TB OR NOT TB:

Treatment of Latent Tuberculosis Infection in Harlem, New York

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ABSTRACT

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An estimated 9 to 14 million persons in the United States have latent tuberculosis infection (LTBI) and are therefore at risk for progression to active disease.[1] Diagnosis and treatment for LTBI has been identified by the Centers for Disease Control and Prevention (CDC) and the Institute of Medicine as a major strategy for elimination of tuberculosis (TB) in the U.S.[2,3] Approximately 200,000 - 300,000 Americans are treated for LTBI each year.[4] This dissertation investigates patient characteristics that are associated with LTBI treatment completion and assesses the impact of a peer-based experimental intervention on adherence to, and completion of, LTBI treatment. A review of the literature (Chapter 2) demonstrates that LTBI treatment completion rates in the U.S. and Canada generally fall below established targets and have been reported to range from 20 to 65% for a 6-month course of self-administered treatment. Associations between patient factors, clinic facilities, or treatment characteristics and adherence to LTBI treatment were found to be inconsistent across studies. Additionally, adherence interventions have been developed but no single intervention has shown consistent effectiveness.

This suggests that a 'one-size-fits-all' approach to LTBI treatment adherence is not likely to succeed across all settings.

The remainder of the dissertation focuses on predictors of LTBI treatment completion and the impact of a peer-based experimental intervention on adherence to, and completion of, LTBI treatment in two separate randomized controlled trials. Data for these analyses are drawn from two sequential randomized controlled trials designed to compare a peer-based intervention to usual care for ensuring completion of treatment for LTBI in an urban clinic setting: the *Pathways to Completion Study* (recruitment from 1996 through 2000) as well as from the *Tuberculosis Adherence Partnership Alliance Study (TAPAS)* (recruitment from 2002 through 2005). Chapter 3 describes the change in demographic, social, and behavioral characteristics between the two study populations.

The first analysis (Chapter 4) examines predictors of LTBI treatment completion in this population. Our results suggest that foreign birth, homelessness, marriage, and alcohol or drug use all influence completion of TLTBI through complex interactions. Overall, married persons had better completion rates, but married foreign-born patients were substantially more likely to complete therapy than unmarried foreign-born patients. Similarly, alcohol users were less likely to complete therapy, but homeless alcohol users were more likely to complete treatment than other homeless patients. The latter is probably an artifact of our clinic population, which includes patients from alcohol and substance abuse rehabilitation programs. Residence in such programs may have a positive effect on treatment completion. Race/ethnicity did not appear to be associated with treatment completion, although the differences between the two study populations made this difficult to assess.

Following from this, an analysis of the effectiveness of a peer-based experimental intervention on adherence to, and completion of, LTBI treatment in two separate randomized controlled trials (Chapter 5) finds peer support experimental intervention to be very effective in the Pathways population but not in the TAPAS population where completion rates increased substantially for both the intervention and control groups. The power for detecting an intervention effect in TAPAS was reduced by the higher than expected completion rates in both groups; however, the effect of the TAPAS intervention is statistically significant in the adherence model. Adherence analysis in TAPAS suggests that it is important to intervene early in the treatment as the first two months of treatment present a danger period where patients tend to default treatment. The most common reasons reported for not adhering to treatment were "forgot", "ran out of medications", and "other priorities." Identifying reasons for missing medications can suggest possible foci for interventions in the early months, such as weekly reminders to take the medications and ensuring that prescriptions are refilled on schedule.

Taken together, the findings of this research have significant implications for improving adherence to and completion of LTBI treatment. Currently, the primary intervention for improving LTBI adherence consists of educational programs to increase knowledge and modify attitudes. Our findings suggest that tangible assistance would be more effective in encouraging treatment completion. Additionally, adherence analysis in TAPAS suggests that it is important to intervene early in the treatment. Close follow-up of patients during the first two months of treatment, with prompt intervention to encourage completion among those stopping treatment, may yield better outcomes and reduce costs over the long term.

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DEDICATION

In memory of my father Michael Hirsch

Chapter 1:

Introduction

Consensus is building that the identification and treatment of latent tuberculosis infection (LTBI) among the reservoir of latently infected persons is the key to the elimination of tuberculosis in North America.[1,2] An estimated 9 to 14 million persons in the United States have LTBI placing them at risk for progression to active disease, and approximately 200,000 - 300,000 Americans are treated for LTBI each year.[3,4] Targeted testing in high risk populations has proved to be an important approach to the identification of at-risk subjects. While these TB control strategies are currently being refined with the use of interferon-gamma release assays in place of tuberculin skin testing, the basic strategies for identifying at-risk persons are time-tested. Less clear is what guidance to offer providers for targeting factors that influence completion so that we could help all patients complete treatment and what interventions may be effective in promoting adherence and completion of treatment.

In the context of moving from TB control to TB elimination in the United States, adherence to and completion of treatment of LTBI are crucial factors in the success of eliminating TB in the U.S. Therefore, it is important to elucidate factors associated with adherence and completion of LTBI treatment. Identifying barriers to adherence and completion of LTBI treatment will facilitate the development of effective, culturally competent interventions. Furthermore, it is important to evaluate new interventions, based on patients' perceptions and behavior, for improving adherence to and completion of LTBI treatment.

Starting in 1955, several reasonably large, adequately conducted studies have examined the efficacy of isoniazid in the prevention of tuberculosis among persons without HIV infection.[5] These clinical trials have shown the effectiveness of isoniazid ranging from 92 percent in preventing active tuberculosis in patients when adherence is high, to 26 percent when adherence is low. The current recommended standard therapy for LTBI, which consists of 9 months of

daily isoniazid taken in a 12-month period, has an efficacy of more than 90%.[6] A large multi-site study reported recently that treatment completion rates of the standard 9-month isoniazid regimen range from 30-60%,[7] far below established targets of 80-85% completion.[8]

Poor adherence to treatment for LTBI and corresponding modest treatment completion rates impede efforts to eliminate TB in this country. This issue is particularly critical in Harlem, a community where the rates of TB greatly exceed the national average (16.7/100,000 vs. 4.2/100,000 in 2008, respectively)[9] and the concomitant HIV epidemic results in a large population vulnerable to TB. The barriers to adherence in this population are significant because of multiple challenges to accessing health care services, including language barriers, transportation, and lack of knowledge about available no-cost health services. The social stigma attached to many infectious diseases gives rise to fears of discrimination and isolation, and often inhibits people from seeking testing and treatment services. Another significant barrier in this population is fragile and inadequate social support networks. Furthermore, the large proportion of immigrants in Harlem may share with the general population a low awareness of the need for preventive health behaviors, such as completion of treatment for LTBI. High substance use rates in the community may further contribute to non-adherence risk.

The objectives of this dissertation were 1) to critically review the literature on adherence to treatment of LTBI, 2) To identify the change in demographic, social, and behavioral characteristics of patients undergoing treatment for LTBI in the Chest Clinic at Harlem Hospital between 1996 and 2005, 3) to identify patient demographic, social, and behavioral characteristics that are associated with LTBI treatment completion, and 4) to assess the impact of a peer-based experimental intervention on adherence to and completion of LTBI treatment in a general clinic population in an urban setting in the U.S. Data for the dissertation are drawn from the *Pathways*

to Completion Study (recruitment from 1996 through 2000) as well as data from the *Tuberculosis Adherence Partnership Alliance Study (TAPAS)* (recruitment from 2002 through 2005). Pathways and TAPAS were sequential randomized controlled trials designed to compare a peer-based experimental intervention to usual care for ensuring completion of treatment for LTBI in an urban clinic setting.

The dissertation is comprised of six chapters. After this introduction, chapter 2 reviews the literature on adherence to treatment of LTBI focusing on the following areas: review of LTBI treatment completion rates in a variety of settings and regimens, discussion of issues in the measurement and analysis of adherence, review of known predictors of adherence to LTBI medications, and review and examination of different interventions developed to improve adherence to and completion of LTBI treatment. Chapter 3 describes changes in demographic, social, and behavioral characteristics of 610 patients undergoing treatment for LTBI in the Chest Clinic at Harlem Hospital between 1996 and 2005. Chapter 4 examines predictors of LTBI treatment completion; foreign birth, homelessness, and current substance use were hypothesized a priori to be predictors for LTBI treatment non-completion. Chapter 5 assesses the impact of a peer-based experimental intervention on adherence to and completion of LTBI treatment in two sequential randomized controlled trials; it was hypothesized that the intervention would have a positive effect on LTBI treatment completion rates. The dissertation ends with a short concluding chapter discussing how these results, taken together, can contribute to our understanding of factors associated with completion of LTBI treatment and the evaluation of effective interventions, delivered in a culturally competent manner, for improving adherence to and completion of LTBI treatment.

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Chapter 2:

Adherence to treatment for latent tuberculosis infection: systematic review of studies in the U.S. and Canada

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SUMMARY

BACKGROUND: There is renewed attention to the critical role of successfully treating latent tuberculosis infection (LTBI) in reducing the overall impact of tuberculosis (TB). However, levels of treatment adherence are consistently low in industrialized countries such as the U.S. and Canada.

OBJECTIVE: A systematic review of studies in the United States (U.S.) and Canada was undertaken to analyze methods of measuring LTBI treatment adherence, rates of adherence and completion of LTBI treatment in different settings and with different interventions, and predictors of LTBI treatment adherence.

METHODS: PUBMED, MEDLINE, and PsycINFO electronic databases were searched for quantitative studies published between 1997 and 2007. Full texts of articles were reviewed for data abstraction, and studies were critically examined for their methodology and rigor. This review presents outcomes from 78 studies.

RESULTS: Adherence and completion rates of treatment of LTBI are suboptimal across high-risk groups, regardless of regimen. LTBI treatment completion rates in the U.S. and Canada generally fall below established targets and have been reported to range from 20 to 65% for a 6-month course of self-administered treatment; a few smaller studies were able to achieve higher completion rates. Associations between adherence and patient factors, clinic facilities, and medication regimen characteristics were found to be inconsistent across studies. Adherence does not appear to be related to patients' age, gender, place of birth, or race. Several adherence interventions have been developed to improve LTBI treatment adherence in the U.S. and Canada; however, no single intervention has shown consistent effectiveness. Incentives, contextual considerations, and professional adherence counseling were successfully applied to

improve adherence, but they need to be tested for reliability in diverse settings. Interventions using DOT, education programs, and peer support report mixed findings and warrant further exploration in the context of TLTBI.

CONCLUSION: LTBI must be effectively treated if the goal of TB elimination is to be realized. Consistently employing tools for measuring and improving adherence are fundamental. Identifying barriers to adherence and treatment completion will facilitate the development of effective, appropriate interventions. A ‘one-size-fits-all’ approach to TLTBI adherence is not likely to succeed across all settings. Innovative approaches can inspire future interventions and suggest solutions for the current problems facing LTBI programs and their patients.

INTRODUCTION

Recognition is growing within the medical community that the promise of efficacious therapies to treat long-term and chronic disease conditions cannot be met unless patients consistently adhere to prescribed drug regimens.[1] Adherence to treatment influences individual health outcomes and the overall cost of health care and, in the case of communicable infections such as tuberculosis (TB) and the human immunodeficiency virus (HIV), can influence the emergence and spread of resistant strains.

In TB, efforts to improve adherence have focused primarily on treating TB disease. Several factors contribute to the public health prioritization of adherence to TB treatment: (1) TB is often highly contagious; (2) non-adherence prolongs the infectious phase; (3) non-adherence augments the development and spread of drug-resistant organisms; and (4) the human and fiscal costs of treating drug-resistant TB are substantial. Nonetheless, there are challenges associated with treatment adherence (Table 1), which have prompted comprehensive adherence interventions for TB disease.

In contrast, treatment for latent TB infection (TLTBI) lacks a similar sense of public health urgency: LTBI is not contagious and it is not associated directly with the development of resistant strains. Instead, patients, and in some cases providers, must be convinced of the need to treat a non-contagious infection that may never develop into active disease and to use prolonged therapy that may cause potential adverse effects. Initiating TLTBI in the United States (U.S.) and Canada is especially challenging among foreign-born persons with a history of Bacillus Calmette-Guérin (BCG) vaccination, who originate from TB endemic regions and often lack trust in the accuracy of the LTBI diagnosis. Successful adherence to LTBI treatment is even

more challenging than it is in the setting of treatment of active infection; Table 1 compares these challenges and the impact on adherence to TLTBI.

Approximately 10% of persons with LTBI go on to develop TB disease, the risk being much higher among HIV-infected persons.[2-4] The World Health Organization, together with the Centers for Disease Control and Prevention (CDC) and the American Thoracic Society (ATS), acknowledge the critical role of TLTBI in mitigating the overall impact of TB.[2,5,6] A key objective of the national strategy for TB control in the U.S. aims for 85% of high-risk persons with LTBI to successfully complete a course of treatment.[7] Clinical trials have shown TLTBI with 6 months of isoniazid results in a 69% reduction in TB, and 12 months of treatment, a 93% reduction. In sub-group analyses the maximum beneficial effect of isoniazid, when considering cost-effectiveness and feasibility, is likely achieved at 9 months assuming high rates of adherence.[2] However, levels of adherence are found to be consistently low in industrialized countries such as the U.S. and Canada that routinely treat LTBI.

We have undertaken a systematic review of studies in the U.S. and Canada to analyze the following: (1) measurement of LTBI adherence; (2) LTBI treatment completion rates; (3) predictors of LTBI adherence; and (4) LTBI adherence interventions. We conclude with some insights and implications for further research.

METHODOLOGY

PUBMED, MEDLINE, and PsycINFO electronic databases were searched for quantitative studies using the following terms: (tuberculosis OR latent tuberculosis) AND (preventive therapy

OR chemoprophylaxis OR treatment) AND (adherence OR compliance OR completion). The search was limited to studies published in peer-reviewed journals in English between 1997-2007, including adult populations in the U.S. or Canada. Over 800 study titles and abstracts were screened based on pre-defined inclusion and exclusion criteria (Table 2).

Titles and abstracts of identified citations were used to exclude studies that clearly did not meet the inclusion criteria. If a study was judged to be potentially eligible for inclusion, the full paper was obtained. Full texts of articles of possible relevance were reviewed independently for data abstraction. Studies were critically analyzed for their methodology and rigor, including study design, sample group(s), operational definitions of outcome variables/measures, and data analysis. A total of 78 studies met the inclusion criteria and were included in this review. Ethics approval was not required for this review.

Definitions

Treatment

In 2000, the ATS/CDC guidelines for TLTBI were revised to recommend 6 or 9 months of isoniazid (INH), regardless of patients' HIV status.[2] In studies examined for this review, unless otherwise noted, TLTBI was with 6 months of INH (6INH); persons with known HIV-infection were treated with 12 months of isoniazid (12INH). Findings from studies using shorter courses of rifampicin (RIF), pyrazinamide (PZA), rifabutin and/or INH are noted as such. Numbers preceding medication acronyms represent the months of treatment prescribed.

Treatment completion rate

We have used treatment completion rates to serve as an operational measure of adherence. TLTBI completion was defined as having ingested at least 80% of prescribed doses, based on the criteria employed within reviewed articles. In calculating a completion rate, some studies used the number of persons diagnosed with LTBI or the number eligible for treatment as the denominator. To allow for reliable comparisons across studies, completion rates noted in this review represent the number completing therapy over those initiating therapy. Therefore, where the completion rate was recalculated to conform to this standard, rates presented here may be higher than those in the original published study.

Directly observed therapy (DOT)

DOT is defined as the supervised ingestion of patients' prescribed doses. This supervision is typically done by a public health advisor or nurse.

Self-administered therapy (SAT)

SAT is defined as patients' self-administration of prescribed doses.

Significance

All findings reported to have statistical significance are within the 95% confidence interval range or $p \leq 0.05$ level. When sequential levels of analysis were applied to study data, findings resulting from the most advanced method are reported.

RESULTS

ADHERENCE MEASUREMENT

Accurate measurement of adherence is necessary to ensure that therapeutic outcomes can be attributed to the recommended treatment. While no "gold standard" exists for measuring adherence,[1,8,9] several *direct* and *indirect* measurement methods are used. Direct methods are generally more objective, yielding more reliable assessments of adherence, but each method has limitations.[10] Benefits and drawbacks of these techniques with respect to TLTBI are discussed below and summarized in Table 3.

Direct methods

Directly observed therapy

DOT has been used in TLTBI.[11-31] However, there is no public health mandate justifying its routine use for TLTBI. Furthermore, it is expensive, has infrastructural requirements, and may be perceived as paternalistic or intrusive by patients.[32]

Drug-level measurement

Drug-levels or their metabolites in body fluids provide an objective measure of adherence. Urine-testing for INH metabolites has been used to measure adherence to TLTBI.[33-35] This method assesses only the most recently ingested dose and results may be influenced by inter-subject pharmacokinetic variability and drug/food interactions. It is unsuitable for multiple drug-regimens, and high laboratory costs render it impractical in most clinical settings.[9,36,37]

Clinic attendance

Monitoring adherence to clinic visits is inexpensive and often applied in LTBI-settings.[11,21,22,34,38-44] However, while poor clinic attendance is a good indicator of non-adherence, good clinic attendance does not necessarily correlate with high medication adherence.[36]

Indirect methods

Patient self-report

Interviewer-based patient self-reports can accurately estimate adherence behavior.[8,9,36,37] Self-report is a quick, inexpensive measure of adherence, and is the only measure that can help identify reasons for non-adherence.[8,37] It has been used for LTBI patients on self-administered therapy.[13,28,33,34,41,45-53] Limitations of self-report measures include recall bias, social desirability bias, and overestimation,[8,9,36,37] all of which result in low sensitivity, although self-report is thought to have high specificity for non-adherence.[37] Self-report better identifies non-adherers than good adherers.[8] To improve accuracy, studies have limited recall to recent time periods, or implemented the concurrent use of pill diaries, audio computer-assisted self-interviews, and adherence questionnaires.[8,36,37]

Provider assessment

Providers tend to overestimate adherence; their assessments of non-adherence have low specificity and low sensitivity,[8,36,37] and are generally used as adjunct measures in LTBI-settings.[44]

Electronic monitoring device (EMD)

Electronic drug monitoring is considered among the most accurate and objective adherence measures.[36,37,54] Prescription bottles equipped with the Medication Event Monitoring System (MEMS®) cap, or Smart-cap®, utilize an electronic device that records dates and times at which the cap is removed. EMD's may be easily applied in clinical practice, and have proven to be reliable assessors for adherence to TLTBI.[33,55,56] They have also been used to validate or detect overestimation of drug intake by alternative measures including self-reports, provider estimates, pill-counts, and urine-tests.[33,36,54,55] However, EMD's do not prove dose ingestion, nor do they track the number of pills removed or ingested at each opening.[8,9] They are subject to decanting and pocket-dosing, or dose removal without simultaneous dose intake.[8,37] EMD's are perceived as cumbersome, costly, subject to malfunctioning,[8,36,37] unsuitable for multiple drug-regimens and may interfere with concurrent use of pillboxes.[8,36,54]

Pill count

Pill counting is inexpensive and has been used in TLTBI.[13,26,33-35,41,44,46,57] However, pill count cannot confirm dose ingestion at prescribed time intervals, and is subject to overestimation.[8,9,36,37] It is time-consuming and seldom used because of difficulty ensuring that pill bottles are returned to clinics. Conducting pill counts during unannounced home visits may yield better info,[37] but accuracy likely declines over subsequent visits.

Prescription refill rate

Pharmacy databases can monitor prescription refill and default rates. TLTBI adherence has been assessed by patients' timely collection of medications from TB clinics,[11,21,22,27,28,44,48,58-61] but is

impractical if patients access several pharmacies.[36] Refill rates are subject to low precision and are unable to prove dose ingestion.[8,9,36,37]

Composite measures

Studies have used a combination of methods to assess TLTBI adherence.[13,26,28,33-35,41,44,48] There is some evidence that composite adherence scores, computed from several adherence measures, may estimate adherence better than any single method.[1,8,9,34,37,54] An Adherence Index was computed in one LTBI-related study.[34] However, the validity of this method depends on that of its individual components and studies demonstrate mixed results regarding its efficacy compared to self-report or DOT alone.[9,54] Its feasibility may be restricted to research, rather than clinical settings.[8,54]

LTBI TREATMENT COMPLETION RATES

While adherence to treatment of TB disease has received substantial attention in the literature, relatively less data have accumulated on adherence to TLTBI. Existing information suggests that completion and adherence rates are low across patient populations and treatment regimens (Table 4).

Adherence to treatment with INH

Completion rates from interventional studies designed specifically to improve adherence to TLTBI are discussed later. Unless otherwise noted, all patients in this sub-section were prescribed 6INH, or 12INH for those with known HIV infection, by SAT.

Contacts

Contacts of infectious TB cases are at increased risk for developing active disease and present an opportunity for preventing future TB cases.[5] In several studies examining contact investigations in large or selected areas of the U.S., completion rates varied between 35-64%.[62-67] Others examined contact investigations in a specific state, city, or community; completion rates varied between 50-89%.[68-76]

Prison and jail inmates

Tuberculosis remains a serious problem in correctional facilities. Medical and social risk factors of inmates render them at higher TB risk than the general population.[2,5] TLTBI completion rates within correctional facilities ranged between 32-61%.[46,77,78]

Foreign-born

An increasing proportion of TB in the U.S. occurs among the foreign-born.[79] Targeted TLTBI for recent immigrants from TB-endemic countries may prevent an estimated 1,300 cases of TB per year in the 5 years after immigration.[79] Several studies were conducted among recent immigrants from TB-burdened countries; completion rates varied from 22-90% depending on study size and type of population.[38,41,45,48,51,53,58,59,80-84]; one study with 9INH found a completion rate of 19%.[59]

Drug-users

Injection drug-users are at increased risk for progression from LTBI to active TB because of their increased risk for HIV infection.[2,3,5] Studies of this population focused on treatment effectiveness or hepatotoxicity. Completion rates varied greatly between 39-70%.[12,19,57,85]

Other high-risk populations

In several studies evaluating TLTBI among the homeless, healthcare workers, and patients of HIV-clinics, completion rates ranged from 27-82%.[39,40,60,86-89]

Adherence to alternate regimens

Isoniazid has been the foundation of TLTBI for over 40 years. Its use has been compromised owing to the required lengthy treatment, its reputation for hepatotoxicity, and increasing influx of foreign-born persons from countries with high prevalence of INH resistance.[90] In 2000, shorter course regimens of RIF with or without PZA were recommended as acceptable alternative regimens for TLTBI.[2]

RIF regimens

When compared with 9INH, better completion rates with 4RIF were found in retrospective medical record reviews,[44,91] as well as in a randomized trial.[56] Those studies reported completion rates between 72-91%. While not evaluated or recommended in the U.S. as an acceptable alternative regimen, combinations of INH/RIF have been studied in Europe and Canada. In a Canadian study, treatment completion with 6INH/RIF was 82%.[26]

RIF/PZA regimens

The basis for the recommendation of RIF/PZA regimens was a large, open-label, randomized, multi-center trial in HIV-infected persons comparing 12INH to 2RIF/PZA.[92] The study found 2RIF/PZA to be similar in efficacy to 12INH, with a significantly higher completion rate. Following the new recommendation, 2RIF/PZA, either alone or in comparison to INH, was studied in high-risk populations. Some comparative studies found the shorter regimen to be associated with higher completion rates,[27,49,93] while others have found similar rates of completion.[35,52,94] Studies that focused on the RIF/PZA regimen alone found completion rates of 46-91%.[14,23-25,28,50,95,96] In 2003, RIF/PZA regimens were withdrawn by the ATS/CDC for safety reasons.[97]

PREDICTORS OF ADHERENCE TO LTBI MEDICATIONS

Several factors relating to patients, clinic facilities, and treatment characteristics have been shown to impact adherence to TLTBI (Table 5).

Demographic characteristics

Many studies have examined associations between demographic factors and adherence to TLTBI. Adherence does not appear to be related to patients' age, gender, place of birth, or race. In the few instances of a significant association, studies exhibit inconsistent results. Age has been positively associated with treatment completion in different age groups: in persons >65 years old,[39] in those <35,[48] and with increasing age.[17,25] Gender associations have also varied in direction, with completion reported better in women than men in some studies,[41,48] and vice versa

in others.[14,20] White Hispanic ethnicity was a significant predictor of completion.[48] Place of birth also demonstrates contradictory findings. Two studies found TLTBI completion to be higher in foreign-born persons than in US-born persons.[39,48] Another study reported better completion rates in both U.S.-born and foreign-born persons in the U.S. more than 5 years compared to new immigrants.[77] Failure to complete has also been associated with specific birthplaces.[58]

Patient-related factors

Recent exposure to TB,[64] marriage,[17] social support,[17] and higher education[17,77] have been positively associated with TLTBI adherence. Conversely, injection drug use,[14] excessive alcohol use,[48] daily alcohol/drug use,[17] alcohol use by men,[40] lack of health insurance,[17] unemployment,[14,44] prior BCG vaccination,[60] and recent hospitalization[17] have been associated with failure to complete. Additionally, attitudes in support of treatment completion,[17] intention to adhere,[17] and perceived risk of progressing to active TB[59] were found to be associated with better adherence. Three studies found patients with stable housing had better TLTBI adherence,[20,21,42] while homelessness has been found to be associated with better completion,[17] or worse completion.[48]

Clinic characteristics

Interventions that enhance clinic characteristics have influenced TLTBI adherence, to the extent that they adequately address patient needs. Outcomes from these adherence interventions, including trials with directly observed therapy, incentives, education programs, context, counseling and support services, are discussed below in the section on adherence interventions.

Treatment characteristics

TLTBI can lead to adverse drug effects including hepatotoxicity, skin rash, and nausea. Patients' concerns about drug toxicity and side effects have been associated with lower treatment completion,[45,48] as has onset of clinical symptoms.[25] Reluctance to undergo venipuncture in the course of monitoring for side effects was also found to be a significant predictor of non-completion.[59]

Parallel medical therapies impact TLTBI adherence. Concurrent methadone treatment has been associated with better completion,[11] or lower completion,[35] whereas concomitant medication use by women has been associated with failure to complete TLTBI.[40]

Shorter courses of TLTBI, including combinations of RIF, PZA, rifabutin and/or INH, have been associated with improved adherence; these outcomes were discussed earlier.

LTBI ADHERENCE INTERVENTIONS

The preceding section highlights risk factors for non-adherence identified in TLTBI studies. Several authors have argued that adherence behavior is influenced by complex interactions among predictive factors, rather than resulting directly from the factors themselves.[98,99] Health behavior theories generally attempt to characterize these interactions: for instance, the Health Belief Model highlights the perceptual foundations of health behavior and posits that behavior is motivated by outcome expectations.[98] It has guided TB screening and treatment programs that attempt to influence individual beliefs about disease susceptibility, severity, treatment efficacy and benefits, and perceived barriers to care, such as difficulties accessing services and

medication side effects.[100,101] In TLTBI, however, interventions seldom address the underlying processes by which multiple factors interact to influence adherence or non-adherence.

Several adherence support interventions not explicitly based on health behavior models have addressed individual or groups of factors associated with low TLTBI completion rates in North America (Table 6). However, no single intervention has shown consistent effectiveness.

Alternative regimens

Findings from studies comparing different drug regimens are discussed above (see treatment characteristics). Generally, observed improvements in adherence with shorter courses, including combinations of RIF, rifabutin or PZA, have been outweighed by their greater risk for hepatotoxicity.

Direct observation

DOT has historically been used to promote adherence to multi-drug TB regimens.[1] A recent review on TB treatment found no evidence that DOT generated better cure or completion than SAT, regardless of the type of direct observation provided.[102] DOT has been tested for LTBI monotherapy to a much lesser degree, with varied results.

Nolan et al.[30] followed 262 jail inmates who volunteered to receive DOT for LTBI while in jail and upon their release. Treatment completion among 157 inmates located post-release was significantly higher for those on DOT compared to SAT (60% vs. 29%). In a study with 111 opioid-dependent patients, Batki et al.[11] found completion was significantly higher for those randomly assigned to DOT with methadone therapy compared to patients on SAT (60-77% vs. 13%). White et al.[22] retrospectively reviewed 1,079 medical records for LTBI patients before

and after institution of a DOT program. Adherence improved overall, with patients on DOT twice as likely to complete treatment as those prescribed SAT (70% vs. 48%). Heal et al.[13] conducted a retrospective review of 608 aboriginal patients in British Columbia receiving TLTBI. Completion was significantly higher with DOT than SAT (75% vs. 61% for 6INH, 51% vs. 37% for 12INH).

In a randomized controlled trial with 300 injection drug-users, Chaisson et al.[33] compared DOT to SAT with or without peer education. There were no significant differences in completion between the groups (overall 79%).

Tulsky et al.[21] tested several LTBI adherence interventions with 118 homeless/marginally-housed patients. Those assigned to DOT with incentive had the highest completion rate compared to patients on DOT with peer support, or on SAT alone (44% vs. 19-26%). In a pilot intervention, Lorvick et al.[15] showed 89% treatment completion among 27 injection drug-users receiving DOT with incentives. O'Connor et al.[18] evaluated 39 opioid-dependent drug-users in rehabilitation. Completion by DOT was 72%, when liquid-INH was dispensed or mixed into daily doses of methadone. Similarly, Snyder et al.[31] showed 75% completion among 378 drug-users receiving DOT with methadone. These studies did not directly compare DOT to SAT.

The literature shows that the effectiveness of DOT can be enhanced by implementing concurrent interventions such as drug rehabilitation,[11,18,31] incentives,[15,16,20,22,31] outreach,[22,31] professional management,[17] and shorter waiting times.[22,31] But notwithstanding the tendency to observe higher adherence with DOT than SAT, actual completion rates in comparative studies remain sub-optimal – as low as 44%[21] to at best 80%.[33]

Incentives

Incentives can enable treatment initiation and help overcome barriers to completion.[15,16,20,21] Malotte et al.[16] showed that incentives were superior to outreach in improving LTBI adherence; 163 injection drug-users were randomly assigned to $5 and off-site DOT, $5 and community-site DOT, or off-site DOT alone. Off-site DOT, or active outreach, was provided at venues chosen by participants, but deterred adherence due to their concerns of being publicly identified as having TB. Treatment completion was significantly higher among the incentives groups, regardless of outreach services (53-60% vs. 4%). Tulsky et al.[21] found incentives more effective than peer health advisors. In a randomized controlled trial with 118 homeless/marginally-housed persons, those receiving $5 were significantly more likely to complete supervised treatment (44% vs. 19%).

