TITLE: ***Ba****rriers to* ***t****uberculosis preventive* ***t****reatment in patients with newly diagnosed diabetes mellitus and latent tuberculosis infection (BATT)*

ABSTRACT

Type 2 diabetes mellitus increases the risk of developing active tuberculosis (TB) disease. An estimated 15-25% of all active TB cases are attributable to diabetes, and globally this represents 1.4-2.3 million cases of TB each year. Despite the important relationship between diabetes and TB, little is known about the relationship between diabetes and risk of latent TB infection. Because diabetes increases the risk of reactivation from latent to active TB, and given the increasing proportion of active TB cases due to reactivation, an increasing proportion of TB cases in the US will likely be attributable to diabetes. Consequently, persons with diabetes are a high priority group targeted for latent tuberculosis screening and treatment. To improve knowledge regarding diabetes and latent TB treatment, we propose to conduct a pilot case-control study (N=170) in collaboration with Grady Memorial Hospital to compare the prevalence of latent TB in patients with and without diabetes, to determine the proportion of newly diagnosed diabetes patients with latent TB infection that begin and complete latent TB treatment, and to identify barriers to successful latent TB treatment in patients with diabetes. The proposed study will be the first to provide an estimate of the burden of latent TB infection among patients with diabetes and to examine whether diabetes is a risk factor for failing to begin or complete latent TB treatment. Data from this study will be used to design interventions aimed at improving latent TB treatment adherence and will be used to apply for external grant mechanisms.

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PROJECT NARRATIVE

SECTION A. INTRODUCTION

A.1 Epidemiology of Tuberculosis and Diabetes: The epidemics of tuberculosis (TB) and type 2 diabetes mellitus (diabetes) are converging, inhibiting effective public health control and clinical management for both diseases and threatening recent gains in global TB control.[1] Annually, 9 million incident cases of active TB occur, and one-third of the world's population is estimated to be infected with *Mycobacterium tuberculosis* (MTB) and at risk of developing active TB disease.[2] The prevalence of adult type 2 diabetes is currently 8.3% (387 million people) worldwide and is expected to surpass 590 million persons by 2035.[3] Diabetes is estimated to triple the risk of progressing to active TB disease and an estimated 15-25% of global TB cases are already attributed to co-morbid diabetes.[4,5] With the prevalence of diabetes increasing rapidly during the next two decades, there is great concern about the further impact that the diabetes epidemic will have on TB control both in the US and internationally.[1,6]

Since 1992 annual active TB incident rates in the US have slightly decreased, and in 2013 there were an estimated 3 cases per 100,000 population per year.[7] As active TB cases continue to decrease due to enhanced case detection and effective treatment, a larger proportion of new TB cases in the US will arise due to reactivation in those with latent TB infection.[8,9] Given diabetes increases the risk of reactivation from latent to active TB and because the increasing proportion of new active TB cases due to reactivation, in the coming decades a larger proportion of TB cases in the US will likely be attributable to diabetes. In the state of Georgia, for example, we recently reported that the 2009-2012 prevalence of HIV (the greatest risk factor for active TB) and diabetes among active TB cases was similar (11.1 vs. 11.4%).[10]

Although diabetes is widely recognized to increase the risk of progression from latent to active TB, little is known about the epidemiology of co-occurring diabetes and latent TB infection. In 1999-2000 the estimated national prevalence of latent TB infection in the US population aged 24-74 years was 5.7%.[11] Certain high-risk subgroups, most notably foreign born persons, have substantially higher prevalence of latent TB infection. A comprehensive latent TB screening program in Atlanta also reported high prevalence in the metro area. For example, 23.4% of patients screened at Grady Hospital were infected with latent TB.[8] Our preliminary data (Table 1) collected at a DeKalb County clinic for foreign-born refugees to the US demonstrated that patients with diabetes had significantly higher prevalence of latent TB infection than those without diabetes (adjusted odds ratio 2.3, 95% CI 1.2-4.5)[12] However, to our knowledge, whether the association between diabetes and latent TB infection is similar in an urban hospital in the US has not been studied.

