Tuberculosis Adherence Partnership Alliance Study (TAPAS)

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1 Specific Aims

The elimination of tuberculosis (TB) in the United States is a national priority [1, 2]. This requires rapid identification of individuals with TB disease and their appropriate management. In addition, with the decreasing TB case rates in the United States noted in the past few years, the effective identification of latent TB infection (LTBI) in individuals at high risk for progression to TB disease and the effective treatment of this latent infection is now an important strategy in the nation’s TB control program [3]. However, completion rates for LTBI have been modest at best[4]. This issue is particularly critical in Harlem, where the rates of TB greatly exceed the national average and the concomitant HIV epidemic results in a large population vulnerable to the development of TB. HIV infection is the most potent risk factor for development of TB resulting in a 100-fold increase in the risk versus the risk among those without HIV infection[5]. The population that is eligible for treatment for LTBI in Harlem includes predominantly minorities and a large proportion of women, and substance users. The barriers to adherence in this population are significant, including limited access to health care, a fragile and limited social support network and difficulty communicating with providers.

This study, the Tuberculosis Adherence Partnership Alliance Study (TAPAS), will utilize the Precaution Adoption Process Model (PAPM) as a basis for interventions to promote adherence with treatment of LTBI [6]. This model recognizes that adoption of a particular precautionary behavior, in this case adherence with LTBI treatment, involve seven distinct stages and that interventions need to be tailored to the individual’s specific stage in order to succeed in moving them from stage to stage and ultimately in achieving and maintaining the desired behavior. In addition, this study will also incorporate constructs from the Health Belief Model that are particularly appropriate to LTBI and its treatment i.e. susceptibility, severity, perceived benefits/barriers of treatment and self efficacy. The intervention will be administered primarily by peers based on their key importance of social support and modeling of desired behavior. The specific aims are the following:

- To assess the impact of a peer-based intervention based on the PAPM model on adherence with treatment for LTBI. Adherence will be measured by participant self-report, computer touch screen methodology, electronic medication monitors and assessments by provider and peers.
- To identify patient demographic, social and behavioral characteristics that are associated with adherence in this inner-city population
- To assess the impact of specific components of the intervention on treatment adherence
- To assess the cost effectiveness of the experimental intervention

2 Background and Significance

2.1 TB in Harlem

A resurgence of tuberculosis (TB) was recognized in New York City (NYC) with TB rates rising from a low of 17.2 cases/100,000 in 1978 to 52.0 cases/100,000 in 1992, a rate significantly higher than the national rate of 10.5/100,000. The Harlem community was especially affected by this resurgence, when the Central Harlem TB rate rose to a high of 240.2 cases/100,000 during the same time period. Since 1992, TB control efforts have resulted in a heightened awareness about TB and populations considered to be at high-risk, as well as effective control strategies, such as directly observed therapy (DOT). These efforts have resulted in the gradual decrease in TB case rates in Harlem to 60.6/100,000 in 1998. Despite this decline, the TB case rate in Harlem is still over nine times the US rate (6.8 cases/100,000) and over twice the NYC rate (21.3 cases/100,000).

Harlem, a predominantly African-America community, suffers from a large variety of socio-economic problems such as drug and alcohol use, homelessness, and HIV infection. Risk factors such as these result in a substantial threat for progression from LTBI to TB disease in this community. People of color in NYC have markedly higher rates of TB than other race/ethnic groups with 68.7% of cases occurring among African Americans and Hispanics. At the same time, the proportion of TB cases among the foreign-born has increased nationwide [7, 8] and similar increases in the foreign-born population are thought to have also occurred in NYC and Harlem. This is demonstrated by the fact that in 1998, 54.7% of new TB cases occurred among the foreign-born in NYC. Additionally, 41.8% of the patients with TB disease or LTBI at Harlem Hospital are foreign-born.

2.2 Latent TB Infection and Its Treatment

At a time of decreasing TB morbidity in the US, current attention has focused on the need to target screening and treatment of LTBI [9]. Increased risk for contracting LTBI and for the progression to active TB disease has been documented for certain vulnerable populations such as the homeless [10, 11], substance users [12], HIV-infected [13-15], and persons with severe mental illness [16-18]. Immigrants from countries with a high TB prevalence are another important target group. Studies have noted high TB incidence rates in such persons especially for the first five years after arrival in the US [19] [20, 21]. In the US, the case rate among Sub-Saharan African immigrants from 1986-1994 was 66/100,000 person-years, while the case rate was 7.8/100,000 person-years among the US-born population [20]. It is estimated that approximately 250,000 African immigrants currently live in...
NYC, with large concentrations in Central and East Harlem. HIV, overcrowding, cultural beliefs, and inadequate health care can provide further obstacles to treatment for LTBI.

A major focus in recent years has been attempts to identify shorter courses of LTBI treatment in an attempt to improve adherence with LTBI treatment. Recent studies have utilized two months short-course LTBI treatment utilizing rifampin (RIF) plus pyrazinamide (PZA)[22]. A large recently published international clinical trial comparing 2 months RIF/PZA to 12 months of isoniazid (INH) among HIV-infected patients with LTBI demonstrated that they were associated with similar efficacy and adverse event rates [22]. In addition, other studies have also assessed this shorter regimen in other studies and in children[23]. Preliminary studies suggest that completion of LTBI treatment may be better with this regimen rather than traditional regimens. However, this has not been rigorously assessed and no adherence intervention has been focused on this issue.

2.3 Adherence

Adherence has been defined as the extent to which a person’s behavior coincides with medical advice [24]. Adherence involves not only taking the prescribed medication doses at the prescribed intervals, but also keeping appointments and following nonmedication-related advice such as diet and exercise [25, 26]. Adherence has been shown to be influenced not only by individual behavior but also by the structure and nature of services offered, the quality of patient-provider communication and the amount of social support offered the patient. Estimates of adherence with therapeutic regimen range from 18% to 80% [25, 27, 28], with partial adherence occurring commonly in all diseases and populations. Unfortunately, there is no test or single characteristic to discriminate between adherers and nonadherers, and physicians have been noted to be poor at predicting adherence in their patients [29-33].