In three studies, monetary incentives were given across all comparison groups.[15,17,33] Their effect on adherence could not be separated from the effect of the primary intervention.

Mangura et al.[35] studied the effect of non-monetary incentives on 55 HIV-positive homeless injection drug-users. Completion, defined as ≥70% adherence, was significantly higher among patients who requested and received a nutritional supplement (76% vs. 31%).

Questions around the most suitable type of incentive and time for distribution have been briefly explored. In their factorial randomized controlled trial, Chaisson et al.[33] compared adherence in 300 injection drug-users assigned to receive $10 at the end of each month of successful treatment or credited $10 monthly but paid only at the end of successful treatment. Completion was not significantly different between the immediate and deferred incentive groups (overall 79%). Tulsky et al.[20] randomly distributed $5 cash or equivalent-valued grocery/fast-food/phone/bus

coupon among 119 homeless persons commencing TLTBI by DOT. Assignment of a cash or non-cash incentive was not significant in determining completion of therapy (overall 86%).

Education

Educational interventions show comparable,[77] if not greater,[42] efficacy in TLTBI adherence than the use of incentives – findings that may relate to the incentive value, timing of disbursement, and quality of education offered. In 1998-99, White et al.[42] studied 325 of 558 inmates who were released from jail subsequent to initiating TLTBI while incarcerated. They were randomly assigned to receive bi-monthly education sessions in jail, $25 equivalent in food/transport vouchers upon attendance of their first clinic visit post-release, or neither intervention. Treatment completion was significantly higher among inmates in the education group, with no difference between incentive and control groups (23% vs. 12%). Group overall remained a significant predictor of completion in a conditional analysis with 104 released inmates who completed their first clinic visit. These 104 inmates were later compared against 164 inmates who received a single education session upon release in 2002-03.[103] Their completion rates were similar (overall 51%).

A five-year follow-up study with 557 of 558 inmates who initiated TLTBI in 1998-99 found no significant difference in completion between those originally assigned to the education, incentive or control groups (overall 32%).[77] Failure of the education intervention in persisting as a significant predictor of adherence was attributed to lack in continuity of care for inmates released into the community while still receiving TLTBI. Both follow-up studies suggest that the role of education in TLTBI adherence has yet to be clearly defined.

Contextual considerations

Several interventions have attempted to address patients' contextual circumstances. Goldberg et al.[47] found case managers matched to patients' cultural backgrounds significantly improved adherence with 389 refugee patients, when compared to historical controls (82% vs. 37%). At a health unit serving foreign-born workers who commonly assumed aliases, Kim et al.[29] reported outcomes of a no-name tracking system. TLTBI completion rose from 48 to 64% over three years. Batki et al.[11] found methadone-maintenance significantly enhanced treatment completion among drug-using patients (60-77% vs. 13%).

Professional counseling

Counseling services have been offered to support patients' motivation and self-efficacy to complete treatment. Nyamathi et al.[17] evaluated a site-randomized nurse-managed intervention with 520 homeless persons, based on integration of a comprehensive health-seeking and coping paradigm into adherence counseling, outreach, and prevention of loss to follow-up. The intervention significantly improved treatment completion compared to standard adherence counseling (62% vs. 39%), despite universal distribution of incentives and DOT. Similarly, Tavitian et al.[61] assessed a pharmacist-managed intervention for healthcare workers, promoting refill reminders, medication counseling, and drug-monitoring. SAT completion rates rose from a historic 1% pre-intervention to 76-93% in years following the intervention.

Among 72 opioid-using patients on DOT and methadone, Batki et al.[11] found TLTBI completion was not boosted in those randomly assigned to receive substance-abuse counseling (overall 68%). That counseling targeted substance abuse rather than adherence management may help explain the contrary outcome.

Peer support

Peer workers, often matched on the basis of race, ethnicity or sexual orientation, have credibility with patients from sharing common reference groups or having faced similar challenges.[104] Findings from LTBI-related studies are mixed.

In their factorial randomized controlled trial with injection drug-users, Chaisson et al.[33] employed peer workers who were former drug-users, had completed TLTBI, and had received extensive training on HIV and TB counseling. Adherence assessed by pill count or INH urine-testing generated no measurable differences (overall 78%). However, among 201 participants on SAT, electronically measured adherence was significantly higher among those assigned to peer workers (57% vs. 49%).

Tulsky et al.[21] evaluated the effect of peer health advisors for homeless LTBI patients; 118 participants were randomized to receive DOT with an incentive, DOT with peer support, or SAT. Completion was significantly higher among those given an incentive, and there was no difference between peer-assigned and SAT groups (44% vs. 19-26%). Failure was attributed to poor training of peer advisors on TB prevention education.

DISCUSSION

This review critically analyzes all aspects of TLTBI adherence, from published adherence rates to TLTBI predictors, as well as adherence interventions that have been tested in diverse patient groups. It was determined that TLTBI adherence and completion rates are suboptimal across high-risk groups, regardless of treatment regimen. TLTBI completion rates in the U.S. and

Canada generally fall below established targets and have been reported to range from 20 to 65% for a 6-month course of self-administered treatment; a few smaller studies were able to achieve higher completion rates.

Associations between patient factors, clinic facilities, or treatment characteristics and adherence to LTBI treatment were found to be inconsistent across studies. Adherence does not appear to be related to patients' age, gender, place of birth, or race. In the few instances of a significant association, studies exhibit inconsistent results. Recent exposure to TB, marriage, social support, and higher education have been positively associated with LTBI treatment adherence. Conversely, injection drug use, alcohol abuse, lack of health insurance, unemployment, prior BCG vaccination, and recent hospitalization have been associated with failure to complete. Homelessness has been found to be a mixed predictor, sometimes demonstrating a positive association and sometimes a negative one. Patients' concerns about drug toxicity and side effects have been associated with lower treatment completion as has onset of clinical symptoms. Concurrent methadone treatment has been associated with better completion or lower completion. Shorter courses of TLTBI, including combinations of RIF, PZA, rifabutin and/or INH, have been associated with improved adherence.

Adherence interventions have been developed to improve TLTBI adherence in the U.S. and Canada; however, no single intervention has shown consistent effectiveness. Incentives, contextual considerations, and professional adherence counseling were successfully applied to improve adherence, but they need to be tested for reliability in diverse settings. Interventions using DOT, education programs, and peer support report mixed findings and warrant further exploration in the context of TLTBI.

This review represents the first attempt to synthesize, integrate, and critically analyze all facets of adherence to TLTBI in the U.S. and Canada including adherence measurement, treatment completion rates, predictors for adherence, and adherence interventions that have been tested in diverse patient groups. The two reviews previously published on TLTBI adherence differ considerably in scope and breadth from this review. An earlier review compared LTBI treatment outcomes among HIV-infected patients in the U.S.[4] The objective of the review was to determine the effectiveness of LTBI treatment in reducing the risk of active tuberculosis and death in persons infected with HIV. The authors concluded that treatment of LTBI reduces the risk of active tuberculosis in HIV positive individuals with a positive tuberculin skin test. A more recent review examined DOT intervention outcomes for LTBI and TB disease worldwide.[102] The authors concluded that while the DOT strategy includes a number of useful components, the available evidence does not provide strong support for the routine adoption of direct observation in favor of self administration of treatment either for people with active tuberculosis or those with latent tuberculosis. In addition, they found no evidence that one form of direct observation is better than the other, i.e., outcomes from clinic-based DOT and community-based DOT were similar as were outcomes for DOT provided by a family member or a community health worker.[102]

This review has some limitations. First, it is limited to evaluating outcomes within adult populations. Studies with adolescents and children were not included in this review because they face significantly different issues in the context of treatment adherence, particularly with parental involvement in adherence. Second, the review focuses on studies published in the U.S. and Canada, in order to represent countries with resources to routinely treat LTBI. Thus the impact and relevance of this review is expected to be most applicable to these regions. Third, the

findings are tempered by methodological limitations of the reviewed studies; most notably the lack of a gold standard to reliably and accurately measure TLTBI adherence. However, every attempt was made to fully describe the advantages and limitations of each measurement method. Finally, many studies were not designed specifically to assess treatment completion but rather to assess program outcomes or medication safety. Therefore, treatment completion calculations varied across reviewed studies. More reliable and comparable comparisons were made by calculating completion rates as the number completing therapy over those initiating therapy.

CONCLUSION

If the goal of TB elimination is to be realized, LTBI must be effectively treated. In 2002, an estimated 291,000-433,000 individuals were treated for LTBI in the U.S., preventing 4,000-11,000 TB cases.[105] Consistently employing tools for measuring and improving adherence are fundamental. Understanding and educating patients, and identifying barriers to treatment adherence will facilitate the development of more effective and appropriate interventions. Our review shows the need for further large-scale studies in TLTBI adherence. In addition to providing important background for research, our findings may help guide program planning and practice in individual clinics and jurisdictional TB control programs. A 'one-size-fits-all' approach to TLTBI adherence is not likely to succeed across all settings. Innovative approaches can inspire future interventions and suggest solutions for the current problems facing some LTBI programs and their patients.

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Table 1 Comparison of disease- and treatment-related factors affecting treatment adherence in TB disease and LTBI

Factors Affecting Adherence	In TB disease	In LTBI	Impact on TLTBI adherence
Perceived severity	Strong	Weak	Hinders
Perceived susceptibility	Strong	Weak	Hinders
Perceived accuracy of diagnosis	Strong	Weak	Hinders
Duration of therapy	Usually 6 months	Usually 9 months[1]	Similar to TB disease
Intensity of therapy	Multiple medications	Usually monotherapy	Facilitates
Directly observed therapy	Standard of care	Not standard of care	Hinders
Symptoms	Symptomatic	Asymptomatic	Hinders
Infectiousness	Infectious	Non-infectious	Hinders
Toxicity concerns	Strong	Strong	Similar to TB disease
Public health threat	Threat	Indirect threat	Hinders

[1] LTBI treatment was traditionally with 6INH or 12INH depending on HIV status but with the 2000 LTBI treatment guidelines, it is now either a course of 6INH or 9INH, regardless of HIV status.
INH = isoniazid; TLTBI = treatment of LTBI.

Table 2 Study inclusion/exclusion criteria

Study inclusion criteria	Study exclusion criteria
- Quantitative studies - Peer-reviewed articles - From 1/1/1997 to 12/31/2007 - Adult populations - U.S. and Canada - English language	- Qualitative studies - Meta-analyses or reviews - Simulations

Table 3 Adherence measurement

Measurement method	Advantages	Limitations	Use in TLTBI
Direct methods			
Directly observed therapy	Objective Ensures dose intake Serves as an adherence intervention	Expensive Time and labor intensive May be impractical May be perceived as paternalistic or intrusive	Batki et al., 2002[11]; Bock et al., 2001[23]; Chaisson et al., 2002[24]; Gourevitch et al., 1999[12]; Heal et al., 1998[13]; Kim et al., 2003[29]; Lobato et al., 2003[78]; Lobato et al., 2005[14]; Lorvick et al., 1999[15]; Malotte et al., 2001[16]; McNab et al., 2000[26]; Narita et al., 2002[27]; Nolan et al., 1997[30]; Nyamathi et al., 2006[17]; O'Connor et al., 1999[18]; Priest et al., 2004[25]; Scholten et al., 2003[19]; Snyder et al., 1999[31]; Stout et al., 2003[28]; Tulsky et al., 2000[21]; Tulsky et al., 2004[20]; White et al., 2003[22]
Drug level measurement	Objective	Expensive May be impractical May reflect recent dose intake only Subject to individual pharmacokinetic variations Subject to drug/food interactions Unsuitable for multiple drug regimens	Chaisson et al., 2001[33]; Dubanoski et al., 1998[34]; Mangura et al., 1997[35]
Clinic attendance	Cost-effective Practical Poor attendance may help identify poor adherence	Does not ensure dose intake Good attendance may not reflect good adherence	Ailinger et al., 2006[38]; Batki et al., 2002[11]; Bock et al., 1999[39]; Dubanoski et al., 1998[34]; Gilroy et al., 2000[40]; Lardizabal et al., 2006[44]; Lavigne et al., 2006[41]; Tulsky et al., 2000[21]; White et al., 1998[43]; White et al., 2002[42]; White et al., 2003[22]
Indirect methods			
Patient self-report	Cost-effective Practical High specificity for non-adherence	Subjective Does not ensure dose intake Low sensitivity for non-adherence Subject to recall bias (may only	Ailinger et al., 1998[45]; Bandyopadhyay et al., 2002[46]; Chaisson et al., 2001[33]; Cook et al.,

Table 3 Adherence measurement

Measurement method	Advantages	Limitations	Use in TLTBI
	Helps identify reasons for non-adherence	reflect short-term adherence) Subject to social desirability bias Subject to overestimation	2006[49]; Dubanoski et al., 1998[34]; Goldberg et al., 2004[47]; Gordin et al., 1997[92]; Heal et al., 1998[13]; Lavigne et al., 2006[41]; Lee et al., 2002[50]; Levesque et al., 2004[51]; LoBue et al., 2003[48]; McNeill et al., 2003[52]; Sackoff et al., 2006[53]; Stout et al., 2003[28]
Provider assessment	Practical	Subjective Does not ensure dose intake Low sensitivity and low specificity for non-adherence Subject to overestimation	Lardizabal et al., 2006[44]
Electronic monitoring device	Objective Helps reflect long-term adherence Easily implemented in clinical settings	Expensive May be impractical or inconvenient Does not ensure dose intake Subject to underestimation (due to decanting or pocket dosing) Subject to malfunctioning Interferes with pillbox use Unsuitable for multiple drug regimens	Chaisson et al., 2001[33]; Menzies et al., 2004[56]; Menzies et al., 2005[55]
Pill count	Objective Cost-effective	Does not ensure dose intake Subject to pill dumping Subject to overestimation Difficult to implement in clinic settings	Bandyopadhyay et al., 2002[46]; Brassard et al., 2004[57]; Chaisson et al., 2001[33]; Dubanoski et al., 1998[34]; Heal et al., 1998[13]; Lardizabal et al., 2006[44]; Lavigne et al., 2006[41]; Mangura et al., 1997[35]; McNab et al., 2000[26]
Prescription refill rate	Cost-effective Practical if patients access one pharmacy or clinic	Does not ensure dose intake May be impractical if patients access multiple pharmacies or clinics Low precision	Batki et al., 2002[11]; Lardizabal et al., 2006[44]; LoBue et al., 2003[48]; Narita et al., 2002[27]; Parsyan et al., 2007; Shieh et al., 2006[59]; Shukla et al., 2002[60]; Stout et al., 2003[28]; Tavitian et al., 2003[61]; Tulsky et al., 2000[21]; White et al., 2003[22]

Table 3 Adherence measurement

Measurement method	Advantages	Limitations	Use in TLTBI
Composite measures			
Combination of methods	May help counter the limitations of individual methods	May be time and labor intensive Difficult to implement in clinical settings	Chaisson et al., 2001[33]; Dubanoski et al., 1998[34]; Heal et al., 1998[13]; Lardizabal et al., 2006[44]; Lavigne et al., 2006[41]; LoBue et al., 2003[48]; Mangura et al., 1997[35]; McNab et al., 2000[26]; Stout et al., 2003[28]
Composite Adherence Score or Adherence Index	May help counter the limitations of individual methods	May be time and labor intensive Difficult to implement in clinical settings Conditional on the validity of individual methods	Dubanoski et al., 1998[34]

TLTBI = treatment of LTBI

Table 4 LTBI treatment completion

Reference (author, year)	Sample	Sample Size - # eligible (N) / # initiating (n)	Study design[1]	Outcomes[2, 3]	Notes
Contact investigations					
Bur et al., 2003[70]	Jail and community contacts; 2000-2001	N=57 / n=34	Retrospective review of CI program data	Overall treatment completion rate = 21/34 (62%) Treatment completion rate: community cases = 11/22 (50%) jail cases = 10/12 (83%)	Treatment not specified. No statistical comparisons made between outcomes in community and jail contacts.
CDC/ MMWR 2000[67]	HIV+ Contacts; 1996-97	N=95 / n=30	Retrospective review of CI program data	Treatment completion rate = 14/30 (47%)	Treatment by DOT in 10% of sample.
CDC/ MMWR 2002[75]	Contacts; 2000-2001	N=21 / n=19	Retrospective review of CI program data at an Indian Reservation in Montana	Treatment completion rate = 13/19 (68%)	Treatment by DOT in 11% of sample.
CDC/ MMWR 2003[72]	Contacts; 1999-2002	N=67 / n=57	Retrospective review of CI program data in Mississippi	Treatment completion (≥ 6INH) rate = 36/57 (63%)	Treatment with 9INH by SAT (DOT to all children and HIV+ adults).
CDC/ MMWR 2004[74]	Contacts; 2001-2004	N=85 / n=49	Retrospective review of CI program data in Indiana	Treatment completion rate = 37/49 (76%)	
Davidow et al., 2003[66]	Workplace contacts	N=144 / n=65	Retrospective medical record review of CI program data	Treatment completion rate = 23/65 (35%)	Sample taken from Reichler et al., 2003.
Driver et al., 2003[68]	Contacts; 1998-2000	N=197 / n=197	Retrospective review of CI program data in New York City	Treatment completion rate = 102/197 (52%)	
Fitzpatrick et al., 2001[73]	Contacts; 1997-1999	N=86 / n=55	Retrospective review of CI program data in Indiana	Treatment completion rate = 49/55 (89%)	Contacts in the workplace were excluded.
Jereb et al., 2003[62]	Countrywide contacts; 1999	N=12,901 / n=9,018	Retrospective review of CI program data in 29 state jurisdictions	Treatment completion rate = 5,746/9,018 (64%)	Treatment and adherence data available for 28/29 jurisdictions.
Li et al., 2007[76]	Contacts; 2002-2003	N=18 / n=10	Prospective cohort study in New York City	Treatment completion rate = 5/10 (50%)	Focus of study was on offering HIV testing in the context of CI.
Marks et al., 2000[63]	Contacts; 1996-1997	N=1,725 / n=1,277	Retrospective medical record review from CDC registry of CI	Treatment completion rate = 707/1,259 (56%)	Treatment with RIF, INH/RIF, RIF/PZA, INH regimens (by unspecified SAT/DOT). 18 patients were continuing treatment at study end.
Reichler et	Contacts; 1996	N=447 / n=398	Retrospective medical	Treatment completion rate = 203/398 (51%)	Treatment by DOT (20%),

Table 4 LTBI treatment completion

Reference (author, year)	Sample	Sample Size - # eligible (N) / # initiating (n)	Study design[1]	Outcomes[2, 3]	Notes
al., 2002[64]			record review of CI program data in 5 US health departments		SAT (48%) and unknown (32%).
Sprinson et al., 2003[69]	Contacts; 1999-2000	N=4,609 / n=3,048	Retrospective medical record review of CI program data in California	Treatment completion rate = 1,958/3,048 (64%)	
Webb et al., 2003[71]	Contacts; 1990-1998	N=5,608 / n=3,540	Retrospective medical record review of CI in Mississippi state	Treatment completion rate not reported	Statewide annual reports showed that the treatment completion rate during the same time period was 8,805/11,544 (76%).
Yun et al., 2003[65]	Contacts of homeless cases	n=61	Retrospective record review of CI program data in 5 health dept's	Overall treatment completion rate = 27/61 (44%) Treatment completion rate: shelter cases = 25/46 (54%) non-shelter cases = 2/15 (13%)	Sample taken from Reichler et al., 2003. Treatment by DOT in 74% of sample. No statistical comparisons made between outcomes in shelter and non-shelter contacts.
Prison and jail inmates					
Bandyopadhyay et al., 2002[46]	Inmates on LTBI therapy released from short term correctional facilities; 1993-1997	N=250 / n=168	Retrospective medical record review	Treatment completion rate = 35/64 (55%) among inmates completing their first clinic visit post-release	Treatment by DOT pre-release and SAT post-release. Adherence data available for 64/168 patients completing their first clinic visit post-release.
Lobato et al., 2003[78]	Inmates in 49 correctional facilities across 12 states;1993-1996	N=23,965 / n=21,479	Retrospective medical record review	Treatment completion rate = 12,002/19,582 (61%)	Treatment by DOT. 1,897 patients were continuing treatment at study end.
White et al., 2005[103]	Inmates released from jail; 1998-1999 and 2002-2003	n=557	Prospective cohort; 5-year follow-up of RCT	Treatment completion rate = 176/557 (32%); 105/176 (60%) completed therapy in jail	
Foreign-born					
Ailinger & Dear, 1998[45]	Latino immigrants, mainly from Central America	n=65	Prospective cohort	Adherence to medications in 6th month = 65%	Treatment completion not reported.

Table 4 LTBI treatment completion

Reference (author, year)	Sample	Sample Size - # eligible (N) / # initiating (n)	Study design[1]	Outcomes[2, 3]	Notes
Ailinger et al., 2006[38]	Latino immigrants, mainly from Bolivia or El Salvador	n=53	Prospective cohort	Adherence in 9th month = 72% Mean number of months adherent = 7.4	
Ailinger et al., 2007[81]	Latino immigrants, mainly from El Salvador, Bolivia, or Guatemala; 2004-2005	N=153 / n=129	Retrospective medical record review	Treatment completion rate: 9INH = 52/153 (34%) 6INH = 72/153 (47%)	
DeRiemer et al., 1998[80]	Refugees and immigrants arriving in San Francisco, CA; 1992-1993	N=296 / n=241	Retrospective medical record review	Treatment completion rate = 178/241 (74%)	Treatment with 6-9INH or RIF regimens. Evaluation of a screening program.
Lavigne et al., 2006[41]	Clinic patients; 87% foreign-born; 1998-2000	n=320	Prospective cohort	Treatment adherence rate (>80% doses) = 217/302 (72%)	Adherence data available for 302/320 patients.
Levesque et al., 2004[51]	Refugee claimants; 1999-2000	N=49 / n=35	Prospective cohort	Treatment completion rate = 24/35 (69%)	Evaluation of a screening program.
LoBue & Moser., 2003[48]	Clinic patients; 79% foreign-born; 1999-2002	n=3,788	Retrospective medical record review	Treatment completion rate = 2,414/3,788 (64%)	
McCurdy et al., 1997[84]	Hispanic migrant farm workers; 73% of original sample foreign-born; 1995	N=23 / n=10	Cross-sectional study	Treatment completion rate = 9/10 (90%)	
Norton et al., 2000[83]	International students; 1997-1998	N=59 / n=34	Retrospective medical record review	Treatment completion rate = 27/34 (79%)	
Parsyan et al., 2007[58]	Clinic patients; ~90% foreign-born; 1998	N=1723 / n=1,572	Retrospective medical record review	Treatment completion rate = 607/1,572 (39%)	
Richards et al., 2005[82]	Immigrants and refugee claimants; 1999-2000	N=215 / n=196	Prospective cohort	Treatment completion rate = 156/196 (80%)	Nearly all treatment was with 6INH; a few with 9INH, 4INH/RIF or 2RIF/PZA
Sackoff et al., 2006[53]	Foreign-born pregnant women; mainly from the Caribbean and Central America;	N=78 / n=72	Retrospective medical record review	Treatment completion rate = 16/72 (22%)	These results represent available data for a sub-sample of the study population.

Table 4 LTBI treatment completion

Reference (author, year)	Sample	Sample Size - # eligible (N) / # initiating (n)	Study design[1]	Outcomes[2, 3]	Notes
Shieh et al., 2006[59]	1999-2000 Clinic patients; 90% foreign-born;2002-2003	n=217	Prospective cohort	Treatment completion rate: 6INH = 63/217 (29%) 9INH = 41/217 (19%)	
Drug users					
Brassard et al., 2004[57]	Injection drug-users; 1999	N=25 / n=13	Prospective cohort	Treatment completion rate = 5/13 (39%)	
Gourevitch et al., 1999[12]	HIV+ injection drug-users; 1985-1996	N=431 / n=155	Retrospective medical record review	Treatment completion rate = 76/155 (49%)	Nearly all treatment was by DOT plus methadone.
Sadaphal et al., 2001[85]	Injection drug-users; 1990-1996	n=146	Prospective cohort	Overall treatment completion rate = 102/146 (70%) Treatment completion rate: 12INH = 27/37 (73%) 6INH = 75/109 (69%)	Sample taken from ALIVE study, Maryland. No difference between 6INH (HIV-) and 12INH (HIV+) groups, p=0.63.
Scholten et al., 2003[19]	Injection drug-users in methadone program; 1993-1995	N=995 / n=607	Prospective cohort	Overall treatment completion rate = 259/607 (43%)	Treatment by DOT plus methadone. Treatment completion measured as ≥95% doses within 3 months of expected completion date.
Other high risk populations					
Bock et al., 1999[39]	Inner-city residents; 1994-1996	N=409 / n=310	Prospective cohort	Treatment completion rate = 84/310 (27%)	Evaluation of a screening program. Sample recruited from jail, homeless clinics, hospital, and community outreach team.
Gilroy et al., 2000[40]	≥35 years old patients; 1994-1996	N=510 / n=500	Retrospective medical record review	6INH treatment completion rate = 253/500 (51%) RIF treatment completion rate = 26/27 (96%)	Safety/hepatotoxicity study. 6INH defaulters offered RIF for a total of 6 months of treatment.
Lobue et.al, 1998[86]	Healthcare workers; 1993-1995	N=259 / n=169	Retrospective medical record review	Treatment completion rate = 77/159 (48%)	Adherence data available for 159/169 patients.
Nolan et al., 1999[88]	LTBI patients; 1989-1995	n=11,141	Prospective cohort	Treatment completion rate = 7,130/11,141 (64%)	Safety/hepatotoxicity study.
Sackoff et al., 1998[87]	HIV+ patients	N=131 / n=119	Retrospective medical record review	Treatment completion rate = 49/119 (41%)	
Schluger et al., 1999[89]	Persons seeking social services at	n=55	Retrospective medical record review	Treatment completion rate = 20/55 (36%)	Evaluation of a screening program

Table 4 LTBI treatment completion

Reference (author, year)	Sample	Sample Size - # eligible (N) / # initiating (n)	Study design[1]	Outcomes[2, 3]	Notes
	community based organizations; 1994-1997				
Shukla et al., 2002[60]	Hospital employees; 1994-2000	N=404 / n=396	Prospective cohort	Treatment completion rate = 318/388 (82%)	Adherence data available for 388/396 patients.
RIF Regimens					
Lardizabal et al., 2006[44]	LTBI patients; 2000 and 2003	n=474	Retrospective medical record review; 2 groups: 4RIF (n=261) vs. 9INH (n=213)	Treatment completion rates: 4RIF = 210/261 (81%) 9INH = 113/213 (53%)	Treatment completion with 4RIF higher than 9INH, p<0.0001.
McNab et al., 2000[26]	Aborigines with LTBI; 1992-95 and 1986-89	n=994	Prospective medical record review; 2 groups: 6INH/RIF (n=591) vs. 12INH (n=403)	Treatment completion rates: 6INH/RIF = 487/591 (82%) 12INH = 77/403 (19%)	Treatment with 6INH/RIF by DOT, with 12INH by SAT. Treatment completion for 6INH/RIF defined completion of ≥90% doses. Non-completion of treatment with 12INH higher than 6INH/RIF, p<0.001.
Menzies et al., 2004[56]	LTBI patients; 2002	n=116	Randomized control trial; 2 groups: 4RIF (n=58) vs. 9INH (n=58)	Treatment completion rates (>80% doses): 4RIF = 53/58 (91%) 9INH = 44/58 (76%) Treatment completion rates (>90% doses): 4RIF = 50/58 (86%) 9INH = 36/58 (62%)	Treatment completion (>80% and >90% doses) with 4RIF higher than 9INH, p<0.05.
Page et al., 2006[91]	LTBI patients; 1999-2004	N=2,255 / n=2,149	Retrospective medical record review; 2 groups: 4RIF (n=1379) vs. 9INH (n=770)	Treatment completion rates: 4RIF = 987/1379 (72%) 9INH = 405/77 (53%)	Treatment by DOT in 9INH (5%) and in 4RIF (1%). Treatment completion with 4RIF higher than 9INH, p<0.001.
RIF/PZA Regimens					
Bock et al., 2001[23]	Jail inmates; 1998-1999	n=168	Prospective cohort; 1 group: 2RIF/PZA	Treatment completion in inmates not released = 81/94 (86%)	Treatment by DOT. 74 inmates were released before completing therapy.
Chaisson et al., 2002[24]	TST+ prison inmates; 1999-2001	n=589	Prospective cohort; 1 group: 2RIF/PZA	Treatment completion rate = 538/589 (91%).	Treatment by DOT.
Cook et al., 2006[49]	LTBI patients (adults and	n=459	Prospective cohort; 3 groups: Long course =	Treatment completion rates: short course$_{1\&2}$ = 241/310 (78%)	Treatment completion with short course$_{1\&2}$ higher than

Table 4 LTBI treatment completion

Reference (author, year)	Sample	Sample Size - # eligible (N) / # initiating (n)	Study design[1]	Outcomes[2, 3]	Notes
	children); 2000-2006		9INH (n=149) vs. Short course$_1$ = 2RIF/PZA (n=291) vs. Short course$_2$ = 4-6RIF (n=19).	long course = 98/149 (66%)	long course, p=0.009.
Gordin et al., 2000[92]	HIV+ patients from 4 countries (1128/1583 from U.S.); 1991-1996	n=1583	Open-label, multi-center RCT; 2 randomized groups: 2RIF/PZA (n=791) vs. 12INH (n=792)	Treatment completion rates: 2RIF/PZA = 636/791 (80%) 12INH = 544/792 (69%)	Most treatment by SAT. Safety and efficacy study in HIV+ persons. Sample included children >16 years old. 1128/1583 patients enrolled in the U.S. – outcomes not distinguished by country. Treatment completion with 2RIF/PZA higher than 12INH, p<0.001.
Jasmer et al., 2002[94]	LTBI patients; 1999-2000	n=589	Open-label, multi-center RCT; 2 randomized groups: 2RIF/PZA (n=307) vs. 6INH (n=282)	Treatment completion rates: 2RIF/PZA = 187/307 (61%) 12INH = 160/282 (57%)	Safety/hepatotoxicity study. Treatment completion similar between groups, p>0.2.
Kandula et al., 2004[96]	Contacts; adult Mexican immigrants; 2001	N=29 / n=23	Retrospective medical record review; 1 group: 2RIF/PZA	Treatment completion rate = 13/23 (57%)	
Lee et al., 2002[50]	LTBI patients; 1999-2001	n=157	Retrospective medical record review; 1 group: 2RIF/PZA	Treatment completion rate = 85/148 (57%)	Adherence data available for 148/157 patients.
Lincoln et al., 2004[93]	Jail inmates; 1998-2000	N=2,127 / n=145	Retrospective medical record review; 2 groups: 2RIF/PZA (n=76) vs. 6-12INH (n=69)	Treatment completion rates: 2RIF/PZA = 67/76 (88%) 6-12INH = 51/69 (74%)	Overall, treatment completion higher with 2RIF/PZA than 6-12INH, p=0.03. Among inmates incarcerated during entire treatment, treatment completion similar between groups, p=0.22.
Lobato et al., 2005[14]	Jail inmates and homeless persons in 8 cities/counties; 2000-2001	n=1211 (844 inmates, 367 homeless persons)	Retrospective cohort: 1 group: 2RIF/PZA	Treatment completion rate (≥80% doses) = 657/1,211 (54%) Treatment completion rate (60 doses in 3 months) = 561/1,211 (46%)	Treatment by DOT for all inmates and for 46% of homeless persons. Safety/hepatotoxicity study. No difference in outcomes between jail inmates and homeless persons, p=0.23.