Table 1. DeKalb Count Refugee Clinic	Total N=694	No diabetes N=406 (58.4%)	Pre-diabetes* N=235 (33.8%)	Diabetes* N=54 (7.8%)
Latent TB prevalence	31.8%	25.9%	39.1%	46.0%
*Pre-diabetes defined by HbA1c 5.7-6.4% and diabetes defined by HbA1c ≥ 6.5%; Chi-square p-value <0.01				

A2. Latent TB and increased risk of type 2 diabetes: Our preliminary data from DeKalb County used a cross-sectional design and therefore we were unable to determine if the study's results were due to diabetes increasing the risk of latent TB infection, or whether having prevalent latent TB infection may have increased the risk of diabetes. Most data from animal studies support the hypothesis that diabetes increases the risk of latent TB infection, however, the immunologic basis for increased risk of TB infection and TB disease among patients with diabetes is not well understood.[13,14] Both innate and adaptive immune responses are thought to be impaired in patients with diabetes, which likely lead to increased susceptibility of initial TB infection and reactivation of latent TB.[15] The innate immune system in patients with diabetes may be inhibited by reduced monocyte activation and signaling[16,17] and reduced secretion of anti-mycobacterial peptides.[18] On the other hand, the innate immune response which leads to inflammation in adipocytes is also triggered by cytokines involved in containing *Mycobacterium tuberculosis* infection. Consequently, there is biologic plausibility that latent TB infection may increase the risk of diabetes.

Despite immune and animal model data, epidemiologic studies have not been conducted to differentiate whether diabetes increases the risk of latent TB infection or if latent TB infection increases the risk of diabetes. In order to definitively determine the direction of the association between diabetes and latent TB infection, a large cohort study with extensive follow-up time is necessary. In the absence of such a resource intensive cohort study design, we propose to conduct a pilot case-control study among patients with diabetes that will improve knowledge regarding the relationship between latent TB and diabetes in an inner-city US setting.

A3. Treatment of Latent TB Infection in Patients with Diabetes: In the US, identification and treatment of the large reservoir of persons with latent TB infection is critical to ensure continued reduction in active TB rates and will be necessary to achieve the nation's goal of TB elimination.[19,20] The US Centers for Disease Control and Prevention (CDC) and American Thoracic Society recommend targeted screening and treatment for latent TB infection in those at increased risk of reactivation.[21] However, the proportion of persons with latent tuberculosis infection who initiate and complete treatment is low.[8] Established risk factors for non-completion of latent TB treatment include younger age, substance abuse, and certain treatment regimens.[20,22]

Because diabetes increases the risk of active tuberculosis disease, persons with diabetes are a high priority group that should be targeted for latent tuberculosis screening and treatment. To our knowledge, no previous studies to date have examined if diabetes increases the risk of non-initiation or non-completion of treatment for latent TB infection. Our proposed study will provide preliminary information regarding the proportion of patients with diabetes who initiate and complete latent TB treatment and will also generate information on barriers to latent TB treatment. Moreover the pilot data will be used design future studies that can definitively answer important questions regarding the epidemiology, pathophysiology, and clinical management of latent TB and diabetes.

SECTION B. SPECIFIC AIMS

We propose to conduct a case-control study among 85 patients with diabetes receiving care at the Grady Diabetes Clinic and 85 community matched controls to examine the following specific aims:

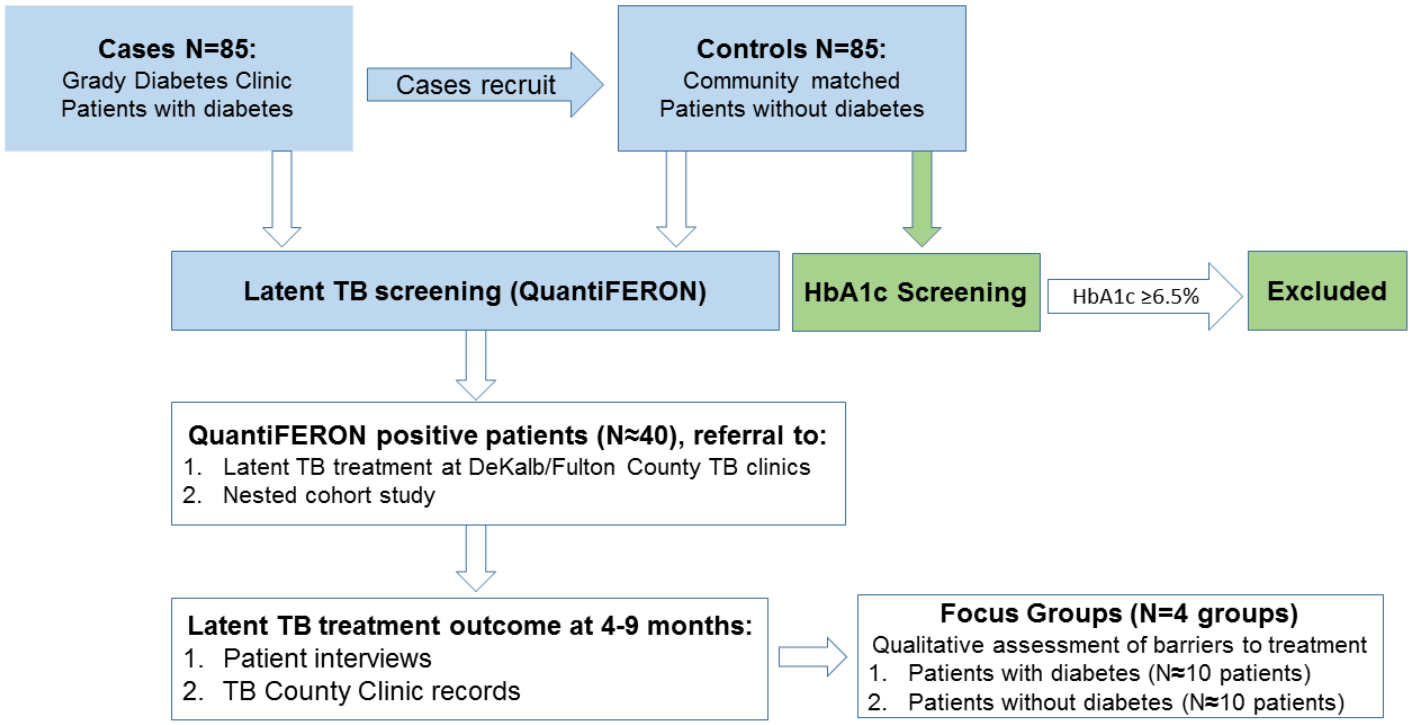
1. Compare the prevalence of latent tuberculosis infection in patients with diabetes at Grady Hospital to the prevalence of latent tuberculosis infection among community-matched controls without diabetes.
2. Determine if the proportion of patients with diabetes that 2A) initiate and 2B) complete latent TB treatment is lower than the proportion of community matched controls who initiate and complete treatment.
3. Identify the barriers to 3A) initiating latent tuberculosis treatment and 3B) completing latent tuberculosis treatment among patients with diabetes at Grady Hospital.

SECTION C. STUDY METHODS

C1. Study Design Overview: The BATT case control study will screen 85 patients with diabetes for latent TB infection at the Diabetes Outpatient Clinic at Grady Memorial Hospital. Each patient with diabetes will be 1-to-1 pair matched to community controls (N=85) who will also be screened for latent TB infection (Figure 1). To determine rates of latent TB treatment initiation and completion, the BATT study will also incorporate a nested prospective cohort study among all enrolled participants (cases and controls) who have latent TB infection. Standard latent TB treatment will be administered by local county health departments (i.e., Fulton County and DeKalb County TB Clinics). Participants in the nested cohort study will be interviewed 4-9 months after TB screening to determine treatment initiation, completion, and side-effects. A subset (N=20) of those in the nested cohort study will also be invited to participate in four focus groups sessions that will use qualitative methods to identify barriers to treatment initiation and completion.

C2. Setting: The BATT study will take place at the Grady Memorial Hospital Diabetes Clinic where co-investigators Drs. Haw and Umpierrez manage patients with diabetes. The Diabetes Clinic operates Monday through Friday and manages care for approximately 900 new referrals per year. Treatment for patients with latent TB infection will be provided for free by Fulton and DeKalb County health departments, per standard of care. Focus groups will be conducted at the School of Public Health, Georgia State University.

Figure 1. Study Flow Diagram



C3. Study Participants and Enrollment: The BATT case control study will enroll 170 patients. Eligible *cases* include any adult (age ≥ 21 years) with type 2 diabetes mellitus (HbA1c ≥ 6.5%) newly referred to the Grady Diabetes Clinic during the study period. Patients with a previous history (medical record or self-report) of active TB and those residing outside DeKalb or Fulton County will be ineligible. The BATT Project Coordinator will spend 2.5 days per week at the Grady Diabetes Clinic to obtain consent and enroll patients.