Studies have demonstrated that certain characteristics were associated with adherence. Although no single factor has been shown to consistently predict adherence, many factors have been associated with adherent or nonadherent behavior.

a. **Patient characteristics** that have been shown to correlate with adherence include the patient’s knowledge of the treatment regimen [34-36] plus 2 aspects of the Health Belief Model [37], having greater perceived benefits from therapy and having fewer perceived barriers to treatment [35, 38, 39]. Characteristics associated with poor adherence include homelessness and the lack of social support [24, 40, 41]. Specific cultural beliefs can also lead to non adherence, as described with the treatment of tuberculosis [42, 43] and hypertension [44]. Studies that have examined the relationship between adherence and patient demographic factors such as age, race, gender, education, and socioeconomic status have yielded unclear and often contradictory findings [24, 40, 45].

b. Provider characteristics and the quality of the patient-provider relationship have been shown to affect adherence [24, 46], particularly the quality of the physician’s interpersonal skills [47, 48]. Positive outcomes are more likely when physicians make efforts to explain treatment regimens [49]. Increased non adherence has been noted in situations where doctors appear insensitive, use medical jargon, view patients as complainers and do not provide clear messages about the cause of the illness or reasons for treatment [50, 51].

c. Adherence has been shown to be inversely related to several treatment-related factors, including the number of medications [24, 49, 52], frequency of dosing [53-57], complexity of regimen [56], duration of regimen [57], side effects [24, 57] and the degree of behavior change required to take the regimen [58].

**Characteristics of the clinical setting** that can lead to non adherence with medical care and treatment include long waiting times, inconvenient clinic hours, lengthy delays between contact and appointments, and substantial travel costs [24, 59, 60].

e. **Disease characteristics** that have been shown to influence adherence include the chronicity of the illness [60, 61] as well as the degree of disability produced by the disease [24]. The resolution of the disease’s symptoms has correlated with poor adherence in some studies, presumably because patients are no longer symptomatic and therefore no longer feel the need for medications.

2.4 Adherence and Tuberculosis

The treatment of both LTBI and TB disease requires an often complex regimen of several months duration [62]. Treatment of each of these conditions is associated with specific challenges. In the setting of TB disease, these include: stigma, need for multiple medications, medication-associated side effects and need to take medication beyond symptomatic phase. On the other hand, treatment of LTBI is associated with a major challenge; to convince the patient of the need for prolonged treatment of an asymptomatic non-contagious infection that may never develop into TB disease using medications with potential side effects.

The treatment of TB disease has received high visibility and priority and has provided a rich arena for the assessment of various adherence interventions. This is due to several factors: 1) TB is a contagious disease with risk of transmission to others, 2) Non adherence is associated with prolonged infectious phase, 3) Non adherence is associated with risk of development of resistant organisms with spread in the community and 4) the substantial human and fiscal costs of treatment of resistant organisms [63].

Non adherence with TB treatment has been associated with various risk factors. In a study conducted in New York City, factors such as homelessness, alcohol use, injection drug use, HIV infection and poverty were
associated with low adherence rates [11]. While these risk factors were associated with non adherence, other studies indicate that providers are unable to predict those likely to adhere with TB treatment [64].

Directly observed therapy (DOT) has been recommended as the preferred method for ensuring completion of treatment of TB disease and has been adopted by the World Health Organization as the primary strategy for the global control of TB. This involves supervising the ingestion of every dose of treatment [65]. In a review of published articles on DOT programs for TB treatment reported from 1966 through 1996, the authors reported that treatment completion rates were ≥90% when therapy was supervised [66]. This high rate was not achieved by programs that used partial supervision of therapy or self administered treatment. However, others have noted that high rates of TB completion have been achieved in some communities without the use of universal DOT [67]. Others have suggested that other methods such as the use of medication monitors, devices that record when the medication is removed from its container, as another strategy to monitor adherence [64]. Additionally, the use of fixed dose combination pills has also been used to prevent the development of resistant organisms in case of non adherence [68].

While adherence with the treatment of TB disease has received substantial attention in the literature, few data have accumulated with regards to adherence with LTBI treatment. LTBI treatment completion and adherence rates have not been very accurately measured. In NYC, LTBI treatment completion rates for contacts identified by the NYC DOH is calculated to be 61.2% based on attendance of clinic visits [69]. Additionally, among health care workers, a recent study demonstrated very low completion rates among eligible candidates for LTBI treatment [70]. Factors associated with non adherence with LTBI treatment have not been well defined. In a study of Hispanic adolescents, the occurrence of side effects was significantly associated with non adherence [71]. In our experience at Harlem, candidates for LTBI have also certain characteristics that may influence LTBI treatment adherence. For example, among those receiving TB/LTBI treatment at Harlem Hospital, 41% are homeless, 31% are HIV-infected, 88% are unemployed, and over one third have been treated for drug or alcohol-related problems. This in addition to their sense of vulnerability and mistrust of the health care system.

Most studies reported to date have focused on measurement of adherence with LTBI treatment rather than on the development of interventions to promote adherence with therapy. For example, a study of LTBI treatment among injection drug users in Baltimore demonstrated that pill adherence rate as measured by MEMS caps (computerized pill bottle top which counts the number of times bottle is opened) was significantly lower than self reported adherence (61% by MEMS caps versus 93% by self report, P<0.01) [72]. In another study, self report, pill counts and urine test for INH metabolites were compared in the assessment of adherence with treatment of LTBI [73]. In this study, only 50% of the participants reported adherence with treatment. Pill counts were associated with urine test results but adherence as measured by the MEMS caps was most strongly associated with results of urine INH metabolite tests.

A study conducted among 30 participants evaluated the role of adherence data obtained via MEMS caps as well as physician and pharmacist counseling on treatment completion [74]. These combined efforts resulted in completion of treatment by 86% of the patients. In another study that evaluated adherence with first evaluation visit for LTBI conducted among homeless persons in San Francisco, subjects assigned monetary incentive or those assigned a peer worker were more likely to adhere than those assigned usual care. In addition, patients who were not using intravenous drugs and older patients were more likely to adhere with this first visit [75].