Table 4 LTBI treatment completion

Reference (author, year)	Sample	Sample Size - # eligible (N) / # initiating (n)	Study design[1]	Outcomes[2, 3]	Notes
Mangura et al., 1997[35]	HIV+ patients	n=55	Retrospective medical record review; 3 groups: 2RIF/PZA vs. 4RIF vs. 6INH	Overall treatment completion rate = 30/55 (54%)	Substudy of a larger safety/hepatotoxicity study. Treatment completion similar between regimens, p>0.05.
McElroy et al., 2005[95]	Countrywide LTBI patients; 3 periods: 2000-2001 ($period_1$=16 months), 2001 ($period_2$=4 months), 2001-2002 ($period_3$=10 months)	n=8,087	Retrospective countrywide survey from 87 sites; 3 groups: daily 2RIF/PZA (n=4,501) vs. daily and twice-weekly 2RIF/PZA (n=2,545) vs. twice-weekly 2RIF/PZA (n=1,041)	Treatment completion rates: overall = 5,145/8,087 (64%) $period_1$ = 3,451/5,327 (65%) $period_2$ = 959/1,528 (63%) $period_3$ = 735/1,232 (60%) twice-weekly = 842/1,041 (81%) daily = 2,679/4,501 (60%)	Safety/hepatotoxicity study. Treatment completion with twice-weekly higher than daily 2RIF/PZA, p<0.001.
McNeill et al., 2003[52]	HIV+ patients; 1999-2001	n=224	Prospective cohort; 2 groups: 2RIF/PZA (n=110) vs. 6INH (n=114)	Treatment completion rates: 2RIF/PZA = 78/110 (71%) 6INH = 67/114 (59%)	Safety/hepatotoxicity study. Sample included children ≥14 years old. Treatment completion similar between groups, p=0.07.
Narita et al., 2002[27]	HIV+ patients; 1996-1998 and 1999-2001	n=228	Prospective cohort with 3 groups: 2RIF/PZA (n=41) vs. 2rifabutin/PZA (n=94) vs. 12INH (historical controls, n=93)	Treatment completion rates: 2RIF/PZA = 89/94 (95%) 2rifabutin/PZA = 37/41 (90%) overall rifamycin/PZA = 126/135 (93%) 12INH = 57/93 (61%)	Treatment with rifamycin/PZA by DOT. Treatment completion with rifamycin/PZA higher than 12INH, p<0.001.
Priest et al., 2004[25]	Hispanic immigrants (mainly from Mexico and Guatemala); 2000-2001	n=423	Retrospective medical record review; 1 group: 2RIF/PZA	Treatment completion rate = 352/423 (83%)	Treatment by DOT.
Stout et al., 2003[28]	LTBI patients (61% homeless); 1999-2002	n=114	Retrospective cohort; daily 2RIF/PZA (n=36) vs. twice-weekly 2RIF/PZA (n = 78)	Treatment completion rate = 77/114 (67%). Time to complete treatment: daily 2RIF/PZA = 75 days twice-weekly 2RIF/PZA = 55 days	Treatment by DOT in twice-weekly group; 1 patient treated by DOT and SAT in daily group. No statistical comparisons reported for treatment completion between daily and twice-weekly groups. Time to complete treatment with twice-weekly DOT higher than daily SAT,

Table 4 LTBI treatment completion

Reference (author, year)	Sample	Sample Size - # eligible (N) / # initiating (n)	Study design[1]	Outcomes[2, 3]	Notes
					p<0.0001.

[1] Unless otherwise noted, treatment is with 6INH for HIV- persons and 12INH for HIV+ persons.
[2] Unless otherwise noted, treatment completion represents ≥80% dose ingestion.
[3] p-values shown where provided in reviewed articles.
DOT = directly observed therapy; HIV- = HIV negative; HIV+ = HIV positive; INH = isoniazid; PZA = pyrazinamide; RCT = randomized controlled trial; RIF = rifampicin; SAT = self-administered therapy; TST = tuberculin skin test; CI = contact investigations.

Table 5 Predictors of adherence to LTBI medications

Predictor	Positively associated with adherence	Negatively associated with adherence
Demographic characteristics		
Age		
>65 years old	Bock et al., 1999[39]	
<35 years old	Lobue and Moser, 2003[48]	
Increasing age	Priest et al., 2004[25]	
	Nyamathi et al., 2006[17]	
Gender		
Female	Lavigne et al., 2006[41]	
	Lobue and Moser, 2003[48]	
Male	Lobato et al., 2005[14]	
	Tulsky et al., 2004[20]	
Race/ethnicity		
White, Hispanic	Lobue and Moser, 2003[48]	
Place of birth		
Foreign-born	Bock et al., 1999[39]	
	Lobue and Moser, 2003[48]	
New immigrants (<5 years)		White et al., 2005[77]
Haiti or Dominican Republic		Parsyan et al., 2007[58]
Patient-related factors		
Recent exposure to TB	Reichler et al., 2002[64]	
Higher education	White et al., 2005[77]	
	Nyamathi et al., 2006[17]	
Substance use		
Injection drug use		Lobato et al., 2005[14]
Excessive alcohol use		Lobue and Moser, 2003[48]
Daily alcohol/drug use		Nyamathi et al., 2006[17]
Alcohol use by men		Gilroy et al., 2000
Living conditions		
Homelessness	Nyamathi et al., 2006[17]	Lobue and Moser, 2003[48]
Stable housing	Tulsky et al., 2004[20]	
	Tulsky et al., 2000[21]	
	White et al., 2002[42]	
Marital status		Nyamathi et al., 2006[17]
Health insurance	Nyamathi et al., 2006[17]	
Unemployment		Lardizabal et al., 2006[44]
		Lobato et al., 2005[14]
Prior BCG vaccination		Shukla et al., 2002[60]
Recent hospitalization		Nyamathi et al., 2006[17]
Importance of treatment completion	Nyamathi et al., 2006[17]	
Intention to adhere	Nyamathi et al., 2006[17]	
Low perceived risk of active disease		Shieh et al., 2006[59]
Social support	Nyamathi et al., 2006[17]	

BCG = Bacillus Calmette-Guérin

Table 5 Predictors of adherence to LTBI medications

Predictor	Positively associated with adherence	Negatively associated with adherence
Treatment characteristics		
Concerns about medication toxicity and side effects		Lobue and Moser, 2003[48] Ailinger and Dear, 1998[45]
Development of clinical symptoms		Shukla et al., 2002[60] Priest et al., 2004[25]
Fear of venipuncture		Shieh et al., 2006[59]
Concurrent methadone treatment	Batki et al., 2002[11]	Mangura et al., 1997[35]
Concomitant medication use by women		Gilroy et al., 2000[40]

BCG = Bacillus Calmette-Guérin

Table 6 LTBI adherence interventions

Reference (author, year)	Sample	Study design	Intervention*	Outcomes#,+	Notes
Batki et al., 2002[11]	Heroin-dependent injection drug-users; 61% male, all HIV-	RCT	3 groups: Standard methadone treatment (MT) + substance abuse counseling + DOT (n=37) vs. Minimal MT + DOT (n=35) vs. Routine care (no MT) + SAT (n=39). DOT given by nurses.	No difference in treatment completion between Standard MT + DOT and Minimal MT + DOT groups (60% vs. 77%). Treatment completion in *either* group higher than Routine care + SAT group (13%, p<0.0001).	Treatment completion not associated with substance abuse counseling.
Chaisson et al., 2001[33]	Injection drug-users; 73% male, 20% HIV+	RCT, with factorial design	3 groups: DOT (n=99) vs. Peer-support + SAT (n=101) vs. Routine care + SAT (n=100). Each group randomized for immediate (n=150) vs. deferred (n=150) $10/month stipend. EMD's introduced after first 200 participants recruited, and used to monitor adherence in SAT groups only: Peer-support + SAT (n=27) vs. Routine care + SAT (n=32).	No difference in treatment completion between DOT and Peer-support + SAT groups (80% vs. 78%, p=0.73). No difference in completion between DOT and Routine care + SAT groups (80% vs. 79%, p=0.86). No difference in treatment completion between immediate and deferred incentive groups (83% vs. 75%, p=0.09). Number of EMD doses taken in Peer-support + SAT group higher than Routine care + SAT group (57% vs. 49%, p<0.001).	Peer-support workers were former drug-users, had completed TLTBI, and were trained on TB and HIV counseling. Introduction to EMD's may have provided an adherence boost to SAT groups masking the intervention effect.
Goldberg et al., 2004[47]	Refugees (mainly from Somalia, Former Soviet Union and Former Yugoslavia); 60% male, 13-19% children	Retrospective cohort	2 groups: Intervention period, 1999-2000 (n=389) vs. Comparison period, 1996-98 (n=557). In Intervention period, 80% (n=312) received cultural case-management.	Treatment completion higher in Intervention period than Comparison period (82% vs. 37%, p<0.001).	Outcomes distinguished by time periods only; no direct statistical comparison made between participants who did/not receive cultural case management.

Table 6 LTBI adherence interventions

Reference (author, year)	Sample	Study design	Intervention*	Outcomes#,+	Notes
Heal et al., 1998[13]	Canadian Aboriginal persons; 50% male	Retrospective cohort	2 groups: DOT (n=165) vs. SAT (n=443). DOT given by nurses or outreach workers.	6INH Treatment completion higher in DOT group than SAT group (75% vs. 61%, p=0.0011). 12INH Treatment completion higher in DOT group than SAT group (51% vs. 37%, p=0.0014).	Baseline differences between groups: DOT group had more males, younger persons and TB contacts, fewer persons with immune-suppression and TB positive skin-test. DOT assignment based on voluntary participation which may lead to bias.
Kim et al., 2003[29]	Mainly foreign-born poultry-plant workers	Retrospective cohort	No-name tracking intervention followed across 1997 (n=284), 1998 (n=338), and 1999 (n=317). The intervention included a card with a unique number to access demographic, medical and contact information, including TB/LTBI history and treatment completion record. Participants received DOT by employee health staff.	Treatment completion was 48% (1997), 54% (1998), and 64% (1999). Outcomes were compared to nation/state-wide treatment completion rates of 62%.	No statistical comparisons made during intervention periods, or between intervention and nation/state-wide completion rates.
Lorvick et al., 1999[15]	Injection drug-users; 59% male, 14% HIV+	Pilot program	DOT + $10/dose (n=27). DOT given by research staff.	89% Treatment completion.	No comparison group.
Malotte et al., 2001[16]	Injection or crack cocaine drug-users; 82% male	RCT	3 groups: Off-site DOT (n=55) vs. Off-site DOT + $5/dose (n=53) vs. On-site DOT + $5/dose (n=55). DOT given by outreach workers. Off-site DOT provided at venues selected	No difference in treatment completion between Off-site DOT + $5 and On-site DOT + $5 groups (53% vs. 60%). Treatment completion in *either* DOT + $5 group higher than Off-site DOT alone (4%,	

Table 6 LTBI adherence interventions

Reference (author, year)	Sample	Study design	Intervention*	Outcomes#,+	Notes
			by participants. On-site DOT provided at study community site.	p<0.0001).	
Mangura et al., 1997[35]	Drug-users; all HIV+	Prospective cohort	2 groups (N=55): Requesting Sustacal® vs. Not requesting Sustacal®. Sustacal® is a liquid nutritional supplement. Participants requesting Sustacal® received case allotments of 6 cans each at no charge.	Treatment completion in the group Requesting Sustacal® higher than the group Not requesting Sustacal® (76% vs. 31%, p=0.001).	Number of participants per study group not reported. Treatment was with 6INH, 4RIF or 2RIF/PZA; no difference in outcomes between regimens. Treatment completion defined as ≥70% completion of regimen months.
Nolan et al., 1997[30]	Jail inmates released on TLTBI; estimated 92% male	Prospective cohort	2 groups: DOT (n=105) vs. SAT (n=52). DOT given by outreach workers.	Treatment completion higher in DOT group than SAT group (60% vs. 29%, p=0.0002).	Adherence data available for 157/262 participants who initiated TLTBI in jail and continued post-release. DOT assignment based on voluntary participation which may bias the results.
Nyamathi et al., 2006[17]	Homeless persons; 80% male	Site-randomized, prospective cohort	2 groups: Nurse case-managed (NCMI) program (n=279) vs. Standard care (n=241). Each group received DOT + $5/dose. DOT given by nurses blinded to randomization.	Treatment completion in NCMI program group higher than Standard care group (62% vs. 39%, p<0.01).	Baseline differences between groups: NCMI group had higher rate of males, recruitment from emergency shelters,

Table 6 LTBI adherence interventions

Reference (author, year)	Sample	Study design	Intervention*	Outcomes#,+	Notes
			NCMI program based on the comprehensive health seeking and coping paradigm with adherence counseling, outreach and prevention of loss to follow-up. NCMI group received 8 education sessions, community escorts, community resources, and tracking. Standard care group received one education session.		lifetime injection drug-use, daily drug and drug/alcohol use, recent hospitalization, and recent enrollment in self-help program. HIV+ participants (number not reported) monitored for 6INH but encouraged to take 9INH.
O'Connor et al., 1999[18]	Drug-users on methadone maintenance ; 72% male, 77% HIV+	Prospective cohort	Liquid INH + DOT + methadone (n=39). DOT given by study nurses. Participants received 'take-home' SAT doses on weekends. 87% (n=34) received a pharmaceutical admixture of liquid INH + methadone.	72% Treatment completion. 90% Treatment completion among participants not discharged from methadone maintenance program (n=31).	No comparison group.
Snyder et al., 1999[31]	Drug-users on methadone maintenance ; estimated 59% male, 21% HIV+	Retrospective cohort	DOT + methadone (n=378). DOT given by methadone program nurses. Participants had lower clinic waiting times and community outreach escorts, and received education sessions, bus tokens, and refreshments.	75% Treatment completion.	No comparison group. Cost-effectiveness study.
Tavitian et al., 2003[61]	Healthcare workers	Retrospective cohort	Pharmacist managed intervention followed across 1993-97 (n=131), 1997-98 (n=39), 1998-99 (n=23), 1999-2000 (n=58), and 2001 (n=43). Intervention included medication counseling, refill reminders, therapeutic and adverse-effects drug monitoring. All	Treatment completion was 93% (1993-97), 76% (1997-98)*, 83% (1998-99)*, 77% (1999-2000)*, and 82% (2000-01)*. Outcomes compared to historical treatment completion rate of 0.8% (1989-92).	No statistical comparisons made during intervention periods, and between intervention and historical periods.

Table 6 LTBI adherence interventions

Reference (author, year)	Sample	Study design	Intervention*	Outcomes#,+	Notes
			treatment by SAT.		*Treatment completion calculations were modified to conform to intent-to-treat standards.
Tulsky et al., 2000[21]	Homeless and marginally housed persons; 86% male, all estimated HIV-	RCT	3 groups: DOT + $5/dose (n=43) vs. DOT + peer-support (n=37) vs. Usual care + SAT (n=38). DOT given by research assistants in $5 group, and by peer health advisors in peer-support group.	Treatment completion higher in DOT + $5 group (44%) than DOT + peer-support (19%) and Usual care (26%) groups combined (p=0.03).	Peer health advisors were homeless or had a recent history of homelessness.
Tulsky et al., 2004[20]	Homeless and marginally housed persons; 85% male, all HIV-	RCT	2 groups: DOT + $5 cash/dose (n=65) vs. DOT + $5 non-cash/dose (n=54). Non-cash group received a choice of fast-food coupon, grocery store coupon, phone card, or bus token.	No difference in treatment completion between cash and non-cash groups (89% vs. 81%, p=0.23).	Baseline differences between groups: Non-cash group had higher rate of participants listing their recent primary housing as a shelter/street. Treatment was with 6INH or 4RIF; outcomes not distinguished by regimen.
White et al., 2002[42]	Jail inmates released on TLTBI; 82% male, 61% foreign-	RCT	3 groups: Education (n_1=107) vs. Incentive (n_1=114) vs. Control (n_1=104). In jail, each group received one informational session (control) and DOT. Education group received bi-monthly	No difference in treatment completion between Incentive and Control groups (12% vs. 12%)*. Treatment completion in Education group higher than *either* Incentive or Control groups	Adherence data available for 325/558 inmates who initiated TLTBI in jail (excluding

Table 6 LTBI adherence interventions

Reference (author, year)	Sample	Study design	Intervention*	Outcomes#,+	Notes
	born, all estimated HIV-		education sessions while in jail. Incentive group received a choice of $25 food or transport voucher, on completion of first clinic visit post-release. Conditional analysis for participants who completed first clinic visit post-release and in whom adverse effects did not stop TLTBI: Education (n_2=37) vs. Incentive (n_2=42) vs. Control (n_2=25).	(23%, p=0.04)* For conditional analysis, treatment completion associated with group (p=0.01): Education (65%) higher than Control (48%) higher than Incentive (33%) group.	participants who discontinued or completed TLTBI before release). 30% participants in the Education group were released before receiving any education session. A community interview with all participants post-release boosted treatment completion similarly across groups. *Treatment completion calculations were modified to conform to intent-to-treat standards.
White et al., 2003[22]	Persons from high-risk referral sites (jail, homeless shelters, substance abuse clinics, screening programs); 79% male	Retrospective cohort	2 groups: Intervention period, 1997-98 (n=460) vs. Comparison period, 1993-94 (n=619). In the Intervention period, 68% (n=315) received SAT, 32% (n=145) received DOT by nurses, health workers or outreach workers. In the Comparison period, all treatment was by SAT. Participants on DOT had lower clinic waiting times, received lunch per visit, meal and bus coupons, and aid from social services; high-risk participants	Treatment completion in Intervention period higher than Comparison period (60% vs. 44%, p<0.001). Treatment completion by participants on SAT in Intervention period higher than Comparison period (55% vs. 44%, p=0.002). Treatment completion by participants on DOT higher than overall SAT (70% vs. 48%, p<0.001).	Baseline differences between groups: Intervention period group had a higher rate of foreign-born and Latino persons, and a lower rate of African-American persons. No direct statistical comparison made between participants on DOT and SAT in

Table 6 LTBI adherence interventions

Reference (author, year)	Sample	Study design	Intervention*	Outcomes#,+	Notes
			(number not reported) received additional movie/food vouchers.		the Intervention period.
White et al., 2005[103]	Jail inmates released on TLTBI and visiting clinic post-release; 91% male, 68% foreign-born	Retrospective cohort	2 groups: Study period, 1998-99 (n=104) vs. Usual care period, 2002-03 (n=164). Participants in the Study period correspond to the conditional analysis from White et al. 2002. Study group received a minimum of one informational session by research staff. Usual care group received one education session by jail discharge planners.	No difference in treatment completion between Study period and Usual care period (50% vs. 52%).	Baseline differences between groups: participants in the Usual care group were in jail longer, and had a longer time between TLTBI initiation and education; groups varied in ethnic composition. Treatment completion calculated as a sum of participants completing TLTBI previously and during the study period.
White et al., 2005[77]	Jail inmates released on TLTBI and followed for 5 years; 91% male, 71% foreign-born	Prospective cohort; 5-year follow-up study to White et al. 2002	3 groups: Education (n=185) vs. Incentive (n=185) vs. Control (n=188). Participants in this study correspond to all participants initiating TLTBI in jail in White et al. 2002, excluding one case of active TB, and including those who completed TLTBI in jail (n=176), stopped TLTBI as per provider (n=46), and self-stopped TLTBI/lost to follow-up/re-started TLTBI in jail (n=335).	No difference in treatment completion between *either* education or incentive group and control group (34% vs. 27%, p=0.07).	

[*] Unless otherwise noted, treatment is with 6INH for HIV-persons and 12INH for HIV+ persons.
[#] Unless otherwise noted, treatment completion represents completion of≥80% dose ingestion.
[+] p-values shown where provided in reviewed articles.
DOT = directly observed therapy; EMD = electronic monitoring device; HIV- = HIV negative; HIV+ = HIV positive; INH = isoniazid; RCT = randomized controlled trial; RIF = rifampicin; SAT = self-administered therapy; TLTBI = treatment of LTBI

Chapter 3:

The Changing Face of Latent Tuberculosis Infection in Harlem, New York: Clues from two studies

SUMMARY

INTRODUCTION: Poor adherence to LTBI treatment and corresponding modest treatment completion rates impede efforts to eliminate TB in this country. While community-level social demographic characteristics are thought to influence adherence, few studies have examined epidemiological changes over time in relationship to adherence patterns. This issue is particularly critical in communities like Harlem, where TB rates have remained above national averages despite significant population changes.

OBJECTIVE: To describe the change in demographic, social, and behavioral characteristics of patients undergoing treatment for LTBI in the Chest Clinic at Harlem Hospital between 1996 and 2005.

METHODS: A cross-sectional examination of baseline data from participants in two sequential randomized controlled trials. Demographic, social, and behavioral characteristic data are summarized using basic descriptive statistics (means, medians, proportions) in two distinct time points: participants recruited between 1996 and 2000, and participants recruited between 2002 and 2005. Differences and similarities between Study A and Study B participants were investigated using student's t-tests, Pearson's χ^2 tests, and Fisher's exact tests.

RESULTS: Of the 610 participants enrolled across both studies, 360 were recruited into Study A and 250 into Study B. Average age of participants in both studies was similar (39 vs. 40, p=0.498). Substantially more participants in Study B were male (70% vs. 58%, p=0.002) and many more were Africans (36% vs. 9%, p<0.001). Substantially more of the Study B participants were married (39% vs. 26%, p=0.001), and more were foreign-born (67% vs. 48%, p<0.001), with less experience of prior LTBI treatment (6% vs. 14%, p=0.003). There was substantially less current homelessness (16% vs. 26%, p=0.005) and unemployment (59% vs.

73%, p<0.001) in Study B than in the Study A. Overall, close to half of all participants enrolled in the studies were current smokers, about a third consumed alcohol and 20% used drugs at the time of enrollment. There is evidence of a trend in changes in drug use, with fewer Study B participants ever (52% vs. 59%, p=0.086) or currently (16% vs. 22%, p=0.057) using drugs. CONCLUSIONS: The cohort of participants receiving treatment for LTBI in Harlem between 2002 and 2005 tend to have higher levels of foreign-birth and marriage, and lower levels of homelessness and unemployment, less experience with prior LTBI treatment, and lower rates of smoking and drug use than patients in the late 1990s. The 2002-2005 participants undergoing treatment for LTBI mirror the NYC and national TB picture in terms of gender, age, and foreign birth; however, the racial distribution is different as the Harlem community does not have a large population of Asians.

INTRODUCTION

An estimated 9 to 14 million persons in the United States have latent tuberculosis infection (LTBI) and are therefore at risk for progression to active disease.[1] Treatment for latent tuberculosis infection (TLTBI) has been identified by the Centers for Disease Control and Prevention (CDC), the Advisory Council for the Elimination of Tuberculosis, the American Thoracic Society, and the Institute of Medicine of the National Academy of Sciences as one of the major strategies for elimination of tuberculosis (TB) in the U.S.[2,3] However, LTBI treatment completion rates in the U.S. generally fall below established targets.[4,5] Poor adherence to LTBI treatment and corresponding modest treatment completion rates impede efforts to eliminate TB in this country. While community-level social demographic characteristics are thought to influence adherence, few studies have examined epidemiological changes over time in relationship to adherence patterns.

This issue is particularly critical in communities like Harlem that were especially affected by the resurgence of TB in the early 1990s. The TB case rate in Central Harlem rose to a high of 240.2/100,000 in 1992,[6] a rate comparable to those found in developing countries. The TB control efforts implemented in NYC have resulted in the gradual decrease in TB case rates in Harlem to 16.7/100,000 in 2008. Despite this decline, the TB case rate in Harlem is still four times the U.S. case rate (4.2/100,000) and more than 50% higher than the NYC rate (10.8 cases/100,000).[7] People of color in NYC have markedly higher rates of TB than whites with 54% of cases occurring among blacks and Hispanics.[7] With TB rates greatly exceeding the national average and the concomitant HIV epidemic, the Harlem community is vulnerable to TB. HIV infection is the most potent risk factor for development of TB, resulting in a 100-fold increase in risk in HIV-infected individuals compared to those without HIV infection.[8-10] Other

risk factors for development of TB include recent immigration, recent conversion of the TB skin test, homelessness, incarceration, and congregate settings.

Historically, Harlem has been a center of African-American culture and a more recent home to many Latino immigrants. Two thirds of the Harlem residents are African-American and 20% are Hispanic compared with the national average of 12% and 13% respectively. It is among the most underprivileged areas in New York City, with approximately one-third of the population living in poverty compared with 21% in NYC and 12% nationally. In addition, the unemployment rate is 9.8% in Harlem vs. 5.5% in NYC and 3.7% nationally.[11] The community suffers from a large variety of socio-economic problems including homelessness and drug and alcohol use. This is also a neighborhood whose population is at an elevated risk for HIV with prevalence rates double that of NYC as a whole (127.1/100,000 vs. 45.8/100,000 HIV diagnoses.[12] Moreover, a recent surge of immigration into the neighborhood has brought new health challenges. The majority of African immigrants living in Harlem come from West African countries in which HIV infection rates range from 2 to 7% and TB is endemic. In 2003, African immigrants accounted for 9.3% of new TB cases in New York City, although they make up less than 1% of the population.[13] Because of crowded housing and other health conditions, immigrants may be at an elevated risk for developing active TB disease, particularly if also HIV-infected. At the same time, these recently arrived members of the community and its traditional African-American population share multiple barriers to health care and lack knowledge about disease prevention strategies, which can exacerbate existing health care disparities in Harlem. The social stigma attached to many infectious diseases gives rise to fears of discrimination and isolation, and often inhibits people from seeking testing and treatment services. Another significant barrier in this population is fragile and inadequate social support for medication

within existing social networks.[14,15] The population that is eligible for treatment for LTBI in Harlem includes predominantly minorities and a large proportion of recent immigrants, women, and substance users.

The objective of this analysis was to describe the change in characteristics of patients undergoing treatment for LTBI in the Chest Clinic at Harlem Hospital between 1996 and 2005.

STUDY POPULATION AND METHODS

Setting and Study Population

Located in Central Harlem, New York City, Harlem Hospital Center is a publicly funded hospital that serves as the primary source of care for many people residing in Northern Manhattan. The hospital's Chest Clinic provides services to patients with TB and with LTBI. Of the patients with TB enrolled in the Harlem Hospital Directly Observed Therapy (DOT) program at the time of these studies, approximately one third were foreign-born and many indicated that English is not their primary language. The Chest Clinic serves a predominantly disadvantaged population with a large proportion of the patients receiving public assistance, large numbers of immigrants, and high rates of unemployment, homelessness and substance abuse. Many of the patients are referred to the clinic by homeless shelters, substance abuse programs and community based organizations where TB skin testing is often required for residency or for services like English language classes.

Between 1996 and 2000 and between 2002 and 2005, patients who initiated treatment for LTBI were recruited from the Harlem Hospital Chest Clinic in New York City into two randomized controlled trials assessing the effect of an experimental intervention. Providers in the TB Clinic used the prevailing CDC/ATS guidelines to determine candidacy for treatment of LTBI. Patients with the following characteristics were eligible for the study: recommended for initiation of a CDC recommended drug regimen for treatment of LTBI; age of 18 years or older; and able and willing to sign consent form. Patients with the following characteristics were excluded: receiving DOT for LTBI; or had evidence of active TB disease. All decisions about starting or stopping treatment for LTBI were made by providers in the Chest Clinic and were based on standard CDC criteria.

Patients who fulfilled these criteria were referred for study participation. Potential study candidates were provided with further information regarding the study and invited to participate. All participants signed a consent form approved by the Columbia University Institutional Review Board at Harlem Hospital. Following a baseline interview with a research assistant, participants were randomly assigned to either the intervention or control group.

The first study, Pathways to Completion, recruited patients from the Chest Clinic between 1996 and 2000. The second Study, Tuberculosis Adherence Partnership Alliance Study (TAPAS), recruited patients between 2002 and 2005. Both studies had a low refusal rate. Demographic characteristics of study participants did not differ significantly from those of the clinic population.

Participant Interviews

Structured questionnaires were developed and pilot-tested prior to each study to ensure clarity and precision of the instruments. Research assistants, who received training for the studies, conducted the interviews in English, French, and Spanish. Completed interviews were reviewed by the study coordinators for completeness.

Interviewers collected detailed demographic, social, and behavioral information including: place of birth, history of homelessness, patterns of substance use, employment, marital status, and prior LTBI treatment. Knowledge of TB transmission, treatment, and diagnosis was assessed using true/false questions. Agreement with attitudes regarding LTBI was measured on a 4-point Likert scale where 1 indicates "strongly disagree", 2 is "disagree", 3 is "agree", and 4 is "strongly agree."

Data Analysis

Pearson's χ^2 test, or Fisher's exact test where appropriate, was used for comparisons of categorical variables. Student's t-test was conducted for comparisons of continuous variables. The two studies had a different number of knowledge items; however, a summary knowledge score for six items that were the same across the two studies was constructed by calculating the sum of correct answers to knowledge items. Statistical analyses were performed using SPSS (v17.0, SPSS, Inc., Chicago, IL).