Controls will be recruited by enrolled cases. Each case will be instructed to invite a community or family member to participate as a study control. Eligible controls include persons without diabetes who are the same sex, age range (within +/- 5 years), and reside in the same zip code (documented by photo identification) as cases. Controls will be screened for diabetes at enrollment, persons with diabetes (HbA1c ≥ 6.5%) or history of active TB (self-reported) are ineligible as controls. Controls will be enrolled and screened for diabetes and latent TB at Grady's ACTSI Clinical Research Unit (Directed by Co-investigator Dr. Umpierrez).

All study participants who screen positive for latent TB infection will be enrolled in the cohort study. Of those participants in the cohort study, we will consecutively invite 10 patients with diabetes (5 who initiated latent TB treatment and 5 who did not) and 10 patients without diabetes (5 who initiated latent TB treatment and 5 who did not) to participate in the focus groups.

The study protocol, consent documents, and materials will be reviewed by the ethical review boards of Georgia State University and Emory University and in collaboration with Grady Hospital, DeKalb County, and Fulton County Boards of Health (Georgia Department of Public Health).

C4. Study Measures: Case control study: The primary study outcome is type 2 diabetes mellitus status which will be defined based on American Diabetes Association 2015 clinical guidelines.[23] Controls will also be screened for diabetes status using Simens DCA Analyzer, a point-of-care HbA1c test. The primary study exposure of interest is prevalence of latent TB infection. All cases and controls will be screened for latent TB infection using the interferon-gamma release assay QuantiFERON-TB Gold In-Tube Test (Quest Diagnostics) and classified according to CDC and the American Thoracic Society guidelines.[24] Additional patient covariates will be collected from a questionnaire administered at study enrollment by trained study staff. The questionnaire will collect basic

demographic information, health behavior data (tobacco use, known comorbidities, access to primary health care), and assess knowledge and attitudes regarding TB and TB treatment.

Cohort study: A nested cohort study will be performed among all cases and controls that screen positive for latent TB infection (N≈40). The primary exposure for the cohort study will be diabetes status as determined at the time of enrollment into the case control study. All patients who have latent TB infection and are eligible to receive latent TB treatment will be referred to DeKalb or Fulton county Health Departments for standard of care latent TB management (Table 2).

The primary outcome of interest for the cohort study will be latent TB treatment initiation which will be measured by 1) a follow-up patient questionnaire administered via telephone 4-9 months after study enrollment, and 2) cross referencing county TB clinic registries to determine if patients initiated latent TB treatment. Similarly, interviews and registry reviews will be used to assess if patients in the cohort study completed (defined as completing 95% of doses) latent TB treatment or experienced side effects from treatment.

Table 2. Standard Latent TB Treatment Regimens

Drug(s)	Duration	Frequency	Total doses
Isoniazid	9 months	Daily	270
		Twice weekly	76
	6 months	Daily	180
		Twice weekly	52
Isoniazid & Rifapentine	3 months	Once weekly	12
Rifampin	4 months	Daily	120

Adapted from CDC's Latent TB Infection: A Guide for Primary Health Care Providers.[25]

Focus Groups: We will conduct four focus groups, each with 5 patients who were defined to have latent TB infection by the BATT study and who were referred to local county health departments for latent TB treatment. Focus groups will be semi-structured to collect qualitative data on individual and structural domains pertaining to latent TB treatment (Table 3). Focus groups will be stratified by diabetes status (2 focus groups including patients with diabetes and 2 focus groups in patients without diabetes) and by latent TB treatment initiation (2 focus groups in patients who initiated latent TB treatment and 2 focus groups in patients who did not initiate treatment). Patients will be recruited consecutively for the focus group sessions during the follow-up telephone interview of the cohort study.

C5. Data Analysis and Management Plan: All questionnaire and medical record data will be collected with paper case report forms and entered into a REDCap (HIPPA compliant) electronic database.[26] All data analyses will be performed using SAS 9.4 (Cary, NC). Bivariate analyses will be performed to assess the association between case/controls status and participant characteristics including the primary exposure (prevalence of latent TB infection). To address aim 1, we will use conditional logistic regression to estimate crude and adjusted odds ratios and 95% confidence intervals for the association between diabetes (primary outcome) and latent TB infection (primary exposure). To address aim 2, we will use a chi-square test compare the proportion of patients that initiate latent TB treatment by diabetes status. To address aim 3, we will use focus group transcripts to identify primary and secondary thematic topics about barriers to treatment initiation and completion within the semi-structured adherence domains (Table 3). A two-sided p-value < 0.05 will be considered statistically significant for all analyses.