Given the intense pressure to reduce health care costs, it is essential that we better understand the effectiveness and cost of different intervention models. Cost effectiveness analysis and cost-benefit analysis can be valuable tools for making rational decisions about the allocation of scarce resources to promote TB control. Cost-effectiveness analysis essentially presupposes the desirability of some policy intervention and is limited to analyzing program effects in a single dimension, unlike cost-benefit analysis, which requires monetization of outcome measures. Because outcome measures for the two programs we propose to study will be identical, the appropriate technique to use in this context is cost-effectiveness analysis [76].

Most TB cost studies to date have focused on patients with active TB disease, examining the cost effectiveness of offering Directly Observed Therapy (DOT) versus self-administered or other forms of therapy [77-80]. Often these studies have been conducted in developing countries where DOT is not routinely offered [81-83]. As with adherence studies, there are fewer studies on the cost-effectiveness of LTBI treatment. Such studies tend to either concern LTBI treatment among persons with HIV infection [84, 85] or use mathematical modeling to estimate costs for different risk groups or program designs.

### 2.5 Tuberculosis Knowledge and Attitudes

Despite the potential contribution to our understanding of adherence and treatment completion, surprisingly few TB knowledge, attitudes, and practices (KAP) studies have been conducted recently in the United States. These studies have found that many participants held misconceptions about TB transmission, including transmission through sexual intercourse and shared dishes [86-89]. Participants tended to confuse LTBI with active TB disease [90-92], and many participants confused information about transmission and treatment for TB with that for HIV [86, 89].
These KAP studies tended to focus on assessing participants’ knowledge about TB and LTBI and gave little attention to describing attitudes. For example, approximately half of the participants in two homeless samples reported feeling susceptible to TB [89, 93]. Around 90% of Vietnamese refugees felt that they would be stigmatized by TB [94], as did 54% of a homeless sample [93].

2.6 Models Used in Adherence Studies:

While the studies described in previous sections yield important insights into the experiential dimensions of TB disease and its treatment, they do not lead directly to theoretical models for adherence interventions. Like studies that identify critical risk factors for non-adherence, they do not address the underlying processes by which those factors operate to hinder therapy [95]. Several authors argue that precisely this interaction of factors is at the heart of adherence and non-adherence [32, 35, 53, 96-98].

Contemporary studies aimed at understanding and influencing adherence to TB and LTBI treatment have generally not been guided by theoretical models of health behavior. When theoretical approaches have been used, the most common has been the Health Belief Model, which was initially developed in the 1950s to explain the failure of people to participate in B screening programs [99]. Over the last 10 years, TB studies in Los Angeles [100], South Carolina [101], Chicago [102], and India [35] have used this model. The Health Belief Model posits that health behavior is essentially motivated by outcome expectations and thus focuses on the perceptual foundations of health behavior. Interventions based on the model communicate information about prevention, diagnosis, and treatment so as to influence beliefs about susceptibility, severity, treatment efficacy, and the advantages of treatment both in terms of the specific condition and the accrual of tangential benefits. At the same time, they work to acknowledge and minimize perceived barriers to health action such as difficulties in obtaining medication and fears about side effects [37, 38, 95, 103, 104]. The construct “cues to action” identifies both general factors that induce people to act on their health beliefs, such as physician reminders about the importance of adherence, and personal strategies, such as routinely taking medicines during a particular meal or television program. More recently, some authors have emphasized that perceptions of risks and benefits are rendered into adherence behavior through individual self-efficacy [105]. Self-efficacy is defined as “the conviction that one can successfully execute the behavior required to produce outcomes” [106, 107]. Interventions that target self-efficacy enhance patients’ confidence in their ability to overcome personal and practical barriers to taking a desired action or adopting desired behaviors [108, 109] [110].

While self-efficacy is a personal attribute, it is tested and reinforced in social interaction. Thus, another group of interventions emanates from the finding that social support can have a profound impact on health outcomes [111-115] [116]. Social support can be divided into four categories: emotional, instrumental, informational, and appraisal. Emotional support involves conveying empathy and care, and builds the basis for trusting communication between the support sender and support receiver. Instrumental support involves the provision of substantive assistance in resolving tangible barriers and includes system navigation, that is, helping patients access the social services necessary for successful treatment [117, 118]. Informational support involves providing advice, suggestions, and information about the condition, its treatment and adherence. Appraisal support involves providing information that is useful for self-evaluation like constructive criticism and helps patients measure and evaluate their progress towards a specific health goal, and to assess the tangential benefits that accrue from successfully achieving those goals. Of course, much of the power of social support derives from who delivers it. Some interventions actively engage the existing social support of family and friends in prevention and treatment processes [40, 119-124]. Other interventions create or supplement social support for patients whose existing networks are weak, some of them using professional staff in supportive relationships [102, 117, 125, 126] [127].

Over the past 20 years, peer collaboration is recognized as a powerful tool to build social support in relationship to adherence, especially in underserved populations. Peer workers have been matched to patients on the basis of ethnicity, gender, sexual orientation, or conditions of homelessness [42, 75, 128]. Whether identified as peer educators, community health workers, or as lay health advisors, all types of peer workers provide similar services [87, 129-134]. They act as system navigators to help patients secure social and community services needed for successful treatment completion, and improve patient-provider communication by relaying medical information in terms accessible to the patient and making the provider aware of specific barriers to communication. They have credibility with patients because they share the patients’ reference group and have faced the same constraints in terms of disease treatment [131, 135]. Peer workers who themselves have completed treatment have proven particularly effective in TB studies [42, 43, 125]. Studies of peer support for various disease treatments have demonstrated its effectiveness in improving adherence and appointment keeping [53, 136, 137]. In developing countries peer workers have provided medication supervision for patients undergoing tuberculosis treatment [81, 138, 139]. Besides helping patients accomplish treatment-related tasks, peer programs cultivate “helping relationships” that bond patient and peer in a uniquely personal alliance for health promoting behaviors [130, 132]. 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.
Increasingly, stage theories are being used to understand and influence a broad range of health behaviors [140]. Two models that have received the most empirical attention to date are the *Transtheoretical Model (TTM)*, and the *Precaution Adoption Process Model (PAPM)*. The TTM incorporates many of their constructs and those of other behavior change theories into a model of ordered stages of decision-making and behavioral change [141-143]. The TTM has been applied to studies and interventions in long-term habitual behaviors and preventive measures as well as to adherence to medication regimens [144-147]. The TTM stands out as a systematic way of adapting interventions to individuals’ stage of readiness to change. However, it is more suitable for attainment of life-long behavior changes rather than in the treatments of finite duration, as for LTBI and specifies specific timeframes.