RESULTS

Of the total 610 participants, 360 were recruited into the Pathways study (Study A) and 250 into the TAPAS study (Study B). Overall, 63% were male, 51% were African-American, 20% were African, 21% Latino, and 55% were less than 40 years old. Slightly more than half of the participants were foreign-born, 22% reported current homelessness, 67% were unemployed, 57% had completed high school, and 31% were married (Table 1).

The average age of participants in both studies was similar (39 vs. 40, p=0.498). Substantially more participants in Study B were male (70% vs. 58%, p=0.002) and many more were Africans (36% vs. 9%, p<0.001). Substantially more of the Study B participants were married (39% vs. 26%, p=0.001), and more were foreign-born (67% vs. 48%, p<0.001), with less experience with prior LTBI treatment (6% vs. 14%, p=0.003). There was substantially less current homelessness (16% vs. 26%, p=0.005) and unemployment (59% vs. 73%, p<0.001) in Study B than in the Study A.

Overall, close to half of all participants enrolled in the studies were current smokers, about a third drank alcohol and 20% used drugs at the time of enrollment. There is a possible trend in changes in drug use, with fewer Study B participants ever (52% vs. 59%, p=0.086) or currently (16% vs. 22%, p=0.057) using drugs.

Knowledge of TB transmission, diagnosis and treatment at baseline was 4.14 out of a possible 6.0 in all participants; Study A participants had a better knowledge score (4.27 vs. 3.94, p<0.001). Overall, participants agreed with the statement, “you believe that you have the TB germ” (mean=3.06), “taking TB medications is important” (mean=3.88), and “you care about what your family and friends think of your TB treatment” (mean=2.77); participants disagreed

overall with the statements, “going to appointments is more trouble than it is worth” (mean=1.37) and “as hard as you try, you are going to miss some of your medicines” (mean=1.91). No significant differences were noted between the two studies on the prior attitudinal items but some differences between the studies were noted in the following attitudinal items. All participants agreed that “TB is a disease you have to take seriously” but the agreement was stronger among Study A participants (3.90 vs. 3.76, $p<0.001$). Stigma as measured by agreement with “you are embarrassed to tell you have TB” was stronger among Study A participants (2.52 vs. 2.23, $p=0.003$). While overall participants strongly disagreed with the statements “you know better than the doctor when it is time to stop taking your medications” and “TB medications are a hassle,” the disagreement was less strong among Study B participants (1.23 vs. 1.59, $p<0.001$; 1.34 vs. 1.60, $p<0.001$ respectively). There was general agreement with the statements “no matter what you do, you can get TB” and “if you do the right thing, you can avoid getting TB”; however, Study A participants more strongly agreed with the prior (3.08 vs. 2.52, $p<0.001$) and Study B participants more strongly agreed with the latter (3.10 vs. 3.37, p0.003). There was stronger agreement among Study A participants that “it takes something bad to not take the TB medicines” (3.15 vs. 2.57, $p<0.001$).

DISCUSSION

There are higher proportions of foreign-born, married, employed African participants receiving treatment for LTBI in Harlem between 2002 and 2005 than in the late 1990s. Current Harlem participants undergoing treatment for LTBI mirror the NYC and national TB picture in terms of

gender, age, and foreign birth; however, the racial distribution is different as the Harlem community does not have a large population of Asians.[7]

Participants in the 2002-2005 cohort tend to have lower knowledge levels regarding TB diagnosis and treatment than past participants. Participants' attitudes were fairly positive with participants believing that they have the TB germ, acknowledging that TB is serious disease and taking TB medications is important, and that doing the right thing may help them avoid TB. Furthermore, negative attitudes regarding the doctor's knowledge of treatment or the hassle involved in the taking the medications were not very strong, though Study A participants were more dismissive of these notions. Stigma appears less strong in the more recent study population (Study B) possibly as more participants are from areas where TB is endemic.

Limitations

This analysis has several limitations. Patients receiving DOT for LTBI were excluded from the study; however, the DOT for LTBI population was found to be similar to the study population of Pathways[16] and no changes in procedures for DOT referrals were implemented in the clinic during that period. When comparing the two clinic populations, we could only evaluate questions that were comparable across the two studies. The TB knowledge and attitudes sections were different across the studies, which limited the number of items that could be compared. However, a reasonable number of attitudinal items were comparable and this did not affect the analysis in terms of demographic characteristics and lifestyle factors as the two studies had very detailed sections that were comparable. This analysis examines changes in study populations, which may differ from the Harlem clinic population in general. Additionally, this analysis looks at the change in clinic populations in only one clinic in one city and the findings may not be

generalizable to other populations. However, while this clinic population may be different than other parts of the country in terms of origin of immigrants, we believe that this clinic is fairly representative of inner city urban populations, which tend to include relatively higher proportions of immigrants and disadvantaged persons. Moreover, this analysis is not limited to a specific high risk group but instead to a general clinic population, albeit one at high risk of developing TB disease.

CONCLUSION

Participants receiving treatment for LTBI in Harlem from 2002-2005 tend to have higher levels of foreign-birth and marriage, and lower levels of homelessness and unemployment, less experience of prior LTBI treatment, and lower rates of smoking and drug use than participants in the late 1990s. The 2002-2005 cohort of Harlem participants undergoing treatment for LTBI mirror the NYC and national TB picture in terms of gender, age, and foreign birth; however, the racial distribution is different as the Harlem community does not have a large population of Asians.

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Table 1: Clinic Baseline Patient Characteristics by Study

	Total (N=610)		Study A (N=360)		Study B (N=250)			
	N	%	N	%	N	%	χ^2	p-value
Male	386	63.3	210	58.3	176	70.4	9.245	0.002
Age <40 y.o.	348	55.2	213	56.2	135	53.8	0.356	0.551
Race								
- Black	309	50.7	222	61.7	87	34.8	77.940	<0.001
- Latino	130	21.3	81	22.5	49	19.6		
- African	123	20.2	32	8.9	91	36.4		
- Other	48	7.9	25	6.9	23	9.2		
Ever homeless	221	36.3	138	38.3	83	33.3	1.592	0.207
Homeless past yr	132	21.7	92	25.6	40	16.1	7.910	0.005
Married/Common-law	190	31.2	93	25.9	97	38.8	11.416	0.001
Foreign-born	339	55.6	172	47.8	167	66.8	21.623	<0.001
Completed high school	336	56.9	183	53.8	153	61.2	3.197	0.074
Unemployed	409	67.0	262	72.8	147	58.8	13.048	<0.001
Prior LTBI treatment	64	10.5	49	13.6	15	6.0	8.917	0.003
Emotional/psych hospitalizations	42	6.9	28	7.8	14	5.6	1.149	0.284
Currently smoke	254	41.6	170	47.2	84	33.6	11.266	0.001
Ever drink alcohol	427	70.9	248	70.5	179	71.6	0.093	0.760
Currently drink alcohol	197	32.3	117	32.5	80	32.0	0.017	0.897
Ever drug use	340	55.7	211	58.6	129	51.6	2.940	0.086
Currently use drugs	120	19.7	80	22.2	40	16.0	3.615	0.057

Table 2: Participants Knowledge and Attitudes by Study

	Total (N=610)		Study A (N=360)		Study B (N=250)			
	Mean	s.d.	Mean	s.d.	Mean	s.d.	T	p-value
Knowledge score	4.14	0.998	4.27	0.988	3.94	0.982	4.088	<0.001
TB is disease you have to take seriously	3.84	0.452	3.90	0.446	3.76	0.448	3.841	<0.001
No matter what you do, can get TB	2.86	1.186	3.08	1.136	2.52	1.184	5.864	<0.001
Taking TB medications is important	3.88	0.452	3.88	0.452	3.88	0.452	-0.014	0.989
Know better than doctor when best to stop medications	1.37	0.845	1.23	0.685	1.59	1.003	-5.014	<0.001
Going to appointments more trouble than worth	1.37	0.764	1.32	0.755	1.44	0.775	-1.822	0.069
If do the right thing, can avoid getting TB	3.21	1.135	3.10	1.205	3.37	1.004	-2.994	0.003
Embarrassed to tell you have TB	2.41	1.263	2.52	1.302	2.23	1.183	2.956	0.003
Believe that you have the TB germ	3.06	1.154	3.06	1.189	3.06	1.101	0.079	0.937
Care what family/friends think of TB treatment	2.77	1.237	2.82	1.257	2.71	1.204	1.091	0.276
As hard as you try, you are going to miss some of your medicines	1.91	1.085	1.86	1.124	1.99	1.020	-1.499	0.134
TB medications are a hassle	1.44	0.848	1.34	0.799	1.60	0.897	-3.636	<0.001
Takes something bad to not take meds	2.92	1.284	3.15	1.247	2.57	1.263	5.677	<0.001

Chapter 4:

Predictors of Latent Tuberculosis Infection Treatment Completion in the U.S.: an Inner City Experience

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SUMMARY

RATIONALE**:** Few studies have examined predictors of latent TB infection (LTBI) treatment completion in inner city urban populations in the U.S.

OBJECTIVE: To assess LTBI treatment completion rates and predictors in an urban clinic cohort.

METHODS: Data from control groups of two sequentially-conducted randomized controlled trials of LTBI treatment were analyzed for treatment completion rates. Participants in Study A (n=183), conducted in 1996-1999, self-administered daily INH for 6-12 months while participants in Study B (n=122), conducted in 2002-2005, self-administered daily INH for 9 months.

RESULTS: Overall, 45.9% of participants completed therapy, with significantly higher completion rates in Study B than Study A (38.7% vs. 56.6%, p=0.0027). Marriage and alcohol use were significant predictors of completion (ARR=1.480, 95% CI 1.174-1.865) and non-completion (ARR=0.740, 95% CI 0.585-0.935) respectively; multivariate analysis indicated increased completion among married persons of foreign-birth and among alcohol users who were homeless. TB knowledge and attitudes were not significant predictors.

CONCLUSIONS: The design provided an opportunity to assess predictors of LTBI treatment completion in this inner city population. Social circumstances were the strongest predictors of treatment completion, suggesting that tangible social services may be more effective than educational programs in encouraging treatment completion.

INTRODUCTION

An estimated 9-14 million persons in the U.S. have latent tuberculosis infection (LTBI) and are therefore at risk for progression to active tuberculosis (TB) disease.[1] Diagnosis and treatment of LTBI has been identified by the Centers for Disease Control and Prevention and the Institute of Medicine as a major strategy for elimination of TB in the U.S.[2,3] Approximately 200-300,000 individuals are treated for LTBI in the U.S. annually, with reported LTBI treatment completion rates in the U.S. ranging from 20-65% for a 6-month course of self-administered treatment; while some studies found higher completion rates.[4] In a national survey, Horsburgh reported 47% completion among patients treated in 2002.[5] Better understanding of factors associated with LTBI treatment completion rates is essential to efforts to eliminate TB in this country.

The challenge of LTBI treatment is particularly critical in inner city urban neighborhoods like New York City's Central Harlem, where rates of TB greatly exceed the national average (16.7/100,000 vs. 4.2.4/100,000 in 2008, respectively)[6] and elevated rates of HIV infection increase the population vulnerable to TB. Harlem has long been a predominantly African-American community and is home to a growing African immigrant population. Potential barriers to medication adherence in Harlem include poverty, drug and alcohol use, homelessness, fragile or inadequate social support networks, low awareness of available low-cost or free health care services, and a dearth of culturally appropriate health care. TB-related social stigma, which gives rise to fears of discrimination and isolation, may also impede acceptance and completion of LTBI treatment.

Few studies have examined predictors of adherence and completion of LTBI treatment and the few that have been conducted in inner city urban populations have focused on selected

demographic groups[7-11] rather than broader clinic populations.[12-15] Additionally, few prior studies have given significant attention to TB attitudes.

The objectives of this study were to assess LTBI treatment completion rates and predictors of completion, including TB knowledge and attitudes, among an inner-city urban cohort. Foreign birth, homelessness, and current substance use were hypothesized a priori to be risk factors for LTBI treatment non-completion.

STUDY POPULATION AND METHODS

Design, setting and sample

This analysis used data from the control arms of two sequential randomized controlled trials evaluating a supportive intervention for LTBI treatment. In 1996-1999 (Study A) and 2002-2005 (Study B), all patients ≥18 years from the Harlem Hospital Chest Clinic diagnosed with LTBI following CDC guidelines[2] were approached for participation using identical inclusion and exclusion criteria. Both studies were approved by the Columbia University Institutional Review Board at Harlem Hospital.

Providers blinded to study status made clinical determination of LTBI treatment completion/non-completion according to CDC guidelines; these data were subsequently abstracted from medical charts by research staff. Datasets from both studies were combined to increase the power for this analysis. Treatment completion and predictor variables were measured identically in both studies. A variable indicating study of origin was used to adjust for differences between studies.

The studies differed in the use of electronic monitoring devices (EMDs), which recorded opening times of medication bottles in Study B but not Study A. Furthermore, Study A participants were prescribed 6-12 months of isoniazid (depending on HIV status), while Study B patients received 9 months of isoniazid.

Instruments

Trained research assistants conducted face-to-face interviews using structured questionnaires on demographics, homelessness (street vs. shelter not distinguished), substance use, life stressors, and TB-related knowledge and attitudes at enrollment. Current substance use was defined as any alcohol or drug use in the past month. TB knowledge items included six true/false questions on TB transmission, diagnosis, and treatment. Twelve attitudinal items were measured on a four-point Likert scale ranging from 'strongly disagree' to 'strongly agree'.

Data Analysis

Student's t-test was used to compare continuous variables, while χ^2 or Fisher's exact test was used to assess association for categorical variables. Binomial regression was used to evaluate predictors while adjusting for study of origin. Variables significant at ≤ 0.10 and variables hypothesized a priori to be predictors were candidates for the final multivariate regression model, which was constructed based on a manual, stepwise assessment of predictors and interactions. Model diagnostics were computed for final models and assessed using the Hosmer and Lemeshow Goodness-of-Fit Test, along with Akaike's Information Criteria (AIC) and Schwartz's Information Criterion (SIC).[16-18] A summary knowledge score was constructed by calculating the proportion of correct answers to knowledge items. Factor analysis was used to develop scale scores for attitudes; scales were produced by taking mean scores for all attitudinal items in a specific factor.

Internal consistency and reliability of scales was tested with Cronbach's alpha, using threshold of >0.6.[19] Attitudinal items were analyzed using the ordinal four-point scale where the response patterns appeared to fit a logistic curve, or categories were collapsed to dichotomous outcomes. Statistical analyses were performed using SAS (version 9.1.3, 2000; SAS Institute Inc, Cary, NC) and SPSS (version 15.0; SPSS, Chicago, IL).

RESULTS

Study Population

Table 1 describes the study population, shown by study of origin (Study B vs. Study A). Overall, participants were more likely to be male (63.9%), African-American or Latino (72.2%), <40 years old (55.1%), unemployed (68.5%), and not married (70.2%). The majority of participants were foreign-born (52.5%), while substantial proportions reported homelessness (25.6%) or substance use (22.6%) at enrollment. There were significant differences between participants in Studies A and B, with the latter more likely to be male, African, foreign-born, employed, married, and on a nine-month regimen, but less likely to be homeless or report drug use.

LTBI Treatment Completion Rates

Overall, 45.9% of participants completed therapy, with a significantly higher completion rate among Study B participants (56.6%) than Study A participants (38.7%) ($p = 0.0027$). A higher completion rate was observed in Study B for every demographic subgroup investigated (Table 2).

Age, marriage, current homelessness, and ever having used alcohol were associated with treatment completion, either in the combined sample (age, marriage, homelessness, lifetime alcohol use) or in Study B population (age, marriage). Place of birth, employment, and race/ethnicity showed significant differences for treatment completion in the combined sample but not in either individual study. Furthermore, the effect of race/ethnicity is inconsistent in the two studies; Latinos had higher completion than African-Americans in Study A but lower completion than African-Americans in Study B.

Predictors of Treatment Completion

Table 3 summarizes predictors of treatment completion, after controlling for study of origin. Lifetime alcohol use (ARR=0.740, 95% CI 0.585-0.935), age (ARR=0.784, 95% CI 0.619-0.993), and marriage (ARR=1.480, 95% CI 1.174-1.865) were the only strongly significant predictors, with homelessness (ARR=0.720, 95% CI 0.511-1.016), and more than 2 life stressors reported (ARR=0.807, 95% CI 0.638-1.021) meeting the 0.10 criterion for consideration in multivariate modeling. Foreign birth (ARR=1.157, 95% CI 0.897-1.494) and current drug use (ARR=0.876, 95% CI 0.635-1.207) were further considered in the multivariate models because they had been hypothesized a priori to be risk factors for non-completion of LTBI treatment.

Table 4 presents a multivariate model for predicting treatment completion. According to this model, foreign birth (ARR=0.709, 95% CI 0.501-1.001), marriage (ARR=0.520, 95% CI 0.239-1.130), current homelessness (ARR=0.603, 95% CI 0.387-0.939), and current alcohol use (ARR=0.759, 95% CI 0.564-1.020) were risk factors for non-completion of LTBI treatment; however, all of these factors were modified by interaction terms. Unmarried foreign-born TB patients were less likely than U.S.-born patients to complete treatment, while married foreign-born

TB patients were substantially more likely than U.S.-born patients to complete therapy (ARR=3.603, 95% CI 1.558-8.330). Similarly, homeless persons who did not use alcohol were significantly less likely than persons with stable living situations to complete therapy; however, homeless persons who did use alcohol were more likely to complete therapy (ARR=2.412, 95% CI 1.234-4.716). As seen in Table 2, completion rates in the two studies varied significantly and study of origin was a significant predictor of completion in the multivariate model (ARR=0.721, 95% CI 0.571-0.909). However, no interactions between potential predictors and study of origin were found. Diagnostic statistics were used to assess the validity of the final model. These diagnostic tests confirmed that the final model conforms to statistical assumptions for binomial regression.

TB Knowledge and Attitudes

Factor analysis of the 12 attitudinal items yielded four factors accounting for 53.2% of the total variation; final factor solution is not shown. Four scales were created but none achieved reliability; therefore, the attitudinal data was analyzed using individual items.

Attitudinal items A1-A5 were distributed normally and were therefore analyzed using the four-point scale. For some of the attitudinal items (A6-A12), better (or worse) completion rates were observed in the two extreme categories (‘strongly disagree’ and ‘strongly agree’) than in the two middle categories (‘disagree’ and ‘agree’). Neither collapsing a four point scale nor combining ‘strongly agree’ with ‘agree’ and ‘strongly disagree’ with ‘disagree’ was appropriate for these variables. Depending on the distribution, the category with most responses was either designated as the reference group or the two middle categories (‘agree’ and ‘disagree’) were collapsed and used that as the reference group.

Table 5 shows the relationship of TB-related knowledge and attitudes with treatment completion, after controlling for study of origin. No individual knowledge items, nor the overall knowledge score, were significantly associated with completion. However, the attitudinal items 'no matter what you do, you can get TB' (A6), 'you are embarrassed to tell you have TB' (A7), 'you believe you have the TB germ' (A8), and 'you care about what your family and friends may think of your TB' (A9) were significantly associated with LTBI treatment completion with $p < 0.10$.

These variables (A6, A7, A8, A9) were each tested in the multivariate model shown in Table 4. Only agreeing with the statements 'you believe you have the TB germ' (A8) (p=0.0151) and 'you care about what your family and friends may think of your TB' (A9) (p=0.0269) were significant risk factors after adjusting for demographic and other characteristics in the multivariate model. The addition of these attitudinal items did not change the association of other predictors in the model shown in Table 4 with treatment completion and model fitting criteria (notably SIC) did not indicate that these variables substantially improved the model shown in Table 4.

DISCUSSION

Ensuring completion of LTBI treatment benefits both the treated individual and society in general by preventing cases of active, infectious disease. Thus, understanding adherence and developing interventions to support it are critical to public health policy.[20,21] This U.S. inner city urban setting provides a valuable opportunity to examine predictors of adherence to LTBI treatment in a clinic population where patients are at increased risk of getting TB and face many barriers to completion of treatment.

Our results suggest that foreign birth, homelessness, marriage, and alcohol or drug use all influence completion of LTBI treatment through complex interactions. Overall, married persons had better completion, but married foreign-born patients were substantially more likely to complete therapy than unmarried foreign-born patients. Similarly, alcohol users were less likely to complete therapy, but homeless alcohol users were more likely to complete treatment than other homeless patients. The latter is probably an artifact of our clinic population, which includes patients from alcohol and substance abuse rehabilitation programs. Residence in such programs may have a positive effect on treatment completion because patients may have had more supervision of medications and appointment keeping. Race/ethnicity did not appear to be associated with treatment completion, although the differences between the two study populations made this difficult to assess.

The few recent studies of LTBI treatment adherence have not found it to be related to age, sex, place of birth or race. Where significant associations are found, studies exhibit inconsistent results.[4] An even smaller number of studies examined predictors of adherence and completion of LTBI treatment in inner city clinic populations. Our finding of lower completion rates among homeless patients and current alcohol users agrees with results of Lobue et al. found in San Diego in a general TB clinic population.[13] Regarding foreign birth, our study found higher completion among married foreign-born patients. However, Parsyan et al. identified birth in Haiti or the Dominican Republic as a risk factor for non-completion in a Boston Public Health TB clinic,[14] while Lobue et al.[13] and Bock et al.[12] found foreign birth to be associated with higher completion rates.

No knowledge items and few attitudinal items were associated with likelihood of completing treatment. Only two (‘believe you have the TB germ’ and ‘care about what your family and friends may think of your TB’) were significant after adjusting for demographic, social, and other characteristics, and both resist meaningful interpretation. Specifically, respondents who either

strongly agreed or strongly disagreed with these statements were less likely to complete therapy than those who moderately agreed or disagreed. The implications of these results are not clear.

Knowledge and attitudes may be less important than social factors in determining treatment completion. If so, educational programs aimed at increasing knowledge and modifying attitudes may be less effective than tangible assistance in encouraging treatment completion. That is, if unmarried persons or those in unstable living conditions have difficulty completing treatment, then outreach programs that address their needs may improve completion rates.

The greatest difference in completion rates was between Study A and B participants. Study B participants were observed to have higher completion rates than Study A participants regardless of race, ethnicity, gender, education level, age, place of birth, life stressors, alcohol or drug use, employment status, marital status, and stability of housing, despite the longer regimen for Study B participants. A primary difference between the studies was the use of EMDs in Study B for monitoring treatment adherence, suggesting that EMDs may have influenced treatment completion.

Recent work has shown the importance of shortened LTBI treatment regimens for ensuring treatment completion,[4] with completion ranging from 71.6% to 91.4% with four months of rifampin.[22] Further research would be required to determine whether factors found to predict completion would remain effective predictors among patients on shortened regimens characterized by higher completion rates.

Limitations

Although both studies were conducted in the same clinic, the study population changed somewhat between the time frames for the two studies. Other differences included treatment regimens and the use of EMDs in Study B. While statistical adjustments were made for these differences, it would have been preferable to have identical populations and protocols. Another possible limitation is that providers may not have been consistent in their determination of treatment completion; however, the small number of providers making this determination was blinded to study status. Another possible limitation is that self-reporting of some items (e.g., alcohol or drug use) may have been subject to social desirability bias in face-to-face interviews; similarly, whether homeless participants were living in the street or in a shelter and possibly receiving services was not assessed and it was not possible to tease it out. Patients receiving DOT for LTBI were excluded from the study; however, the DOT for LTBI population was found to be similar to the study population of Pathways[23] and no changes in procedures for DOT referrals were implemented in the clinic during that period. Finally, since this study was conducted in an inner city urban setting, the results cannot be rigorously generalized to the general U.S. population, although they have strong implications for similar populations.

CONCLUSIONS

In this study of LTBI treatment completion in an inner city urban population, homelessness, foreign birth, alcohol use, and marriage predicted success at completing LTBI treatment. Special efforts to reach patient groups identified with these factors should improve completion rates. Currently, the primary intervention for improving LTBI adherence consists of educational

programs to increase knowledge and modify attitudes. Our findings suggest that tangible assistance would be more effective in encouraging treatment completion.

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Table 1: Patient characteristics of sample[a]

	Combined N=305 n (%)	Study A N=183 n (%)	Study B N=122 n (%)	p-value[b]
Treatment duration				
6 months	176 (57.9)	176 (96.2)	0 (0%)	<0.001
9 months	122 (39.8)	0 (0%)	122 (100%)	
12 months	7 (2.3)	7 (3.8)	0 (0%)	
Demographics				
Age group				
40+	137 (44.9)	78 (42.6)	59 (48.4)	0.3237
<40	168 (55.1)	105 (57.4)	63 (51.6)	
Gender				
Female	110 (36.1)	76 (41.5)	34 (27.9)	0.0149
Male	195 (63.9)	107 (58.5)	88 (72.1)	
Race/Ethnicity				
Black or African-American	157 (51.5)	120 (65.6)	37 (30.3)	<0.0001
Latino	63 (20.7)	39 (21.3)	24 (19.7)	
African	59 (19.3)	13 (7.1)	46 (37.7)	
Other	26 (8.5)	11 (6.0)	15 (12.3)	
Place of birth				
US-born	145 (47.5)	104 (56.8)	41 (33.6)	<0.0001
Foreign-born	160 (52.5)	79 (43.2)	81 (66.4)	
Social Characteristics				
Education – completed high school				
No	130 (44.1)	83 (48.0)	47 (38.5)	0.1073
Yes	165 (55.9)	90 (52.0)	75 (61.5)	
Employment				
No	209 (68.5)	138 (75.4)	71 (58.2)	0.0015
Yes	96 (31.5)	45 (24.6)	51 (41.8)	
Married				
No	214 (70.2)	138 (75.4)	76 (62.3)	0.0142
Yes	91 (29.8)	45 (24.6)	46 (37.7)	
Current homelessness				
No	227 (74.4)	124 (67.8)	103 (84.4)	0.0011
Yes	78 (25.6)	59 (32.2)	19 (15.6)	
Life stressors				
0 or 1 stressors	126 (41.3)	74 (40.4)	52 (42.6)	0.7041
2 or more stressors	179 (58.7)	109 (59.6)	70 (57.4)	
Substance Use				
Ever alcohol use				
No	89 (29.4)	52 (28.7)	37 (30.3)	0.7645
Yes	213 (70.6)	129 (71.3)	85 (69.7)	
Current alcohol use				
No	206 (67.5)	129 (68.9)	80 (65.6)	0.5491
Yes	99 (32.5)	57 (31.2)	42 (34.4)	
Ever drug use				
No	127 (41.6)	65 (35.5)	62 (50.8)	0.0079
Yes	178 (58.4)	118 (64.5)	60 (49.2)	
Current drug use				
No	236 (77.4)	134 (73.2)	102 (83.6)	0.0337
Yes	69 (22.6)	49 (26.8)	20 (16.4)	

[a] N of each variable varies due to missing data; [b] comparing Study A and Study B

Table 2: Completion rates by study group

	Combined sample % (n)	Study A % (n)	Study B % (n)
Overall	45.9% (139/302)	38.7% (70/181)	56.6% (69/122)
Age group			
40+	52.2% (71/136)	41.6% (32/77)	66.1% (39/59)
<40	40.7% (68/167)	36.5% (38/104)	47.6% (30/63)
p-value	0.0459	0.4929	0.0396
Gender			
Female	44.0% (48/109)	40.0% (30/75)	52.9% (18/34)
Male	46.9% (91/194)	37.7% (40/106)	58.0% (51/88)
p-value	0.6303	0.7580	0.6165
Race/Ethnicity			
Black or African-American	39.7% (62/156)	35.3% (42/119)	54.1% (20/37)
Latino	42.9% (27/63)	41.0% (16/39)	45.8% (11/24)
African	61.0% (36/59)	61.5% (8/13)	60.9% (28/46)
Other	56.0% (14/25)	40.0% (4/10)	66.7% (10/15)
p-value	0.0283	0.3160	0.5340
Place of birth			
US-born	40.3% (58/144)	35.0% (36/103)	53.7% (22/41)
Foreign-born	50.9% (81/159)	43.6% (34/78)	58.0% (47/81)
p-value	0.0628	0.2373	0.6458
Education – completed high school			
No	47.7% (62/130)	44.6% (37/83)	53.2% (25/47)
Yes	45.4% (74/163)	34.1% (30/88)	58.7% (44/75)
p-value	0.6957	0.1603	0.5527
Employment			
No	42.0% (87/207)	37.5% (51/136)	50.7% (36/71)
Yes	54.2% (52/96)	42.2% (19/45)	64.7% (33/51)
p-value	0.0485	0.5729	0.1238
Married			
No	39.4% (84/213)	35.0% (48/137)	47.4% (36/76)
Yes	61.1% (55/90)	50.0% (22/44)	71.7% (33/46)
p-value	0.0005	0.0762	0.0085
Current homelessness			
No	50.2% (113/225)	43.4% (53/122)	58.3% (60/103)
Yes	33.3% (26/78)	28.8% (17/59)	47.4% (9/19)
p-value	0.0099	0.0582	0.3792
Life stressors			
0 or 1 stressors	52.0% (65/125)	43.8% (32/73)	63.5% (33/52)
2 or more stressors	41.6% (74/178)	35.2% (38/108)	51.4% (36/70)
	0.0730	0.2411	0.1848

Table 2: Completion rates by study group

	Combined sample % (n)	Study A % (n)	Study B % (n)
Ever alcohol use			
No	56.8% (50/88)	49.0% (25/51)	67.6% (25/37)
Yes	41.3% (88/213)	34.4% (44/128)	51.8% (44/85)
p-value	0.0141	0.0692	0.1055
Current alcohol use			
No	48.5% (99/204)	40.3% (50/124)	61.3% (49/80)
Yes	40.4% (40/99)	35.1% (20/57)	47.6% (20/42)
p-value	0.1831	0.5018	0.1490
Ever drug use			
No	51.6% (65/126)	46.9% (30/64)	56.5% (35/62)
Yes	41.8% (74/177)	34.2% (40/117)	56.7% (34/60)
p-value	0.0922	0.0938	0.9810
Current drug use			
No	47.9% (112/234)	40.9% (54/132)	56.9% (58/102)
Yes	39.1% (27/69)	32.7% (16/49)	55.0% (11/20)
p-value	0.20086888273y	0.3109	0.8779