Table 3. Focus groups and domains for qualitative analysis of barriers to latent TB treatment

Individual Level	Structural
• Knowledge & attitudes about treatment • Substance abuse; comorbidities; mobility • Treatment side effect • Social economic status and costs	• Treatment regimen • Organization of care • Family and community support • Legal

C6. Sample Size: To determine sample size, we used previously published data and assumed that the prevalence of latent TB infection among controls would be similar to the Atlanta inner-city average (17.2%).[8] Also using previously published data from Grady Hospital and estimates from our preliminary data in DeKalb County, we assumed patients with diabetes at Grady Diabetes clinic would have 30% prevalence of latent TB.[8,12] Given these assumptions and using an alpha level of 0.05, with 170 patients (85 cases and 85 controls) we will have 80% power to detect a statistically significant difference in latent TB infection comparing patients with and without diabetes.[27]

C7. Study Team: The BATT study team will consist of an interdisciplinary team with expertise in both latent TB infection and diabetes/endocrinology. Principal investigator Dr. Magee has an established research record focused on the intersection of TB and diabetes, including in the state of Georgia.[10] Drs. Blumberg, Kempker, and Ray are infectious disease clinicians with internationally recognized expertise in the diagnosis and treatment of latent TB. Drs. Haw and Umpierrez are endocrinologists with extensive experience managing patients with diabetes at Grady Hospital, conducting clinical research, and serving the Atlanta metropolitan community.

C8. Timeline

Grady Diabetes clinic receives approximately 17 patient referrals for care per week, therefore we anticipate enrollment of cases will be completed within 2 months of study initiation. Controls will be concurrently enrolled. Patients with latent TB infection will automatically be included in the cohort study.

Activity / Month	1	2	3	4	5	6	7	8	9	10	11	12
Protocols & IRB approvals	X	X										
Staff training	X	X										
Case control data collection		X	X	X	X							
Cohort study data collection		X	X	X	X	X	X	X	X	X	X	
Focus groups									X	X	X	
Data analysis and manuscripts				X				X			X	X

SECTION D. ANTICIPATED RESULTS

We anticipate pilot data from the BATT study will provide the investigators sufficient preliminary information to achieve three future goals. First, the BATT study will provide data which we will use to submit an abstract for presentation at a national or international scientific conference. Similarly, BATT data will be analyzed and submitted as a manuscript for publication in a peer-reviewed journal. Second, we will use the preliminary data to demonstrate to external funders that latent TB treatment in patients with diabetes is worthy of larger and more in depth epidemiologic and clinical-translational investigations. The scientific conference presentation and publication will serve as reference to the study team's ability to collaborate successfully. Moreover, the BATT study data will be useful to plan future recruitment strategies and provide highly accurate sample size estimations for future studies. The study team anticipates submitting a R01 or R21 to the US National Institutes of Health within a year of completing the BATT pilot study. Third, data from the BATT pilot study will provide preliminary information for designing interventions aimed at improving latent TB treatment initiation and adherence in patients with diabetes. Study focus group data will be used to develop an intervention and to plan additional pilot studies to test the intervention. Ultimately we aim to create an intervention that can be tested to assess the efficacy of improving latent TB treatment outcomes in patients with diabetes.

SECTION E. SIGNIFICANCE

Current understanding of the relationship between diabetes and latent TB is critically limited by a paucity of epidemiologic data. The BATT pilot study will importantly increase TB-diabetes knowledge in at least three areas. First, by producing prevalence estimates of latent TB infection in patients with diabetes, we will provide an important indicator of the burden of infection in this high risk group in an inner-city US population. By using an efficient matched case-control design, the pilot study will also generate an estimated measure of association (adjusted odds ratio) between latent TB infection and diabetes. Second, to our knowledge, the BATT study will be the first to investigate barriers to latent TB treatment initiation and completion in patients with diabetes. Similarly, our study will be the first to examine whether diabetes is a risk factor for failure to initiate or complete latent TB treatment. Knowledge regarding the relationship between diabetes and latent TB treatment may inform future clinical guidelines. Third, the BATT study will collect data on side effects of latent TB treatment in patients with and without diabetes. To date few studies have examined the side effects of anti-TB medications in patients with diabetes. Our findings will have important preliminary implications for treatment of latent TB and active TB treatment in patients with diabetes.

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