An alternative staging model, the *Precaution Adoption Process Model (PAPM)*, focuses more on the attitudinal, perceptual processes by which people decide to adopt a health action, and less on the strategies through which they establish new habits and cast off old patterns of behavior. The PAPM identifies 7 critical stages of adopting health behaviors [6, 140] (See figure in Appendix A). “Unaware” is the first PAPM stage in which people simply have no information about a given health risk. In the second they have information but have not applied it to their own lives and are still “unengaged” in the sense that they perceive no risk to their own health. In the “deciding” stage people have a heightened perception of the risks and severity of a health condition and are contemplating the benefits that appropriate action might bring. At the same time, people are evaluating what they perceive to be the barriers to undertaking such action. This evaluation process leads to one of two following stages. The “declined” stage represents a perception that barriers and risks are greater than the expected benefits of a health behavior. Upon processing new information or reformulating their perceptions, people may shift from declined to the alternative stage, “decided”. In this stage, when the benefits of a new health action are salient, cues to action can be powerful aids to overcome perceived risks and tangible barriers to the action. In the next stage, when people have “initiated” the behavior, such barriers may actually increase, and patients will benefit from instrumental support to resolve, or cope with, them and fit their health regimen into their daily lives. In the final stage, “completion”, patients take stock of their accomplishments, either maintaining a behavior when appropriate, or by assessing the direct and tangential benefits of the adopted behavior.

The PAPM is particularly useful for preventive interventions. It divides the decision making process into components so that an intervention can precisely identify and act on steps toward adoption even without the compelling pressure of physical symptoms. Although the model has not been tested empirically to the extent that the TTM has, its stages easily accommodate constructs from the health belief model and those of social support, both of which have been widely used in health interventions.

### 2.7 Rationale and Importance of the Proposed Study:

A recently published statement by the Advisory Council for the Elimination of Tuberculosis which reaffirms support for the goal of TB elimination in the United States [2]. Therefore, achieving at least 80% LTBI treatment completion has become a key national TB control priority. However, LTBI treatment completion rates in the US are modest, a situation that will likely lead to the inability to achieve TB elimination in this country. The recent availability of effective short course LTBI treatment as described above also provides a unique opportunity as this moment in time to attempt to identify a replicable, cost effective intervention that can deliver high LTBI treatment completion rates.

Yet, patients with LTBI are completely asymptomatic, often unaware or doubtful of having this infection, are not aware of the availability of effective preventive treatment, have unrealistic optimism and fail to appreciate the threat of TB disease. In addition, they often do not appreciate the efficacy of LTBI treatment, but may overestimate the potential adverse events. They may also have many competing priorities in their lives and few support networks. Finally, they may not have any role models in their own lives or environment that have adopted this precautionary behavior.

The proposed study will utilize key behavior change models that are especially suited to the treatment of LTBI, the Health Belief Model and the Precautionary Adoption Process Model (PAPM). The Health Belief Model with its focus on susceptibility (infection with TB germ), severity of disease (risk of development of TB disease), perceived benefits (prevention of TB disease, preservation of health, prevention of spread to the community), perceived barriers (side effects from medications, confidentiality concerns) and self efficacy fits well the framework of LTBI. Additionally, the PAPM provides an appropriate staging pattern of the candidates for LTBI treatment that will facilitate the delivery of a stage-specific intervention and the assessment of their progress through the PAPM stages during the intervention. Peers will be utilized to deliver the intervention. Peers, whose lives parallel those of the participant population in many ways, are uniquely equipped to intervene at this perceptual level and to provide patients with much-needed role models. The behavior-oriented constructs, e.g. cues to action and addressing patient barriers, provide guidelines for the interaction between participants and peers, as does the TAPAS emphasis on delivering specific types of social support.

The Harlem community is the ideal setting to evaluate the efficacy of an intervention for the enhancement of LTBI treatment as many of the patients identified for LTBI treatment belong to the groups at high risk for
development of TB disease [148]. Thus, the finding of an intervention that is successful in this community can be of immense value for TB control efforts in the United States and other countries.

3 Preliminary Experience and Expertise

3.1 Preliminary Experience:
The investigators included in this proposed study have had extensive experience in the areas of TB management, adherence research, clinical trials, behavioral research and the development of peer-based programs. The programs and studies noted in the table and described in more detail below demonstrate the breadth of this experience.

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3.1.1 Pilot Studies Regarding Behavioral Models
The TAPAS investigators prior to deciding on the study design and the model to be used discussed and evaluated the relevance of various behavior change models to LTBI treatment adherence. Initially, a questionnaire was developed to assess intentions and readiness to adhere to LTBI treatment based on Prochaska’s Transtheoretical model (TTM) 5 stages of behavior change. The questionnaire was administered to a random sample of 19 patients (68% male, 74% black) who came for tuberculin skin testing (TST) testing to diagnose LTBI and then re-administered the questionnaire to those eligible for LTBI treatment (n=6). Administering this staging questionnaire at the two different time points allowed us to observe the differences in the stage of change that occurred between the time of testing and when the treatment for LTBI was recommended. At TST testing, participants were grouped into the following stages: Precontemplation 16%, Contemplation 11%, Preparation 0%, Action 74% and Maintenance 0%. This pilot demonstrated problems inherent in applying the TTM to LTBI treatment because of the finite nature of the LTBI treatment period in contradistinction to lifetime behaviors in which the TTM has been applied e.g. smoking cessation, HIV prevention. Therefore, another pilot questionnaire was designed utilizing the PAPM stages of change to test that model. The questionnaire was administered to a random sample of 10 patients (70% men, 80% African American) who came for TST testing or were eligible for LTBI treatment. At TST testing, participants were categorized into the following stages: Unaware 57%, Declined to Adopt 14%, and Decided to Adopt 29%. When LTBI treatment was recommended, participants were categorized into the following stages: Unengaged 33%, Decided 33%, and Initiated 33%. Based on these data, available literature and specific LTBI-related characteristics, the investigators felt that the PAPM was the most appropriate model for adopting this precautionary action.