Table 3: Binomial regression analysis of predictors of completion of care, controlling for study of origin

Independent Variables	Regression coefficient	Standard error	Adjusted RR	95% CI	p-value
Demographics					
Age 40+ years	-0.2437	0.1206	0.7837	0.6188-0.9927	0.0433
Male	0.0200	0.1293	1.0202	0.7918-1.3146	0.8770
Race/Ethnicity					
African vs. African-American	0.2609	0.1653	1.2981	0.9388-1.7950	0.1145
Latino vs. African-American	0.0189	0.1767	1.0191	0.7208-1.4408	0.9148
Foreign-born	0.1459	0.1302	1.1571	0.8965-1.4935	0.2624
Social Characteristics					
Completed high school	-0.0560	0.1221	0.9455	0.7443-1.2011	0.6463
Employed	0.1971	0.1228	1.2179	0.9573-1.5494	0.1086
Married	0.3917	0.1180	1.4795	1.1740-1.8646	0.0009
Currently homeless	-0.3283	0.1755	0.7201	0.5106-1.0157	0.0613
Life stressors – 2 or more	-0.2142	0.1199	0.8072	0.6381-1.0210	0.0740
Substance Use					
Ever alcohol use	-0.3015	0.1193	0.7397	0.5854-0.9346	0.0115
Current alcohol use	-0.2046	0.1381	0.8150	0.6218-1.0683	0.1385
Ever drug use	-0.1302	0.1244	0.8779	0.6879-1.1204	0.2953
Current drug use	-0.1330	0.1639	0.8755	0.6350-1.2071	0.4171

RR = Risk Ratio
CI = Confidence Interval

Table 4: Multivariate binomial regression analysis of predictors of completion of care

Independent Variables	Regression coefficient	Standard error	Adjusted RR	95% CI	p-value
Foreign-born	-0.3445	0.1765	0.7086	0.5014-1.0014	0.0509
Married	-0.6538	0.3958	0.5200	0.2394-1.1295	0.0985
Interaction married*foreign-born	1.2817	0.4276	3.6029	1.5583-8.3298	0.0027
Currently homeless	-0.5060	0.2263	0.6029	0.3869-0.9394	0.0253
Current alcohol use	-0.2763	0.1511	0.7586	0.5642-1.0200	0.0674
Interaction currently homeless*current alcohol use	0.8806	0.3420	2.4122	1.2339-4.7158	0.0100
Study of origin*	-0.3276	0.1186	0.7206	0.5711-0.9093	0.0058

RR = Risk Ratio
CI = Confidence Interval
* Study A = 1, Study B = 0

Table 5: Binomial regression analysis of knowledge & attitude predictors of completion of care, controlling for study of origin

Independent Variables	Regression coefficient	Standard error	Adjusted RR	95% CI	p-value
Knowledge items					
K1. Can get TB from crowded conditions	0.1457	0.2356	1.1569	0.7291-1.8357	0.5362
K2. Can get TB through kissing	0.1310	0.1337	0.1400	0.8772-1.4814	0.3271
K3. Can get TB through sharing dishes	-0.1093	0.1418	0.8965	0.6789-1.1837	0.4408
K4. Most TB can be cured with medications	0.4321	0.3668	1.5405	0.7506-3.1616	0.2389
K5. HIV-infected more likely to get TB	-0.1289	0.1355	0.8791	0.6740-1.1465	0.3416
K6. People with TST+ may need TB medications	0.0362	0.2981	1.0368	0.5780-1.8598	0.9034
Knowledge score	0.0130	0.0627	1.0130	0.8960-1.1454	0.8363
Attitudinal variables					
A1. TB is disease you have to take seriously	-0.0613	0.1181	0.9405	0.7462-1.1854	0.6036
A2. Taking TB medications is important	-0.1076	0.0799	0.8980	0.7678-1.0503	0.1783
A3. You know better than the doctor when best to stop medications	-0.0322	0.0744	0.9683	0.8368-1.1204	0.6652
A4. Going to appointments more trouble than worth	0.0172	0.0758	1.0174	0.8769-1.1804	0.8201
A5. If do the right thing, can avoid getting TB	0.0047	0.0542	1.0047	0.9034-1.1173	0.9313
A6. No matter what you do, can get TB					
strongly disagree	-0.4083	0.1615	0.6648	0.4844-0.9124	0.0115
disagree	-0.0001	0.1800	0.9999	0.7026-1.4232	1.0000
agree	-0.0677	0.1551	0.9345	0.6896-1.2666	0.6626
strongly agree	reference				
A7. Embarrassed to tell you have TB					
strongly disagree	-0.3380	0.1409	0.7132	0.5411-0.9401	0.0164
strongly agree	-0.2811	0.1533	0.7550	0.5590-1.0195	0.0666
disagree/agree	reference				
A8. Believe have TB germ					
strongly disagree	-0.2536	0.1638	0.7760	0.5629-1.0697	0.1215
strongly agree	-0.4264	0.1323	0.6529	0.5038-0.8461	0.0013
disagree/agree	reference				
A9. Care about what family/friends think					
strongly disagree	-0.3031	0.1654	0.7385	0.5341-1.0212	0.0668
strongly agree	-0.3488	0.1431	0.7055	0.5330-0.9340	0.0148
disagree/agree	reference				
A10. As hard as you try, you are going to miss some of your medicines					
strongly disagree	-0.5324	0.3343	0.5872	0.3049-1.1308	0.1113
disagree	0.2079	0.1566	1.2311	0.9057-1.6735	0.1844
agree	-0.0149	0.1455	0.9852	0.7408-1.3102	0.9184
strongly agree	reference				

Table 5: Binomial regression analysis of knowledge & attitude predictors of completion of care, controlling for study of origin

Independent Variables	Regression coefficient	Standard error	Adjusted RR	95% CI	p-value
A11. TB medications are a hassle					
strongly disagree	-0.1929	0.1350	0.8246	0.6329-1.0742	0.1529
strongly agree	-0.6941	0.4493	0.4995	0.2071-1.2050	0.1224
disagree/agree	reference				
A12. Takes something bad to not take meds					
strongly disagree	-0.0579	0.1560	0.9437	0.6951-1.2802	0.7104
disagree	0.2070	0.1952	1.2300	0.8389-1.8033	0.2891
agree	0.1735	0.1745	1.1895	0.8448-1.6746	0.3202
strongly agree	reference				

RR = Risk Ratio
CI = Confidence Interval

Chapter 5:
Impact of peer-based interventions on adherence to and completion of LTBI treatment

SUMMARY

RATIONALE: Few randomized controlled trials have examined the impact of interventions for improving treatment completions rates of latent TB infection (LTBI).

OBJECTIVE: To assess the effectiveness of a peer-based experimental intervention on adherence to and completion of LTBI treatment in patients eligible for LTBI treatment in an urban clinic setting.

METHODS: Patients diagnosed with LTBI in an urban chest clinic were recruited for two NIH-funded sequentially-conducted randomized controlled trials for experimental intervention of self-administered treatment of LTBI with peer support versus control of standard of care self-administered treatment alone. The Pathways study enrolled participants between 1996-1999 and TAPAS enrolled participants between 2002-2005. Adherence support was provided by trained peer workers who were community members and had successfully completed either TB or LTBI treatment. The primary outcomes were treatment adherence and completion. Demographics, social support, mental health, TB knowledge and attitudes, and substance use were assessed at baseline and follow up appointments. Adherence was also assessed by self report, electronic monitoring devices and through clinic visits.

RESULTS: Of 360 participants enrolled in Pathways, 58% were male, 71% Black, 23% Latino. Mean age was 40 years, 48% were foreign-born, 54% completed high school, 26% were married. Participants in the control group reported significantly more homelessness and drug use at baseline. In Pathways, 60% of participants in the intervention group completed treatment of LTBI compared to 38% of controls ($p<0.0001$). In multivariate analysis, completion of high school and current homelessness, were found to be predictors for non completion of LTBI treatment after controlling for intervention group. Additionally, agreement with two attitudinal items (“doctors don’t really care about curing your TB,” and “when feel real bad, you would stay

home instead of seeing the doctor,") was identified as predicting non completion of LTBI treatment. Adherence analysis was not possible as many of the monthly adherence interviews were lost and could not be located. Of 250 participants enrolled in TAPAS, 70% were male, 71% Black, and 20% Latino. Mean age was 39 years, 67% were foreign-born, 61% completed high school, and 39% were married. No significant differences were noted in baseline characteristics between groups. In TAPAS, 61% of participants in the intervention group completed treatment of LTBI compared to 57% of controls (p=0.4818). Corresponding LTBI treatment completion rate for clinic patients who did not participate in the study was 44%. Foreign birth, marriage, and history of mental illness were found to be predictors for non completion of LTBI treatment after controlling for intervention group; however, increased completion rates were found among married persons of foreign-birth. Older age (40+) was a predictor of improved treatment completion. Results of the medication adherence analysis in TAPAS demonstrated a substantial difference in adherence rates was observed between study groups (10%) and that non-completers' adherence decreased early during treatment while completers had fairly steady levels of adherence throughout the treatment.

CONCLUSIONS: The peer support intervention was found to be associated with significant increase in LTBI treatment completion rates in the Pathways population but not in the TAPAS population, whereas completion rates increased in the control group as well as in the intervention group in the latter study. The power for detecting an intervention effect in TAPAS was reduced by the higher than expected completion rates in both groups; however, the effect of the TAPAS intervention is statistically significant in the adherence model. Adherence analysis in TAPAS suggests that it is important to intervene early in the treatment as the first two months of treatment present a danger period where patients tend to default treatment.

INTRODUCTION

An estimated 9 to 14 million persons in the United States have latent tuberculosis infection (LTBI) and are therefore at risk for progression to active tuberculosis (TB) disease.[1] Diagnosis and treatment of LTBI has been identified by the Centers for Disease Control and Prevention as one of the major strategies for elimination of tuberculosis (TB) in the U.S.[2] Similarly, the Institute of Medicine has called for programs of targeted tuberculin testing coupled with treatment of LTBI (TLTBI) for individuals with elevated risk of developing TB disease.[3] Completion of treatment for latent tuberculosis infection (TLTBI) is key to reducing the incidence of active TB in the US. It has been estimated that 200,000-300,000 individuals are treated for LTBI in the U.S. annually.[4] However, TLTBI completion rates in the U.S. generally has been largely below established targets and have been reported to range from 20 to 65% for a 6-month course of self-administered treatment; a few smaller studies were able to achieve higher completion rates.[5] A large multi-site study reported recently that treatment completion rates of the standard 9-month isoniazid regimen range from 30-60%,[4]

Over the past decade, several studies in the U.S. have evaluated the effect of different interventions aimed at improving adherence to TLTBI. These interventions included use of supervised therapy and the use of supplementary tools to promote adherence such as the provision of monetary incentives, counseling services, peer education programs, and health professional or cultural case management.[5] However, there are few LTBI adherence interventions that have been rigorously tested in randomized controlled trials.[5] In addition, most LTBI adherence interventions in the US have focused on specific populations, such as jail or prison inmates, injection drug users, homeless persons, health care workers, and immigrants or refugees originating from TB-endemic countries.

Peer collaboration has been recognized as a powerful tool to build social support in relation to adherence.[6-9] Peer workers, also called peer educators, peer advisors, lay health advisors or community health workers, have been matched to patients on the basis of their shared ethnicity, gender, illness experience, sexual orientation, risk behaviors, and/or socio-economic characteristics.[10-12] They act as system navigators to help patients secure social and community services needed for successful treatment completion, liaise with patients and health workers to enhance patient-provider communication, educate and coach patients on adherence behaviors, and provide social and emotional support. Peer interventions cultivate "helping relationships" that bond patient and peer in a uniquely personal alliance for health promoting behaviors. Because they facilitate tailoring treatment to individual patient needs, peer workers may be particularly valuable in interventions that target the complex interaction of factors known to influence adherence.

To date, peer-based interventions have demonstrated mixed results in facilitating optimal medication-taking behavior for LTBI, although few randomized controlled trials have assessed the effectiveness of peers to improve adherence to and completion of LTBI treatment.[5] Chaisson et al. found that electronically monitored adherence was significantly higher subsequent to the implementation of a peer-based adherence intervention with injection drug-using LTBI patients in Baltimore.[13] Tulsky et al. evaluated the effect of peer health advisors for homeless LTBI patients; 118 participants were randomized to receive DOT with an incentive, DOT with peer support, or self-administered therapy. LTBI treatment completion was significantly higher among those given an incentive, and there was no difference between peer-assigned and SAT groups (44% vs. 19 and 26% respectively). Failure was attributed to poor training of peer advisors on TB prevention education.[14] Further research is needed to assess the quality, range

and sustainability of peer interventions, and impact needs to be assessed in relation to the clinical and social context of the patient population to which the intervention is directed.

The effectiveness of peer workers or peer advisors in the management of LTBI merits further exploration. This analysis uses data from two sequential NIH-funded randomized controlled trials, Pathways to Completion Study and the Tuberculosis Adherence Partnership Alliance Study (TAPAS), to assess the impact of a peer-based experimental intervention on adherence to and completion of LTBI treatment in a general clinic population in an urban setting in the U.S.

METHODS

Design, setting and sample

From 1996 through 1999, patients who were diagnosed with LTBI were recruited from the Harlem Hospital Chest Clinic in New York City into the Pathways to Completion study, and from 2002 through 2005 into the TAPAS study. With TB rates greatly exceeding the national average and the concomitant HIV epidemic, the Harlem community is vulnerable to TB. Many of the patients in the clinic are referred by homeless shelters, substance abuse programs, and community based organizations where TB skin testing is often required for residency or for services like English language classes.

Patients in the clinic were offered treatment for LTBI (TLTBI) by their providers in the TB Clinic based on the prevailing CDC/ATS guidelines to determine candidacy for TLTBI.[2] The specific criteria used to determine study eligibility were as follows:

Inclusion Criteria**:**

- Recommended for initiation of a CDC recommended drug regimen for TLTBI
- Age of 18 years or older

Exclusion Criteria**:**

- Receiving Directly Observed Therapy for LTBI
- Evidence of active TB disease

Patients who fulfilled these criteria were referred for study participation. Potential study candidates were provided with further information regarding the study and invited to participate. All participants signed a consent form approved by the Columbia University Institutional Review Board at Harlem Hospital. Following a baseline interview with a research assistant, participants were randomly assigned to either the intervention or control group.

Experimental Intervention

Both studies assessed a peer-based intervention for LTBI treatment in the Harlem population. The peer intervention was compared to traditional self-administered treatment of LTBI. Building on experiences and insights from the Pathways study, the TAPAS intervention utilized the Health Belief Model,[15,16] Social Learning Theory,[17] and the Precaution Adoption Process (PAPM) Model,[18] enriched by social support concepts. This resulted in a more structured, theory-based intervention in TAPAS than in Pathways. The experimental intervention was primarily provided by peers who delivered components tailored to the PAPM model with the ultimate goal of achieving treatment completion. In addition, targeted health education was provided for selected patients in the TAPAS experimental arm. All study participants had access

to the standard clinical services available at the clinic, including a social worker and clinic health educators.

Peer worker qualifications included: successfully completing TB or LTBI treatment; being members of the communities that patients came from; having good communication skills; demonstrating a caring attitude; and being committed to TB control. The peer workers underwent extensive training that included both didactic learning and interactive techniques such as case study and role-playing to develop skills. The peer workers' role was designed to include the following elements: system navigation, referrals, advocacy, and social support. Peer worker responsibilities included: communicating weekly with participants; providing information on the importance of treatment; encouraging medication and visit adherence; offering support and empathy; providing referrals; and advocating for their participants.

Study Measurements

Questionnaires that evaluate key demographic, social, and behavioral characteristics were administered at baseline. Data were gathered from interviews and abstracted from participant clinic charts. Participants were recruited over two three-year periods and were followed at monthly intervals until they completed treatment, stopped treatment without completing it (possibly on medical advice), or were lost to follow-up. Participants were asked to return to the clinic each month in order to obtain medication refills and to be monitored for side effects from the medication as per standard of care. Participants were given coupons for transportation and lunch after each interview. The interviewers were research assistants who had extensive interviewing experience and who received special training for this study. The questionnaires

were translated into French and Spanish and interviews were conducted in English, French, and Spanish. Completed interviews were reviewed by the study coordinators for completeness.

In both studies, information on participants' socio-demographic characteristics, history of substance use, social support, life stressors, and TB knowledge and attitudes was obtained from interviews at baseline using structured questionnaires.

Social support was assessed with a modified version of the University of California, Los Angeles Social Support Inventory,[19] which measures three dimensions of social support over the previous month. *TB knowledge and attitudes* instrument was developed by the study investigators based on their experience in this field. The Knowledge section included True/False knowledge items related to TB transmission, symptoms, diagnosis and treatment; it included 24 items in Pathways and 16 items in TAPAS. The Attitudes section was comprised of attitudinal items measured on a four-point Likert scale and based on constructs suggested by key theoretical models (such as the Transtheoretical Model of Behavior Change, Social Learning, and the theory of Reasoned Action); it included 24 items in Pathways and 14 items in TAPAS. Constructs for attitudinal items included intentions, perceived risk, perceptions of group norms, self-efficacy, cues to action and costs and benefits.

S*tressful life events* were measured using a structured instrument which included assessment for issues such as financial distress, death, legal matters, violence, and partner separation in the past 6 months.[20] Information collected from the *substance use* instrument was used to classify study participants as substance or non-substance users;[21] current use was defined as past month use. A brief standardized version of the Marlowe-Crowne *Social Desirability* Scale questionnaire was

conducted as an adjunct measure to assess the impact of social desirability on self-report measures.[22]

Additional data collection measures for the TAPAS study included, q*uality of life* using the SF-12, which assesses limitations of activities due to physical and mental health.[23,24] D*epression* was assessed using the Center for Epidemiologic Studies Depression (CES-D) Scale, a 20-item self-report instrument designed to assess depressive symptoms in the general population over the past week; scores greater than or equal to 16 are interpreted as a positive screen for depression.[25] The *perceived benefits/perceived barriers* questionnaire was based on decisional balance scales developed for contraceptive use,[26] with the content of the benefits/barriers incorporating input from providers and patients who were on treatment for LTBI at the time.

LTBI treatment completion was determined by the participants' medical providers, who were blinded to study status and made clinical determination of TLTBI completion/non-completion according to CDC guidelines; these data were subsequently abstracted from medical charts by research staff. Information on initiation and completion of therapy, treatment interruptions, and adherence with clinic appointments was abstracted from the medical chart.

Treatment adherence was assessed in both studies on a monthly basis. In Pathways, a brief monthly assessment of adherence was conducted but many of the interviews were lost and could not be located; this did not allow for meaningful imputation of adherence data.

In TAPAS, a monthly assessment of adherence was conducted utilizing a combination of tools including self-report, clinic attendance, and electronic monitoring devices. The first two measures were utilized because they are informative, easy to use and replicate programmatically, and are not too costly or cumbersome for this patient population. Electronic monitoring devices

are costly and have been reported to be cumbersome;[27-29] however, it was thought that they would be useful for measuring adherence in the context of a clinical trial. The self-report adherence questionnaire was administered by interview; it evaluated adherence through an in-depth assessment of pill-taking behavior during the prior three days modeled on a validated ACTG self repot adherence questionnaire. In addition, detailed use of the MEMS caps was ascertained by interview; participants were asked whether they removed multiple doses of medications or opened and closed the cap without removing the medications. Acceptability of the MEMS cap in this population was assessed by interview at the end of the study. Prescription bottles equipped with the Medication Event Monitoring System (MEMS®) cap were distributed to all participants and collected at each monthly visit. The MEMS utilizes an electronic device built into the cap of the prescription bottle that records the date and time that the cap is removed. Clinic visit adherence was tracked for all participants throughout the study by the research assistants, who abstracted information from clinic charts and schedules. The monthly follow up questionnaire also elicited information about possible reasons for missing medications. Participants were asked to react to 25 different possible reasons on a 4-point scale: Never, Rarely, Sometimes, and Often.

Sample Size

The sample size for the Pathways study was based on the assumption that 55% of the intervention arm and 40% of the usual care arm would complete LTBI treatment. Under these assumptions, 151 participants per arm would be sufficient to provide 80% power for testing the primary hypothesis. The sample size was increased to 180 participants per arm to allow for attrition and to increase the power to assess secondary objectives. The sample size for the TAPAS study was based on the assumption that 60% of the intervention arm and 40% of the

usual care arm would complete LTBI treatment, based on results seen in the Pathways study. Under these assumptions, 97 participants per arm would be sufficient to provide 80% power for testing the primary hypothesis. The sample size was increased to 125 participants per arm to allow for attrition and to increase the power to assess secondary objectives.

Randomization

Both studies used a 1:1 randomization design. The random sequence of group assignment was allocated in a permuted 10-block design, generated by a study investigator. Cards indicating study group assignment were sealed in numbered, opaque envelopes and retained by the study coordinator. After completing the baseline assessment with study research assistants, participants were informed by the study coordinator of their random assignment to the peer support or usual care group.

Blinding

Due to the nature of the peer intervention, it was not possible to blind participants and intervention staff to their group assignment. Every attempt was made to ensure blinding of the research assistants, who conducted all follow up interviews.

Statistical Methods

Imputation of Missing Adherence Data

In TAPAS, self-reported adherence over the treatment period was one of the two primary outcomes for this study. For subjects who were missing self-reported adherence data at any time point, imputation procedures were implemented. The first step involved filling in missing data

based on decision rules developed for this project (see Appendix 2 Table 6 for more details), which utilized information from the chart abstraction and electronic adherence monitors (MEMS caps). For example, these rules involved assigning zero adherence for months 2-9 to patients whose charts noted that they were never seen in the clinic after the first appointment. For those data points where it was not possible to impute values based on all available information, hot-deck imputation was used.[30] Imputation was considered essential to (1) construct as complete a longitudinal database as possible and (2) correct bias due to data missing not at random.[31] The hot deck method was chosen because it was the most appropriate given the patterns of missing data. To implement hot-deck imputation, respondents with a missing adherence score at any time point constituted a pool of potential donors, while those missing this information were the recipients. The first critical "boundary" for imputation was whether or not persons completed treatment. Only donors who completed were used to impute missing data for completers; only donors who did not complete treatment were used to impute missing data for non-completers. Recipients were matched to donors based on the months for which data was available and matched to within +/- 2 months, and the actual reported adherence during these months had to match to within a cutoff of +/- 25%. Each recipient was then assigned a value from a matching donor; in cases of multiple matching donors, one donor was selected at random (See Appendix 2 Table 7 for more details).

Data Analysis

All data analyses were performed in accordance with the intent-to-treat principle. The effect of the intervention on *treatment completion* consisted of comparing proportions of subjects who were classified as either success or failure based on completion of therapy. Analysis was conducted using Pearson's χ^2 test, or Fisher exact test where appropriate, for categorical

variables and student's t-test for continuous variables. The potential confounding role of homelessness, substance use, social support, TB knowledge and attitudes, and other independent risk factors for non-adherence on the association between completion of therapy and intervention group was examined using stratified analyses and Mantel-Haenszel summary measures. Due to the large number of prognostic factors, data reduction techniques were used (see below). Variables significant at 0.10 or less were candidates for the final models. Multivariate binomial regression was used to 1) analyze the impact of the experimental intervention on completion of therapy after adjusting for variables identified as significant in the bivariate analyses, 2) potentially confounding variables reported in previous studies, and 3) interaction terms. Models were constructed based on a manual, stepwise assessment of potential predictors and hypothesized interactions. Model diagnostics were computed for final models and assessed using the Hosmer and Lemeshow Goodness-of-Fit Test, along with Akaike's Information Criteria (AIC) and Schwartz's Information Criterion (SIC).[32-34]

For the effect of the intervention on *adherence*, treatment adherence over time was modeled using mixed effects repeated measures models to further evaluate the impact of study arm on adherence. Repeated measures analysis uses all longitudinal data accounting for correlations in the data resulting from multivariate observations, clustering, or repeated measurements, and potentially has more power for comparing the intervention and standard of care arms. A Toeplitz covariance structure was used in the mixed effect models. This covariance structure assumes that the covariance between any two consecutive time points is the same but may be different from two time points that are separated by observations. For example, the covariance between time points 1 and 2 is same as time 2 and 3 but is different than the covariance between time 1 and 3 or 2 and 4, which are equal to each other.

The current standard for graphically displaying and exploring longitudinal data is the use of spaghetti plots, which involves plotting each subject's values for the repeated outcome measure (vertical axis) versus time (horizontal axis) and connecting the dots chronologically. However, there are a number of limitations to spaghetti plots such as trajectories commonly overlapping and with large datasets, the resulting plot is often a confusing jumble of intersecting lines with no discernible patterns. To be able to discern adherence patterns in this dataset, spaghetti plots were utilized with an addition of a small random variation for each datapoint. Because of the problems with spaghetti plots, heatmaps were used as a complementary graphical data exploration technique.[35] Heatmaps use color or shading to depict the magnitude of the outcome measurement and fix the vertical dimension per subject and thus each subject forms a "layer" in the plot. The plot takes advantage of color to provide a third dimension and display information clearly, rather than relying upon the vertical dimension to display overlapping magnitudes of change. There are several advantages of the heatmaps over the spaghetti plots in this type of longitudinal data. Group, cohort, and individual level information are preserved regardless of the number of subjects or time points. In addition, dynamic sorting of the data can be used to ascertain group level behavior over time.[35]

To assess whether MEMS data provided reliable data that can be used to impute adherence data where it was missing, a comparison of MEMS and self report was conducted. For each available interview, the MEMS data was reviewed for the corresponding three days prior to the interview date. Modified MEMS-use interviews were reviewed to check for reports of removing multiple doses of medications in the three days prior to interview day. A kappa statistic was calculated to measure the agreement between the two sources of data. The criteria employed to determine fair to good agreement was kappa of 0.40-0.75.[36]

Data Reduction

Factor analysis was used to develop scale scores for attitudes as well as for reasons given by participants for missing medications. Principal components analysis was utilized with a varimax rotation method in order to produce factors that were orthogonal or uncorrelated. Two criteria were employed to determine the number of factors to be retained: (a) Kaiser-Guttman's criterion (i.e., factors with an eigen value of greater than 1), and (b) examination of the scree plot. A factor loading of 0.50 was selected as the minimum level for item inclusion in a factor. Scales were produced by taking the mean score for all items in a specific factor.

A summary knowledge variable was constructed by calculating the proportion of correct answers to True/False knowledge items. A social support scale was created by taking the mean of the six social support items. Perceived benefits and barriers scales were created by taking the mean of the benefit items and barrier items respectively. Internal consistency reliability of scales was tested with Cronbach's alpha; the criteria employed to determine reliable scales was Cronbach's alpha greater than or equal 0.6.[37]

Statistical analyses were performed using SAS (version 9.2, 2000; SAS Institute Inc, Cary, NC) and SPSS (version 17.0; SPSS, Chicago, IL).

RESULTS - PATHWAYS

Enrollment

Figure 1a describes participant enrollment from July 1996 through June 1999. A total of 866 patients evaluated for LTBI were approached and of these, 536 were determined to be eligible for the study and were invited to participate. Twenty four of eligible patients refused to participate in the study; 153 were missed as study staff was not present to interact with potential candidates prior to initiation of treatment for LTBI; and 379 provided informed consent, completed baseline interviews, and were randomized to the peer support intervention or to the usual care arm, according to the study group allotment procedures described above. Ten participants (four intervention and six usual care participants) were determined to be ineligible for LTBI and were discharged by the clinic. In addition, nine participants (seven intervention and two usual care participants) were determined to be ineligible for the study according to inclusion criteria following randomization and are not included in study results. At the end of assigned treatment, three medical records could not be located: one intervention participant and two usual care participants and were therefore lost to follow up. Since the primary outcome was based on review of the medical records and to be conservative, it is assumed that these participants did not complete treatment.

Study Population

The Pathways Study recruited 379 participants, 188 were randomized to the intervention group and 191 to the control group. After excluding ineligible participants, the intervention group included 177 participants and the control group 183 participants (Table 1). The sample was predominantly male (58%), and study participants were 40 years old on average. The racial

distribution of the sample was Black (71%), Latino (22%) and White/other (7%). Approximately half completed high school or had a GED equivalent (54%). A quarter reported they were married/common law (26%) and almost half (48%) were foreign-born. Over a third of participants (38%) reported a history of homelessness and 26% reported current homelessness. Unemployment rates were high in this population with 73% of participants unemployed at baseline. A small proportion of participants (5%) reported HIV-infection at baseline; however, close to half (43%) did not know their HIV status. Substance use was reported by a third of the sample (33%) currently drinking alcohol and 22% currently using illicit drugs. There were no statistically significant differences between study arms with the exception of participants in the control group reporting more homelessness and lifetime drug use. The Marlowe-Crowne scale was used as an adjunct measure to assess the impact of social desirability on self-report measures; the reliability of the instrument was examined and it was found to be reliable. However, the mean Marlowe-Crowne scales did not differ significantly between study arms, indicating there was no apparent difference in participants' attempts to provide socially desirable responses.

LTBI Treatment Completion Rates

Overall, 48.9% of participants completed therapy. Table 2 presents a comparison of completion in the two study arms that suggests that the intervention was effective with 59.9% of participants in the intervention group completing treatment versus 38.3% in the control group (RR=1.561, 95% CI 1.255-1.942). Both groups had similar proportions of adverse events or medical issues (data not shown).

Table 3 summarizes binomial regression analysis of individual predictors of treatment completion, while controlling for study group. That is, each model contains coefficients for the predictor and treatment/control group. Completion of high school (ARR=0.782, 95% CI 0.638-0.957), current homelessness (ARR=0.696, 95% CI 0.516-0.938), current smoking (ARR=0.789, 95% CI 0.641-0.972), and lifetime drug use (ARR=0.805, 95% CI 0.657-0.986) were the only strongly significant predictors for non-completion of treatment for LTBI.

The social support instrument was not found to be reliable (α=0.475) and therefore was not used. Individual social support items were examined and one item which stated "there are people you feel you can talk to about personal or private matters" was positively associated with completion (ARR=1.248, 95% CI 1.035-1.506).

The overall knowledge score was not significantly associated with completion of treatment. Of 24 knowledge items, three correct answers were found to be significant predictors of non-completion, or showed a trend, in models with treatment group. These items include: "TB skin test is a vaccination against TB" (ARR=0.812, 95% CI 0.664-0.993), and "a person with a positive skin test may need to take TB medications" (ARR=0.705, 95% CI 0.552-0.901), and "HIV infected persons are more likely to get TB" (ARR=0.814, 95% CI 0.653-1.014).

