehurst Scholarship, University of Maryland-Baltimore</td>
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<td>2002</td>
<td>Phi Beta Kappa Inductee, Mount Holyoke College</td>
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<td>2002</td>
<td>Alamara Fellowship, History Department, Mount Holyoke College</td>
</tr>
<tr>
<td>2000, 2002</td>
<td>Bernice MacLean Award for excellence in Biology, Mount Holyoke College</td>
</tr>
<tr>
<td>2001</td>
<td>Abby Howe Turner Award for excellence in Biology, Mount Holyoke College</td>
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<td>2000</td>
<td>The Merrill Prize, English Department, Mount Holyoke College</td>
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**RESEARCH**

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<td>2016 - 2018</td>
<td>Cardiovascular Multi-Morbidity Among South Africans with Drug Resistant Tuberculosis and HIV. Grant # 1F31NR016909-01 Individual, National Institute of Health (NIH), National Institute for Nursing Research National Research Service Award (NRSA); total direct $108,748.</td>
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SCHOLARSHIP

Non-Peer Reviewed Publications

Peer reviewed publications (* Data based)


Peer reviewed abstracts


Conference Meetings/Presentations
International:

PROFESSIONAL ACTIVITIES
2014 - Member, Sigma Theta Tau International, Nu Beta Chapter
2011 - Member, American Public Health Association, Public Health Nursing
2015-2017 Member, Association of Community Health Nurse Educators (ACHNE)
2015-2017 Member, International Network for Doctoral Education in Nursing (INDEN)
2014-2018 Member, Preventive Cardiovascular Nurses Association
2013-2017 Member, American Public Health Association, Public Health Nursing Research Committee

EDUCATIONAL ACTIVITIES
2017 Teaching Assistant Biostatistics
Johns Hopkins University School of Nursing
Baltimore, MD
2016 Guest Lecturer Global Health, Public Health Nursing,
Johns Hopkins University School of Nursing
Baltimore, MD
Epidemiology, Public Health Nursing,
Johns Hopkins University School of Nursing
Baltimore, MD
2015 Teaching Assistant Public Health Nursing,
Johns Hopkins University School of Nursing
Baltimore, MD
2002 Teaching Assistant Cell Biology Laboratory Teaching Assistant,
Mount Holyoke College, South Hadley, MA
2001 Writing Assistant Speaking, Writing, & Arguing Center
Mount Holyoke College, South Hadley, MA
2000 Teaching Assistant Chemistry Department,
Mount Holyoke College, South Hadley, MA

ACADEMIC SERVICE
2016- 2017 Nurse Faculty for the Future Student Advisory Committee
2016 PhD Interest Group Student Leader
2015- 2017 PhD Curriculum Committee, Student Representative,
Johns Hopkins University School of Nursing (elected position)