3.1.2 LTBI Treatment Duration Preference Study
In an ongoing study, we are assessing LTBI treatment preference of patients prior to initiation of treatment. This was prompted by the availability of various LTBI treatment regimens including the short-course two months regimen described above. Patients are presented with a brief description of two treatment options including the number of pills, length of treatment, and possible side effects. Forty-six patients (56% male, 44% female) have been enrolled with 36% preferring 9 months of isoniazid (INH) treatment and 64% preferring 2 months of rifampin and pyrazinamide (RIF & PZA). Reasons stated for INH preference included concern regarding side effects (57%) and the number of pills (36% associated with the short course regimen. Among those with preference for RIF & PZA, this was exclusively due to the short duration of treatment (100%).

3.1.3 Harlem DOT and DOPT Programs
In response to poor TB treatment adherence rates at Harlem Hospital [149], Dr. El-Sadr and colleagues designed an innovative Directly Observed Therapy (DOT) Program that seeks to ensure patient adherence through the provision of social support [125, 150]. In contrast to other DOT programs, the Harlem Family Model DOT Clinic is an on-site program, attracting patients to the Clinic by providing food, bus tokens, and other forms of tangible assistance in a warm, supportive atmosphere with availability of referrals to substance use counselor, a social worker and a health educator. The efficacy of the Harlem Family Model DOT Clinic is now being tested in a randomized clinical trial comparing it to an off site model.

In 1995, we established a directly observed preventive therapy (DOPT) program that utilizes the same “family model” methodology used in the DOT program described above. More than 200 patients with LTBI have been enrolled.
We participated in the implementation of a nationwide compliance study as a participating unit of the Community Programs for Clinical Research on AIDS (CPCRA), an NIH-sponsored national AIDS clinical trials network. This study, a substudy of a larger trial of combination antiretroviral therapy, was designed to examine the relationship of demographic, psychosocial and lifestyle characteristics with adherence. Information was gathered using confidential self-report questionnaires. A total of 557 subjects participated in the study, found to be associated with non-adherence included difficulty with transportation, conflicts with school or work, problems filling prescriptions, taking multiple pills on a specific schedule and confidentiality issues [156].

3.1.4 Pathways to Completion Study
The Harlem Pathways to Completion Program is a randomized clinical trial designed to compare two methods for ensuring completion of treatment for both LTBI and TB disease in an inner city setting [93, 153]. The project compares interventions for treatment of TB disease and LTBI. For TB disease, the project has recruited 205 patients with TB to date. Of these, 70% were male, 85% were African-American, 12% were Latino, 12% married, 29% foreign-born, 41% history of homelessness, and 88% unemployed. Preliminary data indicate that patients’ health status significantly improved during the treatment, and utilization of social support showed significant increase during treatment [154]. For LTBI component, the project has recruited 369 patients. Of these, 58% were male, 72% were African-American, 22% were Latino, 26% married, 48% foreign-born, 38% history of homelessness, and 72% unemployed [155].

3.1.5 The Fast Track Program for LTBI:
Harlem Hospital is the site of the Charles P. Felton National TB Center, one of three CDC funded Centers. Given the recent focus on the targeted screening and LTBI treatment in the Harlem TB Clinic called The Fast Track Program. The program identified barriers including prolonged waiting times, lengthy assessments by multiple providers, lack of reminder/recall systems, and inconsistent provider decisions about indications for LTBI treatment. A multi-disciplinary group consisting of the clinic manager, providers, health educators developed the program which includes a streamlined visit process and evaluation criteria, specialized forms for patients and providers, an interactive database for patient information, color-coded charts, and a computerized reminder/recall system. This program will serve as current clinical practice (CCP) or control intervention for the proposed study described below.

3.1.6 The Harlem Adherence with Treatment Study (HATS):
The Harlem Adherence to Treatment Study (HATS) is a randomized clinical trial of a peer-based intervention to improve HIV-infected patients’ adherence to antiretroviral therapy. The HATS intervention uses the Transtheoretical Model stages of change to tailor the adherence progress of each patient. In cooperation with study case managers, peers help participants to overcome concrete barriers to adherence and access the social services available through the hospital and the community. Peers provide participants with emotional, instrumental, and assessment support for adherence that is reinforced in study support groups. HATS peer workers are themselves HIV_infected, from the Harlem community and adherent to antiretroviral therapy. They complete a six-week training in HIV/HAART education and counseling techniques, and receive on-going training and supervision through the HATS Program. Since 1998, the study has engaged eight part-time peer workers and enrolled 70 participants drawn from Harlem Hospital ID clinics and from two cooperating community-based organizations. These include 39 women (56%), 50 (71%) African American and 13 (19%) Hispanic.

3.1.7 CPCRA/Adherence Study
We participated in the implementation of a nationwide compliance study as a participating unit of the Community Programs for Clinical Research on AIDS (CPCRA), an NIH-sponsored national AIDS clinical trials network. This study, a substudy of a larger trial of combination antiretroviral therapy, was designed to examine the relationship of demographic, psychosocial and lifestyle characteristics with adherence. Information was gathered using confidential self-report questionnaires. A total of 557 subjects participated in the study, 72 from our site. Factors found to be associated with non-adherence included difficulty with transportation, conflicts with school or work, problems filling prescriptions, taking multiple pills on a specific schedule and confidentiality issues [156].

3.1.8 Studies of Knowledge and Attitudes
Dr. Colson has had longstanding interest in the area of LTBI and knowledge and attitudes associated with it. He investigated knowledge and attitudes about tuberculosis and LTBI treatment in two groups: 379 participants in the Pathways to Completion prevention study (described above) and 833 non-patients in seven samples [86, 157]. Both groups showed substantial misconceptions about TB, with sexual activity, kissing, and sharing dishes all viewed as means of transmission. The mean number of knowledge items answered correctly for the Pathways group was 16 out of 24 (67%), 6 out of 10 (60%) for the non-patients. Results are noted in Appendix B.