Factor analysis of the 24 attitudinal items in the questionnaire yielded 10 factors accounting for 56.4 percent of the total variation. Some attitudes did not load on any of the factors; therefore, the analysis was rerun excluding these variables so that the relative importance of each of the remaining items could be assessed. Seven factors including 17 variables emerged accounting for 57.6 percent of the total variation (Appendix 1, Table 2 and Figure 1). Final factor solution is shown in Appendix 1, Table 3. Seven scales were created but no reliable scales were found or

retained (Appendix 1, Table 1). The distribution of each attitudinal item was inspected carefully to examine its distribution. Depending on the distribution, the category with most responses was designated as the reference group or the two middle categories ('agree' and 'disagree') were collapsed and used as the reference group. When examining the 24 attitudinal items individually, 10 were found to be significant, or showed a trend, in models with treatment group. Agreeing with the following statements was associated with lower treatment completion: "you are not embarrassed to tell people you have TB" (ARR=0.752, 95% CI 0.584-0.967), "your family/friends don't care if you keep appointments or take medications" (ARR=0.888, 95% CI 0.773-1.020), "doctors don't really care about curing your TB" (ARR=0.359, 95% CI 0.145-0.887), "you care about what family/friends think of treatment (ARR=0.747, 95% CI 0.590-0.946), and "no matter what you do, you can still get TB" (ARR=0.747, 95% CI 0.597-0.934). The statement "you believe you have the TB germ", was associated with lower completion regardless of agreement (ARR=0.771, 95% CI 0.619-0.960) or disagreement (ARR=0.753, 95% CI 0.568-0.998). Similarly, "as hard as you try, you are going to miss some of your medications", was associated with lower completion regardless of agreement (ARR=0.557, 95% CI 0.357-0.871) or disagreement (ARR=0.814, 95% CI 0.665-0.996); "taking TB medications is a hassle", was associated or showed a trend with lower completion regardless of agreement (ARR=0.432, 95% CI 0.180-1.038) or disagreement (ARR=0.792, 95% CI 0.630-0.997); and "when you feel really bad, you would stay home instead of seeing doctor" was associated or showed a trend with lower completion regardless of agreement (ARR=0.480, 95% CI 0.261-0.882) or disagreement (ARR=0.836, 95% CI 0.676-1.034). Another attitudinal item which is exhibiting unexpected results is "Taking TB medicines is important" (ARR=0.846, 95% CI 0.711-1.007), which is associated with lower completion rates. However, this pattern is only

seen in the control group and moreover, only a small number in the control group agreed with this item.

All predictors significant at 0.10 or less were candidates for the multivariate model. While not significant on their own, foreign birth (ARR=1.049, 95% CI 0.855-1.286) and current drug use (ARR=0.790, 95% CI 0.591-1.057) were further considered in multivariate models because there was an imbalance between the study groups. According to the multivariate model in Table 4, participants in the intervention group were 1.5 times more likely to complete treatment compared with those in the control group (ARR=1.504, 95% CI 1.211-1.869). Completion of high school (ARR=0.800, 95% CI 0.656-0.975) and current homelessness (ARR=0.787, 95% CI 0.580-1.068) were identified as predictors for non-completion of LTBI treatment. Two attitudinal items contributed significantly to this model. The more likely participants were to agree with the statement “doctors don’t really care about curing your TB,” the less likely they were to complete treatment (ARR=0.441, 95% CI 0.183-1.065). Similarly, participants who strongly agreed with the statement “when you feel real bad, you would stay home instead of seeing the doctor,” were significantly less likely to complete treatment (ARR=0.491, 95% CI 0.257-0.936). Diagnostic statistics were used to assess the validity of the final model. These diagnostic tests confirmed that the final model conforms to statistical assumptions for binomial regression.

RESULTS - TAPAS

Enrollment

Figure 1b describes participant enrollment from May 2002 through April 2005. A total of 603 patients evaluated for LTBI were approached and of these, 444 were determined to be eligible for the study and were invited to participate. Of eligible patients, 163 refused to participate in the study (44% were too busy, 26% had no interest, 21% had other reasons, and 8% gave no reason); 29 were missed because study staff were not present when decision to initiate treatment for LTBI was made by clinicians; and 252 provided informed consent, completed baseline interviews, and were randomized to the peer support intervention or to the usual care arm, according to the study group allotment procedures described above. Two participants in the control arm were determined to be ineligible to the study according to inclusion criteria following randomization and are not included in study results. At the end of assigned treatment, three intervention participant medical records and two standard of care participant records could not be located and were therefore lost to follow up in terms of the completion analysis. Since the primary outcome was based on review of the medical records it was conservatively assumed that these participants did not complete treatment. Many participants had partial adherence follow up data but we were able to obtain the primary endpoint (completion) from their medical charts and analyze their data.

Study Population

The TAPAS Study recruited 252 participants, 128 were randomized to the experimental intervention group and 124 to the standard of care control group. After excluding ineligible participants, the intervention group included 128 participants and the control group 122

participants (Table 5). The sample was predominantly male (70%), and study participants were 40 years old on average. The racial distribution of the sample was African-American (35%), Latino (20%), African (36%), and White/other (9%). More than half of participants indicated that they had completed high school or had a GED equivalent (61%). Two thirds (67%) of participants were foreign-born and 39% reported they were married or in common law unions. A history of homelessness was reported by 33% of participants and current homelessness by 16%. Unemployment rates were high in this population with 59% of participants unemployed at baseline. History of mental illness as defined by past psychiatric hospitalizations or currently on psychiatric medications was reported by 8% of participants. Substance use was reported by 32% of the sample currently drinking alcohol and 16% currently using drugs. Approximately a third of the population was depressed by the CES-D measure. There were no statistically significant differences between study arms. The Marlowe-Crowne was used as an adjunct measure to assess the impact of social desirability on self-report measures; the reliability of the instrument was examined and it was found to be reliable. However, the mean Marlowe-Crowne scales did not differ significantly between study arms, indicating there was no apparent difference in participants' attempts to provide socially desirable responses.

LTBI Treatment Completion Rates

Overall, 58.8% of participants completed therapy. Table 6 presents a comparison of completion in the two study arms; 60.9% of participants in the intervention group completing treatment versus 56.6% in the control group (RR=1.096, 95% CI 0.850-1.414). During the study period, 1,035 non-study patients in the clinic initiated and 44.0% completed LTBI treatment.

Table 7 summarizes individual predictors of treatment completion, while controlling for study group. Age 40 years or older (ARR=1.384, 95% CI 1.124-1.704) and history of psychiatric hospitalizations or medications (ARR=0.548, 95% CI 0.297-1.012), were the only significant predictors of completion or non completion of treatment respectively.

The reliability of constructed scales – social support, perceived benefits, and perceived barriers – was examined and all scales were found to be reliable; data is presented in Appendix 2, Table 1. None of the scales were found to be significant predictors.

Of 16 knowledge items, correct answers on two were found to be significant predictors of improved completion, or showed a trend, in models with treatment group. These items include: "you can get TB by kissing" (ARR=1.287, 95% CI 1.046-1.585) and "treatment of LTBI can take one month" (ARR=1.229, 95% CI 0.969-1.558).

Factor analysis of the 14 attitudinal items in the questionnaire yielded 5 factors accounting for 53.2 percent of the total variation (Appendix 2, Table 2 and Figure 1). Final factor solution is shown in Appendix 2, Table 3. Five scales were created but no reliable scales were found or retained (Appendix 2, Table 1). The distribution of each attitudinal item was inspected carefully and depending on the distribution, the category with most responses was designated as the reference group or the two middle categories ('agree' and 'disagree') were collapsed and used as the reference group. When examining the 14 attitudinal items individually, two were found to be significant, or showed a trend, in models with treatment group. Participants who strongly disagreed with the statement "you worry about passing the TB germ to loved ones," were significantly more likely to complete than those who were more neutral (agree or disagree) (ARR=1.367, 95% CI 1.053-1.774). Similarly, those who somewhat agreed with the statement

"you believe you have the TB germ," were significantly more likely to complete than those who strongly disagreed (ARR=1.459, 95% CI 1.032-2.064).

All predictors significant at 0.10 or less were candidates for the multivariate model. While not significant on their own, foreign birth (ARR=1.056, 95% CI 0.843-1.322) and marriage (ARR=1.105, 95% CI 0.893-1.368) were further considered in multivariate models because of suspected interactions. According to the multivariate model in Table 8, participants in both groups were equally likely to complete treatment (ARR=1.039, 95% CI 0.854-1.264). Foreign birth (ARR=0.854, 95% CI 0.649-1.123) and marriage (ARR=0.508, 95% CI 0.258-0.998) were identified as predictors for non-completion of LTBI treatment; however, these factors were modified by interaction terms. Unmarried foreign-born TB patients were less likely than U.S. born patients to complete treatment, while married foreign-born TB patients were substantially more likely than U.S. born patients to complete therapy (ARR=2.379, 95% CI 1.148-4.930). Age 40 or older was identified as a predictor of completion of treatment (ARR=1.303, 95% CI 1.054-1.612) while history of mental illness (AOR=0.561, 95% CI 0.307-1.023) was identified as an additional predictor for non-completion of treatment. No knowledge or attitude items remained in the multivariate model. Diagnostic statistics were used to assess the validity of the final model. These diagnostic tests confirmed that the final model conforms to statistical assumptions for binomial regression.

LTBI Adherence

Some problems were noted by study staff regarding the MEMS being lost, expiring, or needing to be replaced due to damage. But in general, results of the MEMS acceptability questionnaires indicate that the MEMS were used always or often by most participants (86%). Additionally,

participants reported that it was easy to understand how to use the cap (94%) and overall found using the cap to be easy (98%). When self reported adherence was compared with data from the MEMS cap, good agreement (kappa=0.687) was found. Where information did not match between the two methods, it was generally because MEMS adherence was lower than self reported adherence. This suggests that when MEMS data was used for imputation, adherence may have been imputed at lower values than the self reported adherence.

Models were run on 232 participants with 2,043 records of adherence: 1,257 (62%) of those were reported via interview, 589 (29%) were determined from chart and MEMS data, and 188 (9%) were imputed via the stochastic adherence algorithm. Data for 18 participants could not be imputed following the imputation algorithm rules outlined above as no information was available.

Figure 2a plots adherence by completion status over the duration of treatment based on a repeated measures model. As expected, average adherence in the non-completers group is lower than in the completers group from the initiation of treatment and steadily drops from about 45% at month 1 to less than 5% by month 6. Figure 2b plots adherence over time for individuals using spaghetti plots. In the first couple of months of treatment, not much difference is evident in this plot between completers and non-completers; however, after the second month a big difference appears where non-completers do not adhere with the treatment. These patterns are easier to detect with the heatmaps in Figure 2c, where each participant is represented by a layer instead of a line and intensity of the color is utilized to show the level of adherence. It is clear from this plot that non-completers' adherence decreased early in the treatment while completers had fairly steady levels of adherence throughout the treatment.

Repeated measures analysis was conducted to compare adherence as a continuous–valued variable over the duration of the treatment and the final multivariate model is presented in Table 9. The repeated measures analysis potentially has more power for comparing the intervention and control groups. In addition, a substantial difference in adherence rates was observed between study groups (9.7%). For those who are in the intervention group, married, foreign-born, 40 years or older, not homeless, not using alcohol, and correct on knowledge item "TST+ can mean need for medications," expected adherence over time is 76%.

The most common reasons reported for not adhering to treatment were "forgot", "ran out of medications", and "other priorities." Factor analysis of the 25 reasons for missing medications yielded 7 factors accounting for 56.0% of the total variation. Some reasons did not load on any of the factors. Therefore, the analysis was rerun excluding these variables so that the relative importance of each of the remaining items could be assessed. Four factors including 17 variables emerged accounting for 53.7% of the total variation (Appendix 2, Table 4 and Figure 2). Final factor solution is shown in Appendix 2, Table 5. Four scales were created, three of which were determined to be reliable scales (Appendix 2, Table 1). The first factor includes fears of side effects and harmful effects of the drugs as well as feeling good and a dislike of taking pills. The second factor includes reasons relating to current intoxication or planned alcohol use and general negative feelings about having to take the medications. The third factor includes the most common reason – simply forgot as well as other competing priorities such as work/family and pills not fitting in daily routine. The last factor relates to running out of pills and problems with getting the medications.

DISCUSSION

Adherence to and completion of LTBI treatment are crucial factors in the effort to eliminate TB in the U.S. and are therefore of major public health relevance. The two randomized controlled trials described above assessed an innovative peer support intervention for enhancing adherence to and completion of LTBI treatment among individuals in an urban setting in the U.S. The inner city urban setting provided the opportunity to evaluate the impact of peer-led interventions to increase treatment completion rates in a disadvantaged population often faced with multiple barriers to adherence and completion of treatment for LTBI. The interventions were multifaceted and addressed recognized barriers to adherence using an approach that could be replicated in other clinical settings.

Participants in the Pathways intervention group were 1.5 times more likely to complete treatment compared with those in the control group, after controlling for other factors. Despite this significant increase in the likelihood of completing LTBI treatment, the completion rate remained modest, with only 60% of participants in the Pathways intervention group completing LTBI treatment. The rate of LTBI treatment completion in the control group is consistent with completion rates in this clinic population as well as in other populations.[5] In TAPAS, LTBI treatment completion rates were similar in participants assigned to receive peer support and those assigned to the control group; however, study participants in both study arms of TAPAS had considerably higher treatment completion rates than non-study patients who initiated LTBI treatment in the same clinic, during the study period.

MEMS monitoring was used for all TAPAS participants as an adherence measurement tool; it was not used in Pathways. Apart from some minor changes in the clinic population (see Chapter

3) and a more structured intervention based on a theoretical model in TAPAS, the use of MEMS was the only methodological difference between the studies. Moreover, higher completion rates in TAPAS were present despite longer treatment duration, which has been associated in other studies with decreased adherence.[4,38-40] While the MEMS were utilized in this study as a measurement tool to monitor adherence in all participants, it seems that there might have been an unintended intervention effect. Researchers have acknowledged the unintended use of the MEMS as an adherence intervention. The power for detecting an intervention effect was reduced by the higher than expected completion rate in the control group, which reduced the anticipated treatment effect from a 20 percentage point difference (based on Pathways results) to less than 5 percentage points. An intervention effect for completing LTBI treatment was observed in both studies but it was statistically significant only in Pathways; however, the TAPAS intervention was found to be statistically significant for improving adherence.

In the Pathways study, completion of high school, current homelessness, and agreement with two attitudinal items ("doctors don't really care about curing your TB," and "when you feel real bad, you would stay home instead of seeing the doctor,") were found to be predictors for non-completion of LTBI treatment after controlling for intervention group.

In the TAPAS study, foreign birth, marriage, and history of mental illness were found to be predictors for non completion of LTBI treatment after controlling for intervention group; increased completion rates were found among married persons of foreign-birth. Older age (defined as 40+ years old) was an additional predictor of improved treatment completion. Similar results were found in the adherence analysis regarding foreign birth, marriage, and older age. Homelessness and current alcohol use were additional predictors of non adherence; understanding that a positive TST may mean the need for LTBI treatment was found to be a

predictor of improved adherence. In both studies, current homelessness was found to be a strong predictor of adherence to and completion of LTBI treatment.

Adherence was assessed longitudinally over the course of treatment in both studies but could only be analyzed in the TAPAS study. Prior studies found adherence in the first month of treatment to predict treatment completion.[41-44] In a retrospective study in patients seen at an urban TB clinic, Parsyan et el. found that among those who failed to complete LTBI treatment, more than half (54%) defaulted during the first month of treatment.[42] In another study, Sebastian et al. found that failure to attend the first appointment identified all defaulters[43] and in an open-label randomized trial comparing 4 months of RIF with 9 months of INH, the percent of doses taken and the variability of the interval between doses in the first month was found to be a highly significant predictor of LTBI treatment completion.[41] This is similar to the findings in Trajman et al.'s multicenter study, where regularity of treatment and percentage of doses taken were found to be predictive of successful treatment completion.[44] In the TAPAS study, we found that non-completers' adherence decreased early in the treatment while completers had fairly steady levels of adherence throughout the treatment. This finding suggests that it is important to intervene early in the treatment as the first two months of treatment are when patients tend to default treatment. Identifying reasons for missing medications can suggest possible foci for interventions in the early months, such as weekly reminders to take the medications and ensuring that prescriptions are refilled on schedule.

Pathways and TAPAS are unique in that they offer a systematic in-depth examination of TB knowledge and attitudes. In Pathways, three knowledge items were found to be possible predictors of improved treatment completion but the relationship did not hold in multivariate modeling. Similarly, in TAPAS, three knowledge items were found to be possible predictors of

improved treatment completion but the relationship did not hold in multivariate modeling. In Pathways, 10 attitudinal items were found to be significant, or showed a trend, in models with treatment group but only two remained significant in the multivariate models; in TAPAS, two were found to be significant, or showed a trend, in models with treatment group but the relationship did not hold in multivariate modeling. This suggests that knowledge and attitudes may be less important than social factors in determining treatment completion.

The randomized controlled design of the studies provided an opportunity to establish a causal link for the impact of the intervention between the independent variables and the treatment outcome. There have been a limited number of studies that used a randomized controlled trial design to evaluate interventions to promote LTBI treatment completion.[5] Furthermore, the few prior randomized controlled trials to date were conducted in specific high risk groups such as the homeless,[14,45] drug users,[13,46,47] and jail inmates.[48] Our studies are not limited to a specific high risk group but instead to a general clinic population, albeit one at high risk of developing TB disease because of its location in an inner city urban setting where the risk for TB is greater. Using a clinic population offers generalizability of study findings to similar settings, which is an important issue in considering how the study may be able to inform public health practice.

Limitations

The main outcome variable, completion of treatment, was abstracted from medical charts; these data were typically not entered for study purposes, and therefore the quality of information obtained could not be verified through participant interview. However, key variables such as treatment outcomes are submitted routinely to the Department of Health and are an integral part of the medical record; thus we can assume that they are reliable. In addition, a few medical

records could not be located; however, these participants were similarly distributed among the treatment groups. To be conservative, it was assumed that a chart not found equals failure to complete. Another possible limitation is that providers may not have been consistent in their determination of treatment completion; however, the small number of providers making this determination was blinded to their patients' study status. Self-reporting of some items (e.g., alcohol or drug use) may have been subject to social desirability bias in face-to-face interviews; however, this is a randomized controlled trial and most risk factors were balanced between the groups, as were Marlowe-Crowne scores measuring the tendency to present oneself in a socially desirable way. Patients receiving DOT for LTBI were excluded from both studies; however, the DOT for LTBI population was found to be similar to the study population of Pathways[49] and no changes in procedures for DOT referrals were implemented in the clinic during that period. Finally, this study was conducted in an inner city urban setting in the U.S. and the sample may reflect inner city populations but may not be representative of the general U.S. population. While our results cannot be rigorously generalized to the U.S. as a whole, they nonetheless have strong implications for the U.S. population.

CONCLUSIONS

The design of the two studies, Pathways and TAPAS, provided an opportunity to evaluate an innovative peer support intervention to increase LTBI treatment completion rates in an inner city urban setting in the U.S. The peer support intervention was found to be associated with significant increase in LTBI treatment completion rates in the Pathways population but not in the TAPAS population, whereas completion rates increased in the control group as well as in the

intervention group in the latter study. The power for detecting an intervention effect in TAPAS was reduced by the higher than expected completion rates in both groups; however, the effect of the TAPAS intervention is statistically significant in the adherence model. Adherence analysis in TAPAS suggests that it is important to intervene with more tangible support early in the treatment as the first two months of treatment present a danger period where patients tend to default treatment. Identifying reasons for missing medications can suggest possible foci for interventions in the early months, such as weekly reminders to take the medications and ensuring that prescriptions are refilled on schedule.