In the non-patient sample, subsequent analyses have focused on exploring the relative importance of knowledge and attitudes in predicting imagined adherence, using multiple logistic regression. Preliminary results suggest that imagined adherence problems are associated with having low self-efficacy, being in the gay men’s sample, being ashamed to have TB, and having less than a college degree [157]. In the Pathways sample, further analyses have focused on changes over time. While overall knowledge scores and many attitudes associated with adherence improved, some attitudinal factors, such as self-efficacy and anticipated adherence, showed declines [157].
3.1.9 Positive Links Program
In 1989, we established the Positive Links program at Harlem Hospital Center. This program was initially developed to enhance HIV/AIDS prevention education services and treatment information for women in the Harlem community. The staff consists of HIV-infected women who were recruited from the Infectious Disease Clinic at Harlem Hospital Center and trained to be peer educators. The staff members also serve as patient navigators and provide social support for women at high risk for HIV infection or already HIV-infected. The success of the Positive Links program has resulted in its recently being expanded to include a group of men who provide the same services for their peers.

3.1.10 Critical Time Intervention Study
Dr. Colson was involved in the design and implementation of the Critical Time Intervention study, a randomized clinical trial testing an intervention to reduce recurrent homelessness among mentally ill men [158]. The study sample was similar to the Harlem Hospital patient population; indeed, many study participants came from the Harlem community. The intervention focused on the creation of a system of support that would take responsibility for the individual’s care in the community. Residence staff, family members, friends, mental health providers and personnel in other community agencies were enlisted in this effort. The intervention was associated with a three-fold reduction in homeless nights in the experimental group [159] and has been shown to be cost-effective [160, 161].

3.1.11 Clinical Trials Programs (CPCRA and TBTC):
The investigators have extensive experience in the design and implementation of TB-related clinical trials. As part of the CPCRA, the Harlem Unit participated in all TB-related studies among HIV-infected patients. More than 200 patients were enrolled in studies of the treatment of LTBI, TB disease and multidrug resistant TB. These included two ground breaking studies of the treatment of LTBI, the study of its treatment in anergic HIV-infected patients [162] and an international multicenter study of LTBI treatment among TST positive HIV-infected patients [22]. In addition, Dr. El-Sadr chaired one of the key studies that evaluated two regimens for the treatment of TB disease [163] and co-chaired the anergic study described above. Dr. El-Sadr participated in the design and conduct of a study of the treatment of multidrug-drug resistant TB [164], a study of the risk of development of resistant TB [165] and a study of the risk of TB infection among health care workers who provide care for HIV-infected patients [166].

Harlem Hospital Center is also one of the sites of the CDC-funded Tuberculosis Trials Consortium (TBTC). In this capacity, the site has participated in the recruitment and followup of close to 50 patients enrolled in studies evaluating various treatment regimens for TB disease including studies of treatment of HIV-related TB, of INH-resistant TB and of various doses of rifapentine. Several pharmacokinetic studies evaluating the relationship between TB drug levels and treatment outcomes and studies of the drug-drug interactions between TB medications and antiretroviral medications.

3.2 Expertise of the Research Team (See Appendix J for Publications and Presentations)
Wafaa El-Sadr, M.D., M.P.H. (Principal investigator), is the Director of the Center for Infectious Diseases at the Division of Epidemiology of the Mailman School of Public Health at Columbia University. She is also Chief of the Division of Infectious Diseases at Harlem Hospital Center and Professor of Clinical Medicine at Columbia University and in Public Health. She has long been a leader in TB and HIV research, with special interest in issues related to women, minorities and injection drug users. She has successfully obtained funding from federal, state, local sources for research and service projects. She is a member of the CDC Advisory Council for the Elimination of Tuberculosis (ACET). She has extensive experience in participation in multicenter research networks through the Tuberculosis Treatment Consortium (TBTC) and the Community Programs for Clinical Research on AIDS (CPCRA), the HIV therapeutic clinical trial network funded by the National Institute of Allergy and Infectious Diseases. She is a member of the Core Science Group of the TBTC and has participated actively in the design and implementation of TB-related studies.

Dr. El-Sadr is experienced in developing programs that are both service related and research oriented. She developed the Harlem DOT/DOPT programs. She is the Director of the Charles P. Felton National TB Center at Harlem Hospital. This Center is dedicated to the development of innovative TB control programs, training programs and research. She is a site investigator for the Tuberculosis Treatment Consortium, a multicenter TB clinical trials network funded by the Centers for Disease Control and Prevention. In this capacity, more than 10 TB-related clinical trials are currently ongoing. She has also successfully led the Harlem AIDS Treatment Group which has consistently performed well in terms of recruitment of underrepresented populations, achieved excellent follow-up rates (greater than 97%). Dr. El-Sadr has also developed a comprehensive HIV Program at Harlem Hospital with particular focus on substance users and people of color. Dr. El-Sadr has also developed various behavioral studies. She developed the Pathways to Completion Study, a clinical trial evaluating several behavioral interventions for TB. This study has enrolled over 500 participants from Harlem in these interventions [172]. Another area of recent study has been adherence with antiretroviral therapy. In collaboration with Dr. Sharon Mannheimer, Dr. El-Sadr developed a NIDA-funded HATS study described above and a HRSA-funded study comparing an interviewer-
conducted HIV self-reported adherence questionnaire with a computer screen self-administered questionnaire and a qualitative assessment of the nature of the participant-peer relationship.

Dr. El-Sadr is well-experienced in design and conduct of clinical trials. She has originated or participated in development of many of the research ideas that were developed into research protocols over the past 10 years especially in the area of the prevention and treatment of opportunistic infections. These have included studies of tuberculosis,[162, 173, 174] P. carinii pneumonia,[173, 175] M. avium complex disease,[176] cytomegalovirus,[177] candidiasis,[178] and bacterial pneumonia.