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FIGURES AND TABLES

Figures

Figure 1a: Pathways Study Participant Flow

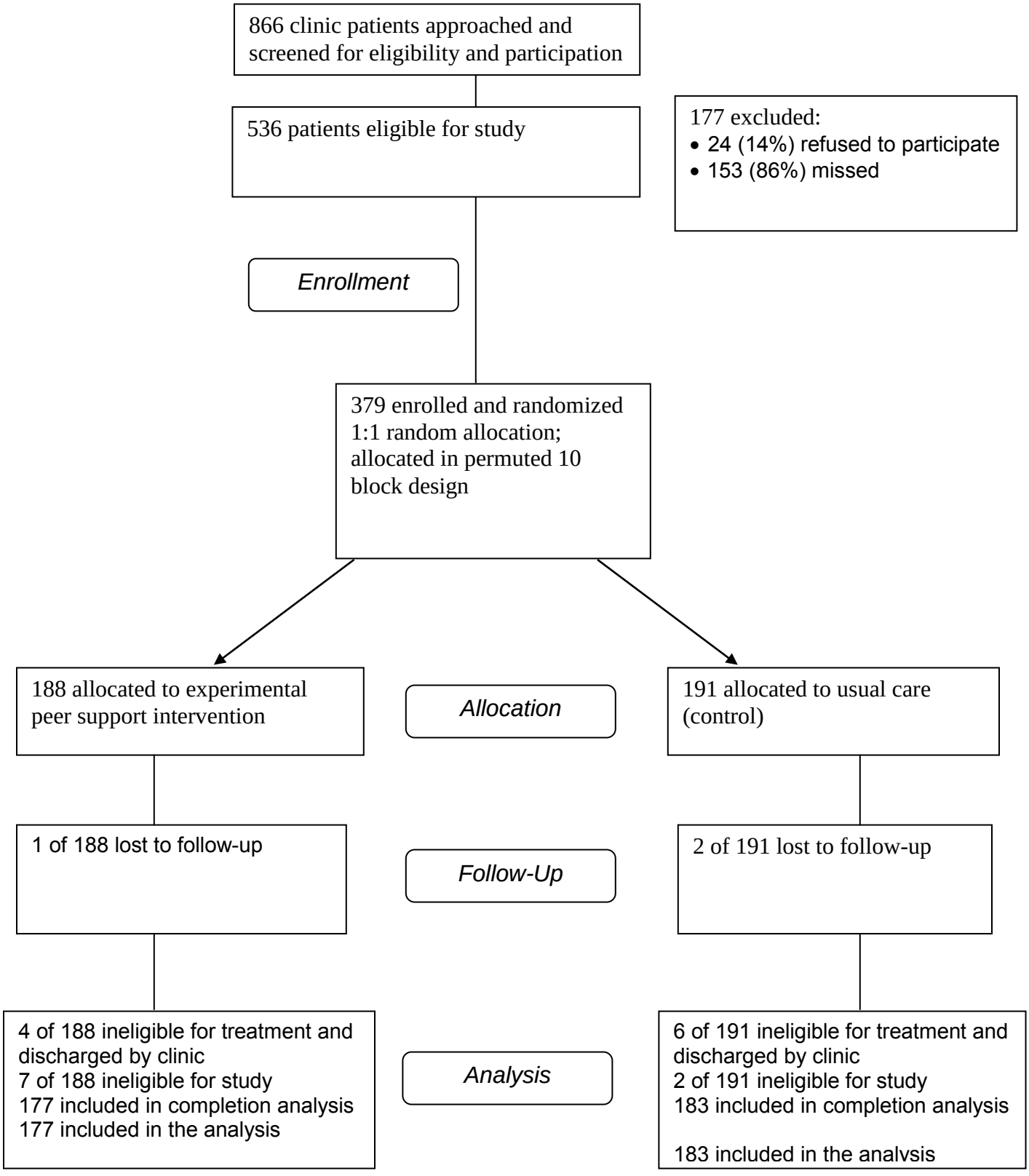


Figure 1b: TAPAS Study Participant Flow

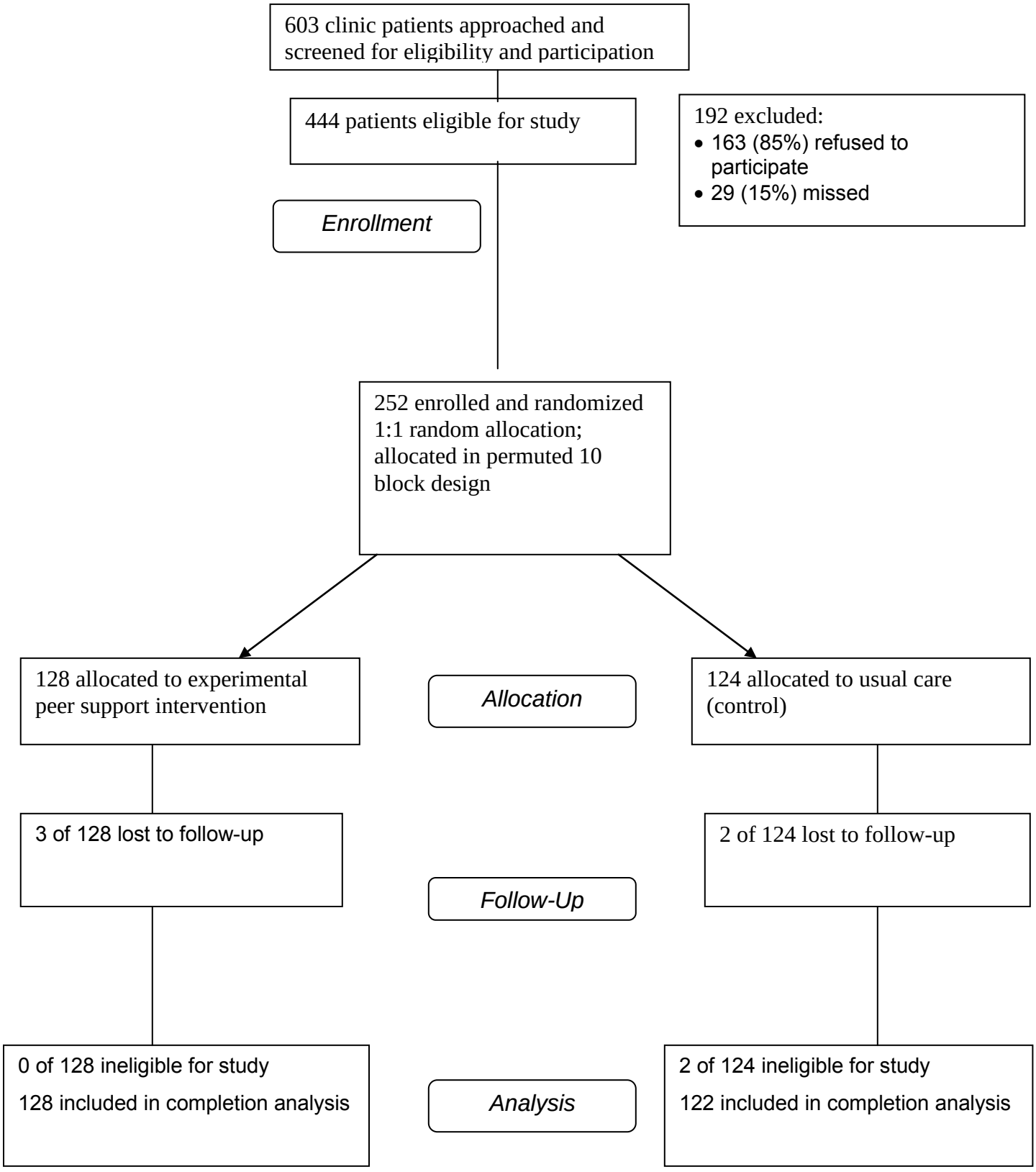


Figure 2a: TAPAS Adherence over time using repeated measures model

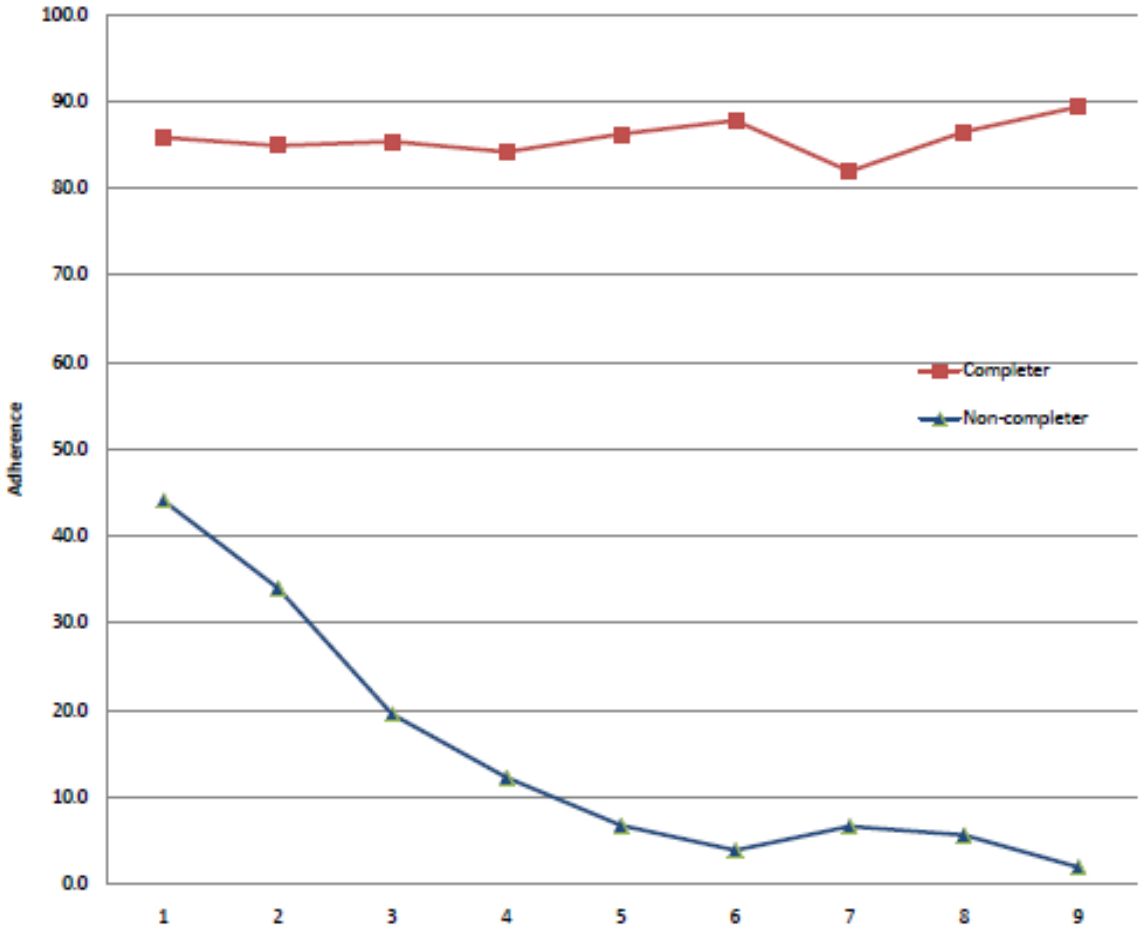


Figure 2b: TAPAS Adherence over time using spaghetti plots

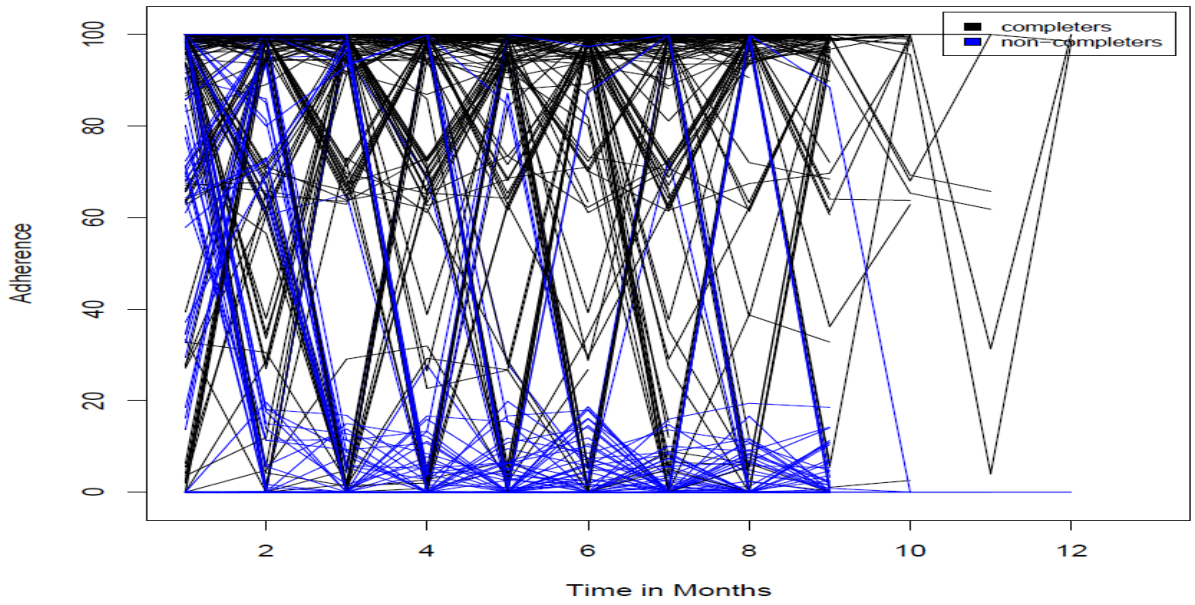
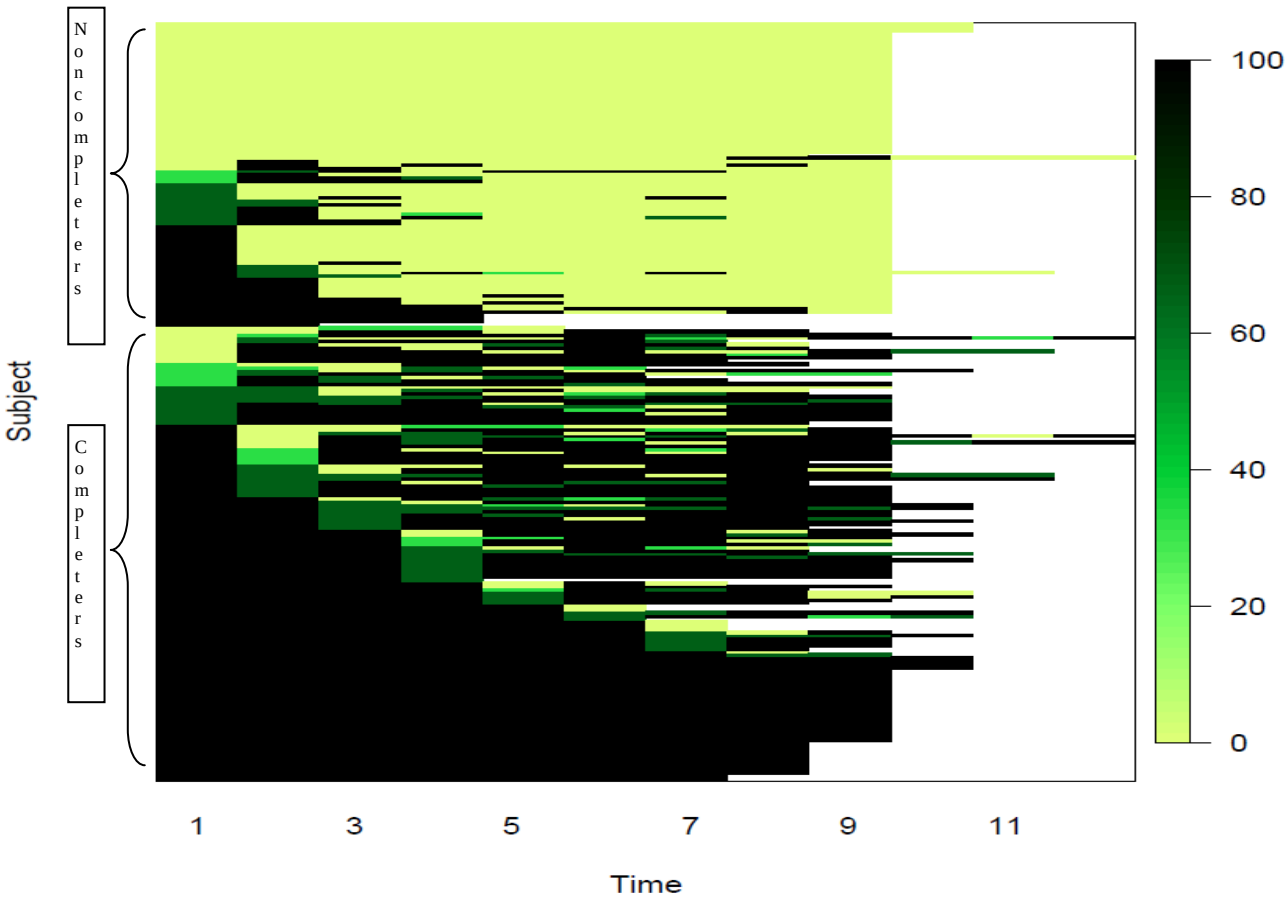


Figure 2c: TAPAS Adherence over time using heatmaps



Tables

Table 1: Baseline Characteristics of Participants in the Pathways Study

	Total (N=360)		Intervention (N=177)		Control (N=183)		p-value
	N	%	N	%	N	%	
Age <40	203	56.39	98	55.37	105	57.38	0.7007
Male	210	58.33	103	58.19	107	58.47	0.9574
Race							0.6255
- Black	254	70.56	121	68.36	133	72.68	
- Latino	81	22.50	42	23.73	39	21.31	
- Other	25	6.94	14	7.91	11	6.01	
Ever homeless	138	38.33	51	28.81	87	47.54	0.0003
Homeless past yr	92	25.63	33	18.75	59	32.24	0.0034
Married/Common-law	93	25.91	48	27.27	45	24.59	0.5619
Foreign-born	172	47.78	93	52.54	79	43.17	0.0751
Completed high school	183	53.82	93	55.69	90	52.02	0.4979
Unemployed	262	72.78	124	70.06	138	75.41	0.2539
Prior LTBI tx	49	13.61	26	14.69	23	12.57	0.5574
Emotional/psych hospitalizations	28	7.84	13	7.43	15	8.24	0.7751
HIV infected	17	4.72	10	5.65	7	3.83	0.3486
Currently smoke	170	47.22	83	46.89	87	47.54	0.9020
Ever drink alcohol	248	70.45	119	69.59	129	71.27	0.7299
Currently drink alcohol	117	32.50	60	33.90	57	31.15	0.5775
Ever drug use	211	58.61	93	52.54	118	64.48	0.0215
Currently use drugs	80	22.22	31	17.51	49	26.78	0.0346

Table 2: Pathways Completion of Treatment by Study Group

	Intervention (N=177)		Control (N=183)		Risk Ratio	95% CI	p-value
	N	%	N	%			
Completed treatment	106	59.9	70	38.3	1.561	1.255-1.942	<0.0001
- Yes	71	40.1	113	61.8			
- No							

Table 3: Pathways binomial regression analysis of predictors of completion of care, controlling for randomization group

Independent Variables	Regression coefficient	Standard error	Adjusted RR	95% CI	p-value
Demographics					
Age 40+ years	-0.1091	0.1026	0.8966	0.7333-1.0963	0.2875
Male	-0.1426	0.1022	0.8671	0.7097-1.0593	0.1626
Race/Ethnicity					
Latino vs. Black	-0.0603	0.1265	0.9415	0.7348-1.2062	0.6334
Other vs. Black	-0.0668	0.2093	0.9354	0.6206-1.4097	0.7495
Foreign-born	0.0474	0.1042	1.0486	0.8549-1.2861	0.6489
Social Characteristics					
Completed high school	-0.2465	0.1033	0.7816	0.6383-0.9570	0.0171
Employed	-0.0844	0.1180	0.9190	0.7293-1.1582	0.4743
Married	0.0816	0.1116	1.0850	0.8718-1.3503	0.4649
Ever homeless	-0.1855	0.1173	0.8307	0.6601-1.0454	0.1138
Currently homeless	-0.3622	0.1523	0.6961	0.5164-0.9384	0.0174
HIV infected	0.1305	0.0974	1.1394	0.9415-1.3790	0.1800
Life stressors – 2 or more	-0.0617	0.1038	0.9402	0.7671-1.1522	0.5521
Substance Use					
Current smoking	-0.2365	0.1060	0.7894	0.6412-0.9717	0.0257
Ever alcohol use	-0.0653	0.1125	0.9368	0.7514-1.1679	0.5616
Current alcohol use	0.0270	0.1089	1.0273	0.8298-1.2719	0.8045
Ever drug use	-0.2172	0.1037	0.8048	0.6567-0.9863	0.0363
Current drug use	-0.2355	0.1486	0.7901	0.5905-1.0573	0.1130
Social Support					
There are people who make you feel liked or loved	0.0749	0.1326	1.0778	0.8312-1.3975	0.5721
There are people you feel you can talk to about personal or private matters	0.2219	0.0955	1.2484	1.0353-1.5055	0.0202
There are people who come to you when they need help	0.0329	0.1001	1.0335	0.8494-1.2575	0.7423
If needed immediate help, had people who would help	0.0801	0.0927	1.0834	0.9035-1.2992	0.3873
If needed help getting things done, had people who would help	0.1298	0.0934	1.1386	0.9481-1.3675	0.1647
There are other people who give you information about services need	-0.0238	0.0748	0.9765	0.8433-1.1307	0.7503
Knowledge- Transmission					
K1 – by breathing air with TB	0.3314	0.2456	1.3929	0.8608-2.2539	0.1772
K2 – by having sex without condom	-0.1195	0.1050	0.8874	0.7223-1.0901	0.2551
K3 – by living in crowded conditions	0.3576	0.2694	1.4299	0.8434-2.4243	0.1843
K4 – by eating food prepared	0.0014	0.1045	1.0014	0.8159-1.2291	0.9895
K5 – through kissing	-0.0093	0.1235	0.9908	0.7778-1.2621	0.9402
K6 – by sharing dishes or bottle	-0.1671	0.1111	0.8461	0.6806-1.0519	0.1324
Knowledge - Symptoms					
K7a – losing weight	0.0092	0.1154	1.0093	0.8050-1.2653	0.9363
K7b – coughing	0.3432	0.2538	1.4094	0.8571-2.3177	0.1763
K7c – vomiting	0.0006	0.1142	1.0006	0.7999-1.2517	0.9956
K7d – losing hair	0.0449	0.1062	1.0459	0.8494-1.2879	0.6725
K7e – coughing up blood	0.0758	0.1351	1.0787	0.8278-1.4056	0.5747
Knowledge – Testing					
K8 – TST is vaccination against TB	-0.2081	0.1026	0.8121	0.6642-0.9930	0.0425
K9 – CXR can tell if sick with TB	-0.1178	0.2279	0.8889	0.5687-1.3894	0.6053
K10 – TST+ means already sick with TB	-0.0344	0.1087	0.9662	0.7808-1.9555	0.7514
K11 – CXR can tell if have DR TB	-0.1829	0.1213	0.8328	0.6566-1.0564	0.1316
K12 – family doesn't need to be checked	-0.0840	0.1188	0.9194	0.7284-1.1605	0.4795
K13 – TST+ can give TB to others	0.0176	0.1043	1.0177	0.8295-1.2486	0.8664

Table 3: Pathways binomial regression analysis of predictors of completion of care, controlling for randomization group

Independent Variables	Regression coefficient	Standard error	Adjusted RR	95% CI	p-value
Knowledge – Treatment					
K14 – most cases can be cured by meds	0.1191	0.2415	1.1265	0.7017-1.8083	0.6219
K15 – HIV+ more likely to get TB	-0.2060	0.1123	0.8138	0.6531-1.0141	0.0665
K16 – okay to stop meds once feel better	-0.0847	0.1620	0.9188	0.6688-1.2621	0.6010
K17 – patients can be ordered to take meds	-0.0525	0.1059	0.9489	0.7710-1.1678	0.6202
K18 – TST+ may need to take meds	-0.3495	0.1250	0.7050	0.5519-0.9007	0.0052
K19 – may get rash from TB meds	-0.1534	0.1026	0.8578	0.7015-1.0489	0.1349
K20 – treatment can be completed in 1 month	-0.0813	0.1311	0.9220	0.7130-1.1921	0.5354
Knowledge Score	-0.0192	0.0146	0.9809	0.9532-1.0095	0.1884
Attitudes					
K22 – TB is disease you have to take seriously	-0.0237	0.1275	0.9766	0.7607-1.2537	0.8524
K23 – if someone gets TB, it is their own fault	0.0929	0.0591	1.0974	0.9773-1.2322	0.1161
K24 – taking TB medications is important	-0.1668	0.0886	0.8464	0.7114-1.0069	0.0598
K25 – TB is something you and friends talk about	-0.0537	0.0443	0.9477	0.8689-1.0337	0.2256
K26 – would continue treatment even if had to pay	-0.0778	0.0544	0.9251	0.8316-1.0291	0.1523
K27 – know better than the doctor when best to stop medications	-0.0436	0.0833	0.9573	0.8131-1.1272	0.6010
K28 – not embarrassed to tell people have TB					0.0967
Strongly agree	-0.2857	0.1288	0.7515	0.5839-0.9672	0.0265
Strongly disagree	-0.1253	0.1168	0.8822	0.7017-1.1090	0.2830
Disagree/agree	Ref				
K29 – not important to keep appointments					0.2033
Strongly agree	-0.2366	0.2219	0.7893	0.5109-1.2195	0.2864
Strongly disagree	-0.3397	0.1523	0.7120	0.5283-0.9596	0.0257
Disagree/agree	Ref				
K30 – medications today powerful in fighting TB	-0.0675	0.0752	0.9347	0.8066-1.0831	0.3692
K31 – family/friends don't care if keep app'ts/meds	-0.1188	0.0706	0.8880	0.7732-1.0199	0.0927
K32 – since word spread about TB, people avoid you	-0.0589	0.0654	0.9428	0.8294-1.0717	0.3676
K33 – takes something bad to not take medications					0.8989
Strongly agree	0.0489	0.1478	1.0501	0.7861-1.4028	0.7407
Strongly disagree	-0.0315	0.1793	0.9690	0.6818-1.3771	0.8606
Disagree/agree	Ref				
K34 – appointments more trouble than worth	0.0811	0.0578	1.0845	0.9684-1.2145	0.1601
K35 – usually follow doctor's advice	0.0425	0.1000	1.0435	0.8577-1.2695	0.6706
K36 – as hard as you try, you are going to miss some of your medications					0.0266
Strongly agree	-0.5845	0.2275	0.5574	0.3568-0.8707	0.0102
Strongly disagree	-0.2058	0.1030	0.8140	0.6652-0.9962	0.0458
Disagree/agree	Ref				
K37 – doctors don't really care about curing TB					0.0398
Strongly agree	-1.0254	0.4621	0.3587	0.1450-0.8872	0.0265
Strongly disagree	-0.1588	0.1395	0.8532	0.6490-1.1214	0.2550
Disagree/agree	Ref				

Table 3: Pathways binomial regression analysis of predictors of completion of care, controlling for randomization group

Independent Variables	Regression coefficient	Standard error	Adjusted RR	95% CI	p-value
K38 – care about what family/friends think of treatment					0.0266
Strongly agree	-0.2921	0.1206	0.7467	0.5895-0.9458	0.0154
Strongly disagree	-0.1305	0.1232	0.8777	0.6894-1.1175	0.2898
Disagree/agree	Ref				
K39 – taking TB meds is a hassle					0.0270
Strongly agree	-0.8392	0.4472	0.4321	0.1798-1.0380	0.0606
Strongly disagree	-0.2336	0.1164	0.7917	0.6301-0.9946	0.0448
Disagree/agree	Ref				
K40 – when feel real bad, stay home instead of seeing dr					0.0186
Strongly agree	-0.7338	0.3104	0.4801	0.2613-0.8821	0.0181
Strongly disagree	-0.1793	0.1083	0.8359	0.6760-1.0336	0.0978
Disagree/agree	Ref				
K41 – family is ashamed have TB	-0.1292	0.0907	0.8788	0.7357-1.0498	0.1543
K42 – if feel worse taking meds, would stop taking it	-0.0056	0.0411	0.9944	0.9175-1.0778	0.8916
K43 – doctors know how to treat TB	-0.0264	0.0866	0.9739	0.8218-1.1541	0.7602
K44 – believe have the TB germ					0.0494
Strongly agree	-0.2604	0.1122	0.7707	0.6186-0.9604	0.0204
Strongly disagree	-0.2841	0.1437	0.7527	0.5679-0.9975	0.0480
Disagree/agree	Ref				
K45 – will not get sick with TB because lucky	-0.0008	0.0473	0.9992	0.9107-1.0964	0.9873
K46 – no matter what you do, can still get TB					0.0484
Strongly agree	-0.2919	0.1142	0.7468	0.5971-0.9342	0.0106
Strongly disagree	-0.1158	0.1354	0.8907	0.6830-1.1614	0.3925
Disagree/agree	Ref				
K47 – if do right think, can avoid getting TB	0.0007	0.0436	1.0007	0.9186-1.0900	0.9880

RR = Risk Ratio
CI = Confidence Interval

Table 4: Pathways Multivariate binomial regression analysis of effect of the intervention on treatment completion

Independent Variables	Regression coefficient	Standard error	Adjusted RR	95% CI	p-value
Intervention group	0.4084	0.1109	1.5043	1.2106-1.8694	0.0002
High school	-0.2235	0.1010	0.7997	0.6561-0.9748	0.0269
Currently homeless	-0.2399	0.1558	0.7867	0.5796-1.0678	0.1237
K37 – Doctors don't really care about curing your TB					
Strongly agree	-0.8191	0.4500	0.4408	0.1825-1.0648	0.0687
Strongly disagree	-0.1588	0.1303	0.8532	0.6609-1.1014	0.2229
Disagree/agree	Ref				
K40 – when you feel really bad, you would stay home instead of seeing the doctor					
Strongly agree	-0.7117	0.3292	0.4908	0.2574-0.9358	0.0306
Strongly disagree	-0.0923	0.1056	0.9118	0.7414-1.1214	0.3818
Disagree/agree	Ref				

RR = Risk Ratio
CI = Confidence Interval

Table 5: Baseline Characteristics of Participants in the TAPAS Study (N=250)

	Total (N=250)		**Intervention (N=128)**		**Control (N=122)**		**p-value**
	N	%	N	%	N	%	
Age <40	134	53.6	71	55.5	63	51.6	0.5439
Male	176	70.4	88	68.8	88	72.1	0.5583
Race							0.2655
- African-American	87	34.8	50	39.1	37	30.3	
- Latino	49	19.6	25	19.5	24	19.7	
- African	91	36.4	45	35.2	46	37.7	
- Other	24	9.2	8	6.3	15	12.3	
Ever homeless	83	33.3	44	34.7	39	32.0	0.6540
Homeless past yr	40	16.1	21	16.5	19	15.6	0.8363
Married/Common-law	97	38.8	51	39.8	46	37.7	0.7287
Foreign-born	167	66.8	86	67.2	81	66.4	0.8940
Completed high school	153	61.2	78	60.9	75	61.5	0.9305
Unemployed	147	58.8	76	59.4	71	58.2	0.8499
Prior LTBI tx	15	6.1	7	5.5	8	6.6	0.7165
Any psychiatric history	21	8.4	11	8.6	10	8.2	0.9099
Currently smoke	84	33.6	46	35.9	38	31.2	0.4229
Ever drink alcohol	179	71.6	94	73.4	85	69.7	0.5093
Currently drink alcohol	80	32.0	38	29.7	42	34.4	0.4220
Ever drug use	129	51.6	69	53.9	60	49.2	0.4548
Currently use drugs	40	16.0	20	15.6	20	16.4	0.8684
Depressed by CESD16	86	34.4	48	37.5	38	31.2	0.2906

Table 6: TAPAS Completion of Treatment by Study Group

	Intervention (N=128)		**Control (N=123)**		**Risk Ratio**	**95% CI**	**p-value**
	N	%	N	%			
Completed treatment					1.0962	0.850-1.414	0.4818
- Yes	78	60.9	69	56.6			
- No	50	39.1	53	43.4			

Table 7: TAPAS binomial regression analysis of predictors of completion of care, controlling for randomization group

Independent Variables	Regression coefficient	Standard error	Adjusted RR	95% CI	p-value
Demographics					
Age 40+ years	0.3247	0.1061	1.3837	1.1238-1.7036	0.0022
Male	-0.0512	0.1186	0.9501	0.7529-1.1988	0.6660
Race/Ethnicity					0.1790
African-American vs. African	-0.1468	0.1190	0.8635	0.6838-1.0904	0.2174
Latino vs. African	-0.3449	0.1692	0.7083	0.5084-0.9868	0.0415
Other vs. African	-0.0814	0.1826	0.9218	0.6445-1.3185	0.6558
Foreign-born	0.0541	0.1149	1.0556	0.8428-1.3221	0.6374
Social Characteristics					
Completed high school	-0.1249	0.1062	0.8826	0.7168-1.0867	0.2393
Employed	0.0897	0.1059	1.0939	0.8888-1.3462	0.3969
Married	0.0999	0.1088	1.1051	0.8929-1.3678	0.3584
Ever homeless	-0.0804	0.1168	0.9227	0.7339-1.1602	0.4913
Currently homeless	-0.1877	0.1676	0.8288	0.5968-1.1511	0.2626
Prior TB	-0.1042	0.2474	0.9010	0.5549-1.4632	0.6736
Any psychiatric history (hospitalization or meds)	-0.6013	0.3131	0.5481	0.2967-1.0124	0.0548
Depressed by CESD>16	0.0478	0.1096	1.0489	0.8462-1.3002	0.6630
Substance Use					
Current smoking	-0.0185	0.1127	0.9817	0.7871-1.2244	0.8699
Ever alcohol use	-0.1675	0.1075	0.8458	0.6851-1.0442	0.1192
Current alcohol use	-0.1559	0.1227	0.8556	0.6727-1.0883	0.2040
Ever drug use	0.0003	0.1058	1.0003	0.8130-1.2309	0.9974
Current drug use	-0.1958	0.1675	0.8222	0.5921-1.1416	0.2423
Benefits and barriers					
Benefits scale	0.0386	0.1237	1.0394	0.8157-1.3244	0.7548
Barriers scale	-0.1704	0.1484	0.8433	0.6305-1.1280	0.2509
Quality of life – physical (mean)	-0.0034	0.0060	0.9966	0.9850-1.0083	0.5690
Quality of life - mental (mean)	0.0056	0.0051	1.0056	0.9956-1.0157	0.2731
Social Support scale	-0.0085	0.0560	0.9916	0.8886-1.1065	0.8800
Knowledge- Transmission					
ka1 TB from crowded conditions	0.0986	0.1894	1.1036	0.7613-1.5998	0.6029
ka2 TB from sharing dishes etc.	0.1014	0.1161	1.1067	0.8814-1.3895	0.3826
ka3 TB through kissing	0.2526	0.1061	1.2874	1.0457-1.5849	0.0173
ka4 TB from stranger vs family	0.0526	0.1058	1.0540	0.8567-1.2968	0.6190
Knowledge – Testing/Treatment					
ka5 TST+ means have disease	-0.1315	0.1081	0.8768	0.7093-1.0837	0.2238
ka6 sleeping TB is contagious	0.1485	0.1103	1.1601	0.9345-1.4402	0.1783
ka7 TST+ can mean need for meds	0.6988	0.4857	2.0113	0.7763-5.2108	0.1502
ka8 most TB can be cured with meds	0.2275	0.2826	1.2554	0.7215-2.1845	0.4209
ka9 HIV+ means more likely to get TB	-0.1380	0.1070	0.8711	0.7063-1.0742	0.1969
ka10 TLTBI can take 1 month	0.2060	0.1210	1.2287	0.9692-1.5577	0.0888
ka11 undocumented person can be deported for TB treatment	0.0185	0.1086	1.0187	0.8234-1.2603	0.8645
Knowledge – Symptoms					
ka12 – losing weight	0.1869	0.1713	1.2055	0.8617-1.6864	0.2753
ka13 – swollen feet	-0.1739	0.1159	0.8404	0.6695-1.0547	0.1336
ka14 – coughing	0.2686	0.3779	1.3081	0.6237-2.7438	0.4773
ka15 – vomiting	0.0090	0.1142	1.0090	0.8067-1.2620	0.9375
ka16 – coughing up blood	0.0567	0.1585	1.0584	0.7757-1.4440	0.7205
Knowledge Score	0.0451	0.0292	1.0461	0.9878-1.1078	0.1231

RR = Risk Ratio; CI = Confidence Interval

Table 7: TAPAS binomial regression analysis of predictors of completion of care, controlling for randomization group

Independent Variables	Regression coefficient	Standard error	Adjusted RR	95% CI	p-value
Attitudes					
ka17 BCG vaccine prevents TB disease	0.0313	0.0541	1.0318	0.9280-1.1472	0.5633
ka18 no matter what could still get TB germ					0.1137
Somewhat agree	-0.0127	0.1378	0.9874	0.7537-1.2934	0.9265
Somewhat disagree	0.0809	0.1380	1.0843	0.8272-1.4212	0.5578
Strongly agree	-0.2876	0.1589	0.7501	0.5493-1.0241	0.0703
Strongly disagree	Ref				
ka19 taking TB meds is important	0.2409	0.1852	1.2723	0.8851-1.8290	0.1933
ka20 you know better than doctor when to stop meds	-0.0174	0.0552	0.9828	0.8819-1.0951	0.7530
ka21 clinic appt's are more trouble than worth	-0.0158	0.0726	0.9843	0.8537-1.1349	0.8278
ka22 do not trust doctor for best care					0.3364
Strongly agree	-0.1216	0.3272	0.8855	0.4663-1.6814	0.7101
Strongly disagree	0.1601	0.1444	1.1736	0.8844-1.5574	0.2675
Disagree/agree	Ref				
ka23 do right thing can avoid getting TB					0.1757
Strongly agree	0.2654	0.1450	1.3040	0.9814-1.7326	0.0672
Strongly disagree	0.1650	0.2211	1.1794	0.7647-1.8190	0.4554
Disagree/agree	Ref				
ka24 worry about passing TB germ to loved ones					0.0753
Strongly agree	0.0665	0.1289	1.0688	0.8302-1.3759	0.6058
Strongly disagree	0.3124	0.1330	1.3667	1.0531-1.7739	0.0189
Disagree/agree	Ref				
ka25 embarrassed to tell you have TB germ					0.6854
Strongly agree	-0.0485	0.1408	0.9527	0.7229-1.2555	0.7304
Strongly disagree	-0.0904	0.1200	0.9136	0.7221-1.1558	0.4512
Disagree/agree	Ref				
ka26 believe that you have the TB germ					0.0728
Somewhat agree	0.3780	0.1768	1.4594	1.0319-2.0639	0.0325
Somewhat disagree	0.0098	0.2576	1.0098	0.5884-1.7333	0.9715
Strongly agree	0.1559	0.1791	1.1687	0.8228-1.6601	0.3839
Strongly disagree	Ref				
ka27 care about what family and friends think of TB treatment					0.9674
Strongly agree	0.0401	0.1243	1.0409	0.8158-1.3282	0.7472
Strongly disagree	0.0160	0.1368	1.0161	0.7771-1.3287	0.9069
Disagree/agree	Ref				
ka28 try hard, will still miss some meds					0.8239
Somewhat agree	0.0887	0.1202	1.0928	0.8635-1.3829	0.4603
Somewhat disagree	-0.0315	0.1564	0.9690	0.7132-1.3167	0.8406
Strongly agree	-0.0804	0.2421	0.9227	0.5741-1.4830	0.7397
Strongly disagree	Ref				
ka29 taking TB meds is a hassle					0.2019
Strongly agree	0.4126	0.1645	1.5107	1.0944-2.0855	0.0121
Strongly disagree	0.1033	0.1247	1.1088	0.8684-1.4158	0.4073
Disagree/agree	Ref				
ka30 only something really bad would prevent from taking TB meds					0.9460
Strongly agree	0.0483	0.1302	1.0495	0.8131-1.3546	0.7108
Strongly disagree	0.0518	0.1341	1.0532	0.8097-1.3698	0.6994
Disagree/agree	Ref				

RR = Risk Ratio; CI = Confidence Interval

Table 8: TAPAS Multivariate binomial regression analysis of effect of the intervention on treatment completion

Independent Variables	Regression coefficient	Standard error	Adjusted RR	95% CI	p-value
Intervention	0.0380	0.1000	1.0387	0.8538-1.2636	0.7043
Married	-0.6778	0.3447	0.5077	0.2584-0.9977	0.0492
Foreign-born	-0.1581	0.1399	0.8537	0.6490-1.1231	0.2584
Married and Foreign-born	0.8666	0.3718	2.3787	1.1477-4.9302	0.0198
Age 40+	0.2649	0.1085	1.3033	1.0536-1.6121	0.0146
Psychiatric history	-0.5788	0.3068	0.5606	0.3072-1.0228	0.0592

RR = Risk Ratio
CI = Confidence Interval

Table 9: TAPAS Predictors of treatment adherence over time by repeated measures analysis

	Estimate	**Standard error**	**t-value**	**p-value**
Base adherence level	15.8189	14.9026	1.06	0.2896
Intervention group	9.7063	4.7684	2.04	0.0430
Married	-15.1533	9.8339	-1.54	0.6430
Foreign-born	-6.9232	6.5853	-1.05	0.3421
Married and foreign-born	24.9865	11.6543	2.14	0.0331
Age 40+	16.8777	5.0227	3.36	0.0009
Currently homeless	-15.2774	6.8059	-2.24	0.0258
Current alcohol use	-10.4141	5.1117	-2.04	0.0428
Correct on TST+ can mean need for medications	30.0988	13.0337	2.31	0.0218

Chapter 6

Dissertation Summary and General Discussion

DISSERTATION GOALS

The objectives of this dissertation were 1) to critically review the literature on adherence to treatment of LTBI, 2) To identify the change in demographic, social, and behavioral characteristics of patients undergoing treatment for LTBI in the Chest Clinic at Harlem Hospital between 1996 and 2005, 3) to identify patient demographic, social, and behavioral characteristics that are associated with LTBI treatment completion, and 4) to assess the impact of a peer-based experimental intervention on adherence to and completion of LTBI treatment in a general clinic population in an urban setting in the U.S. This was achieved by using data from the ***Pathways to Completion Study*** (recruitment from 1996 through 2000) as well as data from the ***Tuberculosis Adherence Partnership Alliance Study (TAPAS)*** (recruitment from 2002 through 2005). Pathways and TAPAS were two sequential NIH-funded randomized controlled trials designed to compare an experimental peer-based intervention to standard of care for ensuring completion of treatment for LTBI in an inner city urban setting.