Dr. El-Sadr has also been able to successfully recruit and retain the exact populations that are the target of this application. Since it inception, the Harlem CPCRA unit has enrolled 1,017 patients in 32 HIV clinical trials for the treatment of HIV and its complications. These participants have reflected the characteristics of the affected community with 36.1% women, 61.9% African American and 21.8% Latino. In addition 14.9% of the participants had a history of injection drug use. An important accomplishment of the site has been the ability to achieve over 98% retention rates in these studies. In another clinical trial program, the Pathways to Completion study described below, 584 patients with LTBI or TB disease have been recruited and the loss to follow-up rate is less than 5%.

**Paul Colson, PhD** (Co-Principal Investigator) is Program Director, Charles P. Felton National Tuberculosis Center at Harlem Hospital. Dr. Colson has extensive experience studying TB, HIV and service delivery issues related to the homeless mentally ill [13, 16, 179, 180]. He served as Research Director of the Critical Time Intervention, a randomized clinical trial testing a time-limited, supportive intervention for homeless mentally ill men in transition from shelter to community living [159-161]. He served as Co-Investigator on two NIMH-funded studies of HIV among homeless persons with mental illness, a survey exploring HIV sexual and drug-taking risk behaviors [181, 182] and HIV risk reduction intervention tested in a randomized clinical trial [183]. During this period, Dr. Colson served as the Principal Investigator of a survey of TB knowledge and attitudes (see above). He has continued this area of inquiry with participants of the Pathways to Completion study (described above) where he serves as Co-Investigator. He is also currently a co-principal investigator on the HATS study described above. During the previous four years, Dr. Colson was an Assistant Professor in the School of Social Welfare, University at Stony Brook.

**Yael Hirsch, M.S.** is a researcher on the Pathways to Completion study. In this capacity, Ms. Hirsch is responsible for statistical analysis and database management, as well as summarizing the data for national and international conferences. She has extensive experience in designing and administering questionnaires, designing databases, and writing reports and presentations. She has also designed databases and analyzed the data for the LTBI Treatment Duration Preference Study in Harlem (see section 3.1.2.) and the Harlem DOPT program (see section 3.1.3.). In addition, she has also been involved in conducting the pilot studies regarding behavioral models (see section 3.1.1.), as well as analyzing the results. She also serves as a co-investigator on the HATS Study (described above). Ms. Hirsch has a Masters degree in Operations Research from the School of Engineering and Applied Science, Columbia University. She is currently completing an M.P.H. in Epidemiology in the Mailman School of Public Health at Columbia University.

**Bill Bower, M.P.H.** worked with international health programs for 20 years, first with community-based organizations and then as an Assistant Clinical Professor at the Mailman School of Public Health at Columbia University. He has focused on the training of lay health workers and physicians for community-level health interventions, and has contributed to several books and articles on training [184, 185] Thousands of participants in New York City, Latin America, Africa, and Asia have benefited from his practical, results-oriented approach to training and education. In the international arena, he developed, conducted and evaluated courses on management of primary health care (PHC)/maternal-child health/family planning programs. More recently, in the US he has directed TB education and training efforts for six years as a Research Scientist for the New York City Department of Health TB Control Program and with the Charles P. Felton National TB Center. In this capacity, he has been responsible for staff orientation and training, professional education conferences, public education about TB, and materials development/dissemination. He has overseen the process of development of numerous TB-related short courses for lay and professional health workers, as well as TB education brochures, posters, and videos.

**Charon Gwynn, Ph.D.** is an epidemiologist with experience in environmental issues and TB control. She has contributed to various human exposure and epidemiological projects and studied the impact of toxic air pollutants. Most recently, she has been the epidemiologist at the Charles P. Felton National TB Center at Harlem Hospital. In this capacity, she has developed a database for the capture of data on all patients who are screened for LTBI and those initiated on treatment for LTBI. In addition, she has also played a key role in developing strategies for the conduct of tuberculin skin test screening and for the organization of treatment of LTBI. She has also led the efforts for the analysis of data on treatment of TB disease, directly observed therapy outcomes and other programs at the Center.

**Sharon Mannheimer, M.D.** is an assistant professor at the College of Physicians and Surgeons of Columbia University. She has experience studying TB and HIV and has designed and conducted several epidemiological research projects. Dr. Mannheimer also performed an epidemiological investigation of multidrug-resistant
Sherry Glied, Ph.D. is a social scientist with expertise in immigrant community formation and in medical anthropology. She is the research coordinator for the HATS program described above. In this capacity, she is conducting a qualitative evaluation of this intervention and assessing a computer touch screen adherence questionnaire. She received her doctorate in Latin American history from the State University of New York at Stony Brook. She has conducted field research on peasant community formation in Bolivia and the Dominican Republic [188-190]. As a Rockefeller fellow at the Dominican Studies Institute, she studies Dominican immigrant community formation in New York. As a member of the Department of Puerto Rican and Hispanic Caribbean Studies at Rutgers University, she collaborated in curriculum development for women’s studies and Latino studies that incorporates medical sociology and medical anthropology.

Beverly E. Diamond, D.S.W. is the Informatics Core, Director at the Irving Center for Clinical Research (ICCR) at Columbia University. In this capacity is responsible for the multi-user computer and network and provides biostatistical and data management support to investigators. She has served as the Data Management Coordinator/biostatistician on a number of projects including the Muscular Dystrophy Study Group, the TMJ Osteoarthritis Study, the HIV Center for Clinical and Behavioral Studies and the Urban Health Institute. She is a non-voting member of the Scientific Advisory Committee for the ICCR and is responsible for reviewing the statistical and data management plans of studies submitted to the center. She is a co-investigator on the Harlem Adherence to Treatment Study (described above) (Sharon Mannheimer, Principal Investigator). In addition, Dr. Diamond served as statistical consultant to the Programs in Occupational and Physical Therapy and as an information specialist at the Naomi Berrie Diabetes Center both at Columbia University.