SUMMARY OF FINDINGS

Chapter 2 of the dissertation reviews the literature on adherence to treatment of LTBI. Chapter 3 provides an in-depth look at the specific urban population that was included in this dissertation. Chapter 4 examines factors that are associated with completion of LTBI treatment. Chapter 5 evaluates the effects of an experimental peer support intervention on adherence and completion of LTBI treatment.

In reviewing the LTBI adherence literature we found that consistently employing tools for measuring and improving adherence is fundamental. Identifying barriers to adherence and treatment completion will facilitate the development of effective, appropriate interventions. A 'one-size-fits-all' approach to LTBI treatment adherence is not likely to succeed across all settings. Innovative approaches can inspire future interventions and suggest solutions for the current problems facing LTBI programs and their patients.

An examination of the change in demographic, social, and behavioral characteristics of patients undergoing treatment for LTBI in the Chest Clinic at Harlem Hospital between 1996 and 2005 found that the cohort of participants receiving treatment for LTBI in Harlem between 2002 and 2005 tend to have higher levels of foreign-birth and marriage, and lower levels of homelessness and unemployment, less experience with prior LTBI treatment, and lower rates of smoking and drug use than patients in the late 1990s. The 2002-2005 participants undergoing treatment for LTBI mirror the NYC and national TB picture in terms of gender, age, and foreign birth; however, the racial distribution is different as the Harlem community does not have a large population of Asians.

In these studies of LTBI treatment in an inner city urban population, homelessness, foreign birth, alcohol use, and marriage predicted success at completing LTBI treatment. Special efforts to reach patient groups identified with these factors have the potential to improve completion rates. Our findings suggest that tangible assistance would be more effective than educational interventions, which are currently the primary strategy used to improve LTBI treatment completion.

The peer support experimental intervention was found to be very effective in the Pathways population but not in the TAPAS population where completion rates increased substantially for both the intervention and control groups. The power for detecting an intervention effect in TAPAS was reduced by the higher than expected completion rates in both groups; however, the effect of the TAPAS intervention is statistically significant in the adherence model. Adherence analysis in TAPAS suggests that it is important to intervene early in the treatment when patients tend to default treatment. Close follow-up of patients during the first two months of treatment, with prompt intervention to encourage completion among those stopping treatment may yield better outcomes and reduce costs over the long term.

STRENGTHS AND LIMITATIONS

The design and analysis of this dissertation involved multiple strengths as well as potential limitations that must be considered for drawing inferences regarding the findings. Among the strengths are the inner city urban setting and the prospective nature of both studies, which afforded an opportunity to establish causal relationships in a general clinic population as well as offered some generalizability to the findings. Moreover, adherence to and completion of LTBI treatment are crucial factors in the effort to eliminate TB in the U.S. and are therefore of major public health relevance. The potential or actual limitations of the study include the abstraction of key variables from medical charts, the inability to locate a small number of medical records, and reduced statistical power for TAPAS analyses due to higher than expected completion rates in both groups.

Limitations of the study

The main outcome variable, completion of treatment, was abstracted from medical charts; these data were typically not entered for study purposes, and therefore the quality of information obtained could not be verified through participant interview. However, key variables such as treatment outcomes are submitted routinely to the Department of Health and are an integral part of the medical record; thus we can assume that they are reliable. In addition, a small number of medical records could not be located; however, these participants were similarly distributed among the treatment groups. To be conservative, it was assumed that a chart not found equals failure to complete.

An accurate measurement of adherence is very challenging. While every effort was made to carefully and correctly assess adherence, it is not certain that measurement error was not introduced. This was especially problematic as the degree of missing or incomplete adherence data in TAPAS was fairly high. However, a very structured approach for imputation was developed and utilized. Final models were run on the partial as well as total sample (including imputed data) and results did not vary.

Both studies were designed to have adequate sample sizes that allow for sufficient power to test the proposed hypotheses; however, the power for detecting an intervention effect in TAPAS was reduced by the higher than expected completion rates in both groups. An intervention effect for completing LTBI treatment was observed in both studies but it was statistically significant only in Pathways; however, the effect of the TAPAS intervention is statistically significant in the adherence model.

The Pathways study collected self-reported HIV status at baseline but the TAPAS study did not collect that information. Considering the risk associated with HIV infection in progression from latent infection to active disease, and the possible impact of HIV status on perceived severity and susceptibility, this information is important. It was not possible to collect HIV information for the TAPAS population for this analysis. The predictors analysis in Chapter 4 was based on a combined sample of control patients from both studies, which means that self-reported HIV status could not be used as a predictor in this analysis. The interventions analysis in Chapter 5 was based on separate analyses for each study; therefore, self-reported HIV status was tested in the Pathways analysis and was not found to be a predictor of treatment completion.

Strengths of the study

The inner city urban setting provided a valuable opportunity to examine predictors of adherence to and completion of LTBI treatment in a clinic population where patients are at great risk of getting TB and face many barriers to the completion of treatment. Additionally, the prospective nature of both studies allowed us to establish a temporal relationship for the predictors study and establish a causal link for the impact of the peer-based interventions between the independent variables and the treatment outcome in this disadvantaged population. Comparing and contrasting two patient populations enrolled in two separate RCTs added richness to the analyses.

Adherence measurement plays an important role in assessing patient outcomes. While there is no single universally preferred measure of adherence, several measures provide valuable, if partial, information. A combination of indirect assessment like self-report with a direct measure like record of clinic attendance is considered the current “state-of-the-art” in measurement of

adherence behavior. Furthermore, the self report and clinic record are informative, easy to use and replicate, and are not too costly or cumbersome for this patient population. Both studies used these methods. The TAPAS study adopted an additional method, electronic monitoring devices to record prescription bottle openings.

The generalizability of study findings is an important issue in considering how the study may be able to inform public health practice. Our studies are not limited to a specific high risk group but instead to a general clinic population, albeit one at high risk of developing TB disease because of its location in an inner city urban setting where the risk for TB is greater. Using a clinic population offers generalizability of study findings, which is an important issue in considering how the study may be able to inform public health practice.

Adherence to and completion of LTBI treatment are crucial factors in the effort to eliminate TB in the U.S. and are therefore of major public health relevance. The findings from this study contribute to our understanding of barriers and facilitators associated with adherence and completion of LTBI treatment and the effectiveness of a peer-led intervention for improving adherence to and completion of LTBI treatment. This understanding facilitates the development of effective, culturally relevant interventions.

FUTURE RESEARCH DIRECTIONS

Our findings point to several questions requiring further discussion and investigation in future research studies. Recent work has shown the importance of shortened LTBI treatment regimens for ensuring treatment completion.[1] A recent study found completion rates ranging from 71.6%

to 91.4% with four months of rifampin.[2] Some of the newer shorter regimens have intermittent dosing, which present new challenges that will need to be explored. Further research is required to determine whether factors found to predict completion would remain effective predictors among patients on shortened regimens characterized by higher completion rates.

Adherence analysis in TAPAS suggests that it is important to intervene early in the treatment course as the first two months of treatment present a danger period where patients tend to default treatment. Developing and testing interventions that focus on the early part of the treatment is imperative. Examples of such interventions are daily reminders to take the medications by utilizing cell phone technology (such as text messages or interactive voice response) and pharmacy linkages to ensure that prescriptions are refilled on schedule. Another intervention that needs to be evaluated is the use of wireless medication bottles that transmit a signal when opened, providing an opportunity to intervene in real time. Because adherence is dynamic and declines either gradually (such as from pill fatigue) or suddenly (from family emergencies), real-time monitoring represents a shift from reactive responses to proactive interventions designed to prevent treatment failure. Close follow-up of patients during the first two months of treatment, with prompt intervention to encourage completion among those stopping treatment, may yield better outcomes and reduce costs over the long term.

REFERENCES

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2. Ziakas P, Mylonakis E. 4 months of rifampin compared with 9 months of isoniazid for the management of latent tuberculosis infection: a meta-analysis and cost-effectiveness study that focuses on compliance and liver toxicity. Clin Infect Dis 2009;49:1883-9.

Appendix 1 – Pathways Tables and Figures

Appendix 1 Table 1: Reliability scores for TB attitudes scales

	# Items in factor	Cronbach's alpha
Social support	6	0.475
Attitudes Factor 1	3	0.474
Attitudes Factor 2	3	0.322
Attitudes Factor 3	2	0.578
Attitudes Factor 4	3	0.273
Attitudes Factor 5	2	0.292
Attitudes Factor 6	2	0.278
Attitudes Factor 7	2	0.246

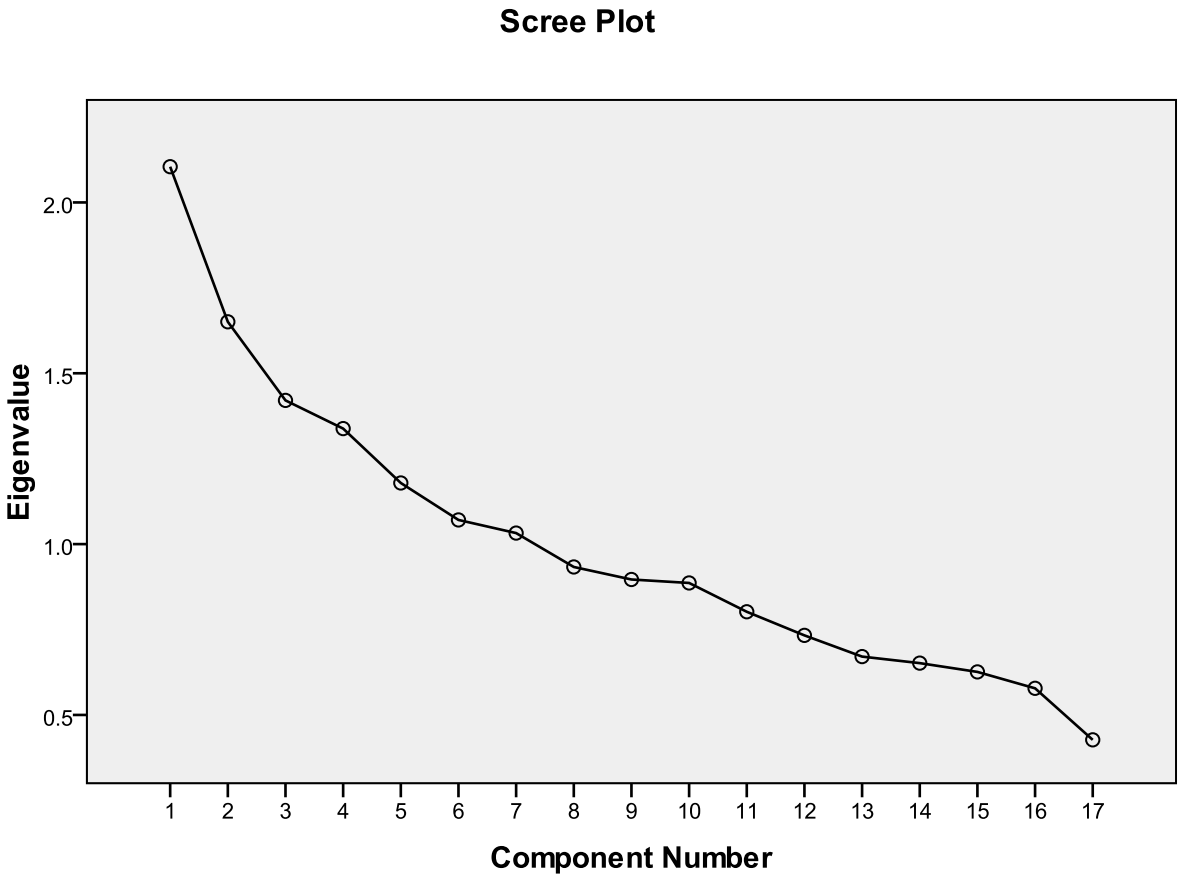
Appendix 1 Table 2: TB Attitudes Number of Factors and Variance Explained

Total Variance Explained

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	2.105	12.380	12.380	2.105	12.380	12.380	1.586	9.329	9.329
2	1.651	9.710	22.090	1.651	9.710	22.090	1.528	8.986	18.315
3	1.421	8.357	30.446	1.421	8.357	30.446	1.522	8.952	27.267
4	1.338	7.871	38.317	1.338	7.871	38.317	1.419	8.346	35.612
5	1.179	6.935	45.252	1.179	6.935	45.252	1.254	7.377	42.989
6	1.071	6.298	51.550	1.071	6.298	51.550	1.252	7.362	50.351
7	1.032	6.072	57.623	1.032	6.072	57.623	1.236	7.271	57.623
8	.933	5.489	63.112						
9	.896	5.273	68.385						
10	.886	5.213	73.598						
11	.802	4.718	78.316						
12	.733	4.311	82.627						
13	.671	3.946	86.572						
14	.652	3.833	90.406						
15	.626	3.682	94.088						
16	.578	3.400	97.488						
17	.427	2.512	100.000						

Extraction Method: Principal Component Analysis.

Appendix 1 Figure 1: Pathways Attitudes Scree Plot



Appendix 1 Table 3: TB Attitudes: factor loadings for principal components analysis with varimax rotation

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7
k43-Drs know how to treat TB	.685						
k30-Meds today are very powerful in fighting TB	.614						
k35-You usually follow doctors advice	.612						
k24-Taking TB medicine is important		.737					
k22-TB is disease have to take seriously		.608					
k44-You believe that you have TB germ		.587					
k41-Family is ashamed that you have TB			.808				
k32-Since word has spread that have TB, people avoid you			.802				
k27-You know better that the Dr when to stop meds				.728			
k29-Not important to keep your appointments				.631			
k33-It takes something really bad to not take meds				-.537			
k40-When you feel really bad, stay home instead seeing Dr					.758		
k42-If feel worse when taking meds, would stop taking it					.580		
k38-You care about what family/friends think of tb treatment						-.714	
k31-Family and friends do not care if keep appointments						.714	
k45-Will not get TB b/c you are lucky							.725
k25-TB is something you & friends talk about							.714

Appendix 2 – TAPAS Tables and Figures

Appendix 2 Table 1: Reliability scores for all scales

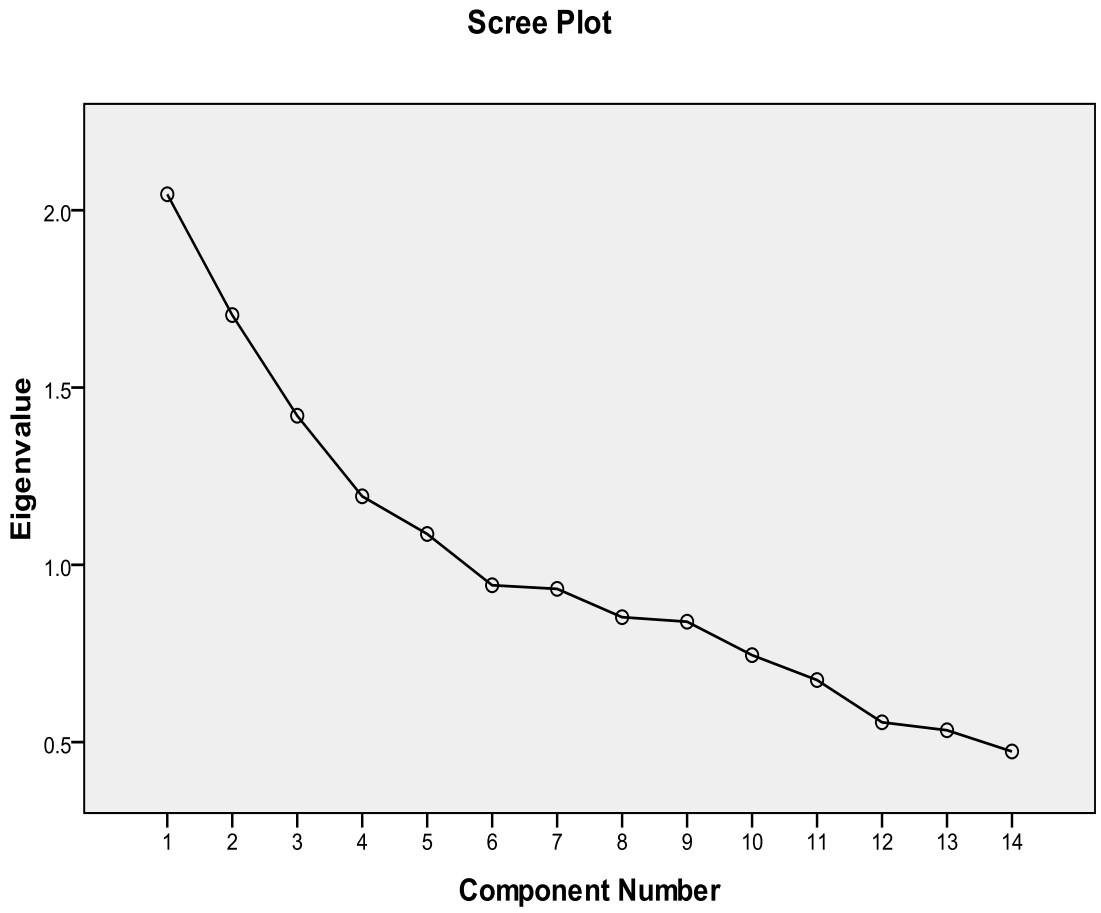
	# Items in factor	Cronbach's alpha
Social support	6	0.779
Perceived benefits	8	0.795
Perceived barriers	8	0.644
Attitudes – Factor 1	3	0.530
Attitudes – Factor 2	3	0.511
Attitudes – Factor 3	2	0.318
Attitudes – Factor 4	3	0.320
Attitudes – Factor 5	3	0.298
Reasons – Factor 1	5	0.788
Reasons – Factor 2	5	0.714
Reasons – Factor 3	3	0.717
Reasons – Factor 4	3	0.428

Appendix 2 Table 2: TB Attitudes: Number of Factors and Variance Explained

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	2.045	14.607	14.607	2.045	14.607	14.607	1.768	12.628	12.628
2	1.704	12.174	26.781	1.704	12.174	26.781	1.658	11.841	24.468
3	1.420	10.146	36.928	1.420	10.146	36.928	1.370	9.782	34.251
4	1.193	8.523	45.451	1.193	8.523	45.451	1.328	9.488	43.739
5	1.087	7.764	53.215	1.087	7.764	53.215	1.327	9.476	53.215
6	.942	6.731	59.946						
7	.932	6.659	66.605						
8	.852	6.088	72.693						
9	.840	5.997	78.690						
10	.745	5.324	84.014						
11	.675	4.822	88.836						
12	.556	3.971	92.807						
13	.533	3.810	96.617						
14	.474	3.383	100.000						

Extraction Method: Principal Component Analysis.

Appendix 2 Figure 1: TAPAS Attitudes Scree Plot



Appendix 2 Table 3: TB Attitudes: factor loadings for principal components analysis with varimax rotation

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
ka29 taking TB meds is a hassle	0.733				
ka21 clinic appts are more trouble than worth	0.707				
ka28 try hard, will still miss some meds	0.599				
ka27 care about what family and friends think of TB treatment		0.772			
ka25 embarrassed to tell you have TB germ		0.672			
ka24 worry about passing TB germ to loved ones		0.540			
ka26 believe that you have the TB germ			0.683		
ka23 do right thing can avoid getting TB disease			0.575		
ka18 no matter what could still get TB germ				0.702	
ka30 only something really bad would prevent from taking TB meds				0.552	
ka20 you know better than doctor when to stop meds				-0.512	
ka17 BCG vaccine prevents TB disease					0.688
ka22 do not trust doctor for best care					-0.581
ka19 taking TB meds is important					0.540

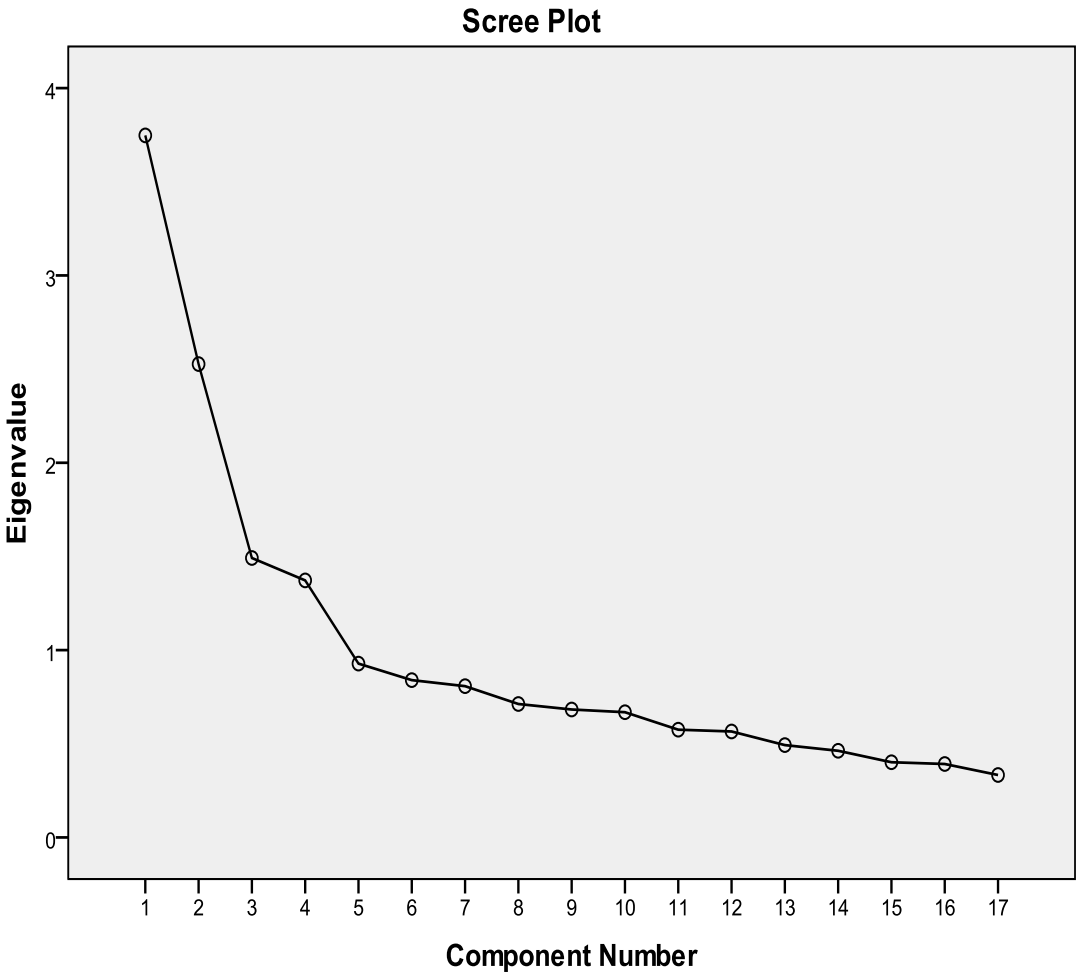
Appendix 2 Table 4: Reasons for Missing Medications: Number of Factors and Variance Explained

Total Variance Explained

Component	Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %
1	2.718	15.986	15.986
2	2.595	15.267	31.253
3	2.373	13.957	45.210
4	1.452	8.543	53.753

Extraction Method: Principal Component Analysis.

Appendix 2 Figure 2: TAPAS Reasons Scree Plot



Appendix 2 Table 5: Reasons for Missing Medications: factor loadings for principal components analysis with varimax rotation

Rotated Component Matrix

	Component			
	1	2	3	4
11e - felt drug was harmful	.795			
11o - knew what was best for you	.759			
11d - wanted to avoid side effects	.754			
11n - felt good	.654			
11p – didn't feel like taking pills	.615			
11q - were drunk or high		.797		
11m - going to drink alcohol		.716		
11f - not want others to notice you taking meds		.619		
11w - you were angry that you have to take the pills		.603		
11x - pills remind you that you have the TB germ		.602		
11b - simply forgot			.713	
11s - were too busy with work/family			.711	
11g - slept through dose time			.682	
11a - pills not fit in with daily routine			.636	
11r - you were away from home			.613	
11l - ran out of pills				.775
11u - had problems getting the medications				.746

Appendix 2 Table 6: Adherence Imputation Decision Rules – Deterministic Process

- In cases where participants reported never taking any medications, assign 0% adherence for all missing months.
- We assume that there is a need to stochastically impute data for the month after a clinic visit as the participant had the prescription and may have taken the medications. Once clinic visits stop and participants don't have medications, we are assuming 0% adherence for all subsequent months.
- In cases with no MEMS data available, no interview data, and no clinic visits documented, it is assumed that adherence for months 2-9 is 0%. Month 1 will be stochastically imputed because participants had 1-month supply of medications available to them.
- In cases where MEMS information is available, use to impute missing interviews as good agreement between MEMS and self report was found in this dataset.
- In cases where there appears to be a conflict in the information provided by interview and by MEMS, interview data was not changed.

Appendix 2 Table 7: Adherence Imputation Algorithm – Stochastic Process

Step	Recipient file	Donor file
1. Import files	Import recipient file	Import donor file

2. Prepare files	2a. Drop records with complete data.
	
	2b. Make sure all vars that are the same across files start with 'recip_' or 'donor_' except for total_months, which will be the matching variable.
	
	2c. Create/initialize imputation variables:
	imp_donor_PID = '.' (ID of imputing donor)
	pattern = character string indicating which months have data available (e.g., ACDEFH)
	alphabet = ABCDEFGHIJKL (character array)
	recip_adhere = average adherence for cells with reported adherence
	
	2d. Sort by completion and total months available
		2a. Drop records with missing data and records with no potential recipients.
		
		2b. Make sure all vars that are the same across files start with 'recip_' or 'donor_' except for total_months, which will be the matching variable.
		
		2c. Create/initialize imputation variables:
		randnum = ranuni(32769) (random # sequence)
		num_donat = 0 (number of donations)
		best_num_donat = '.'
		best_don_PID = '.'
		don_adhere = '.'
		adh_diff = '.' (difference b/w donor and recip adherence values)
		imp_recip_PID = '.' (ID of imputed recipient)
		cutoff = 25 (tolerance level for matching)
		
		2d. Sort by completion and total months available

3. Subset recipients	Create a reduced recipients file so that each cell defined by completion × total_months contains only one recipient record.	
4. Merge donors and recipients	Merge reduced recipient and donor files by completion and total_months. This data step is a "one-to-many" merge and will pair the recipient in a given completion × total_months cell with all potential donors in that cell. As the data step progresses, the object is to find the donor who matches most closely on adherence.	

Appendix 2 Table 7: Adherence Imputation Algorithm – Stochastic Process

Step	Recipient file	Donor file
5. Find donor with best fit	5a. Create an array of donor adherence values based on d_mt1 to d_mt12. 5b. Calculate don_adhere using recip_pattern and array of adherence values 5c. Set adh_diff to equal the absolute difference between don_adhere and recip_adhere. Check the difference between adherence of each donor and recipient until identify the smallest difference that is ≤ cutoff, i.e. ≤20% or 30%. If there are multiple donors with the same adherence level that qualify as the smallest difference, use the random number generator to select one of them.	
6. Repeat loop for each recipient	Repeat steps 3-5 for each recipient. Retain information such as number of donations every time files are merged.	
7. Search for donors with 1 month more than recipient	For recipients where no donors were found, repeat step 3 and 4 to merge recipient file with donor file where total_months is changed to be total_month+1 in donor file, then run steps 5 and 6 on this new merged file.	
8. Search for donors with 1 month less than recipient	For recipients where no donors were found, repeat step 3 and 4 to merge recipient file with donor file where total_months is changed to be total_month-1 in donor file, then run steps 5 and 6 on this new merged file.	
9. Search for donors with 2 months more than recipient	For recipients where no donors were found, repeat step 3 and 4 to merge recipient file with donor file where total_months is changed to be total_month+2 in donor file, then run steps 5 and 6 on this new merged file.	
10. Search for donors with 2 months less than recipient	For recipients where no donors were found, repeat step 3 and 4 to merge recipient file with donor file where total_months is changed to be total_month-2 in donor file, then run steps 5 and 6 on this new merged file.	
11. Search for donors with matching neighboring months	For recipients where no donors were identified using the previous steps, donors and recipients are match based on having matching neighboring months and the months for which data are available should match to within +/- 2 months.	