Marita K. Murrman, Ed.D. is an Assistant Clinical Professor of Public Health at the Mailman School of Public Health at Columbia University and the Director for Distance Education in the Division of Sociomedical Sciences. Prior to her current position at the School of Public Health, Dr. Murrman was Director for Professional Education at the CDC-funded Charles P. Felton National Tuberculosis Center where she designed, implemented and evaluated a two-year TB training program for medical residents. In addition, she assisted in designing education programs for health care workers in drug and alcohol treatment centers throughout the Harlem community. In addition, she has designed and implemented the peer training program for the ongoing Pathways to Completion and the Harlem Adherence with Treatment studies described above. She is the Principal Investigator for the Eliminating Health Disparities Through Research and Education Opportunities for Preventive Medicine Residents and Public Health Graduate Students training grant funded by the CDC as part of the Harlem Health Promotion Center.

Julie Franks, Ph.D. is a social scientist with expertise in immigrant community formation and in medical anthropology. She is the research coordinator for the HATS program described above. In this capacity, she is conducting a qualitative evaluation of this intervention and assessing a computer touch screen adherence questionnaire. She received her doctorate in Latin American history from the State University of New York at Stony Brook. She has conducted field research on peasant community formation in Bolivia and the Dominican Republic [188-190]. As a Rockefeller fellow at the Dominican Studies Institute, she studies Dominican immigrant community formation in New York. As a member of the Department of Puerto Rican and Hispanic Caribbean Studies at Rutgers University, she collaborated in curriculum development for women’s studies and Latino studies that incorporates medical sociology and medical anthropology.

Sherry Glied, Ph.D. is Associate Professor and Head of the Division of Health Policy and Management of Columbia University’s Mailman School of Public Health. She holds a B.A. in economics from Yale University, an M.A. in economics from the University of Toronto, and a Ph.D. in economics from Harvard University. In 1992-1993, she served as a Senior Economist for health care and labor market policy with focus on the problems of women and children. She is a recipient of a Robert Wood Johnson Investigator Award and has worked on mental health policy with focus on the problems of women and children.

4 Research Design and Methods
4.1 Overview of study:

The study will be a randomized clinical trial in which candidates for LTBI treatment will be randomized to experimental intervention versus current clinical practice (CCP). The experimental intervention will be based on Health Belief and the Precaution Adoption Process Models with enrichment with social support concepts. The experimental intervention will be primarily provided by peers who will deliver components tailored to PAPM stage and with the goal of moving the patient from one stage to the next with the ultimate goal of achieving treatment completion. A total of 360 patients will be enrolled who will receive the interventions for the duration of LTBI treatment. Questionnaires that evaluate adherence and other key demographic, social and behavioral characteristics will be administered at predetermined schedule. The primary outcome of the study will be completion of prescribed therapy on time.

4.2 Study Hypotheses

Primary hypothesis: We hypothesize that participants assigned the peer-based experimental intervention will achieve higher rates of completion of LTBI treatment than those assigned to current clinical practice (CCP) based on
criteria established by the CDC. These criteria depend on the ingestion of specific number of doses of medications within specific timeframes (See Appendix C).

**Secondary hypotheses:** We hypothesize that the peer-based experimental intervention will be more cost effective than current clinical practice and that specific socio-demographic and attitudinal factors will be associated with adherence.

4.3 **Study Objectives:**

1. **Primary objective:**
   To achieve targeted CDC-recommended LTBI treatment completion rates.

2. **Secondary objectives**
   a. To identify baseline demographic, clinical and social characteristics of patients that are associated with LTBI medication adherence.
   b. To determine the impact of baseline TB knowledge and attitudes on adherence with LTBI treatment.
   c. To assess impact of social support on adherence with LTBI treatment.
   d. To compare the effect of the interventions on self reported adherence rates.
   e. To assess impact of the interventions on completion of LTBI treatment beyond the CDC-recommended time frame.
   f. To determine the most effective component(s) of the intervention for enhancing adherence from the perspective of the participant.
   g. To compare the effect of the interventions on adherence with clinic appointments.
   h. To compare the participants’ self-reported adherence rates to the provider’s and the peer’s assessments of the participant’s adherence.
   i. To compare the participants’ self-reported adherence rates to the adherence as measured by MEMS caps.
   j. To compare the participants’ self-reported adherence rates with pharmacy record of medication dispensation.
   k. To compare the participants’ adherence collected via interviewer versus computer assisted touch screen.
   l. To assess the impact of the choice of the LTBI treatment regimen (i.e. short course versus long course regimens) on adherence and completion rates.
   m. To identify the impact of medication-related adverse events on the LTBI treatment completion rates.
   n. To assess acceptability of the intervention by the participants.
   o. To compare the costs of the two interventions.
   p. To compare the proportion of patients who had periods of interruption of LTBI treatment e.g. interruptions due to adverse events, non adherence, pregnancy, incarceration.

4.4 **Study Outcomes**

1. **Primary outcome:** Completion of LTBI treatment as prescribed in terms of recommended number of doses within the recommended time span.

2. **Secondary outcomes:**
   a. Participant baseline demographic, clinical or social characteristics that are correlated with adherence/non adherence.
   b. Baseline TB knowledge and attitudes that are correlated with adherence/non adherence.
   c. Baseline social supports that are correlated with adherence/non adherence.
   d. Adherence as reported by participant’s self-reported interview.
   e. Time required to complete LTBI treatment.
   f. Participant assessment of the intervention components (e.g. social support by peer worker, peer’s translation of medical information from the provider, medication reminders/chart, etc.) at the completion of the intervention.
   g. Adherence with clinic appointments.
   h. Peer and provider assessments of participant adherence.
   i. MEMS caps assessment of participant adherence.
   j. Pharmacy record of medication dispensing.
   k. Computer assisted touch screen assessment of participant adherence.
   l. Choice of LTBI treatment regimen correlated with adherence/non adherence and completion rates.
   m. Medication-related adverse events correlated with completion rates.
n. Participant assessment at the exit interview (upon completion) of the various components of the study including staff and setting

o. Cost of the interventions

p. Number and duration of treatment interruptions

4.5 Study Design

The proposed study is a randomized clinical trial that will compare the impact of enhanced, peer-based, social support on patient adherence to LTBI treatment versus that of those receiving the Harlem Hospital current clinical practices (CCP) procedures. The randomization of the participants will be stratified by the duration of prescribe LTBI treatment regimen duration (<2 months versus >2 months duration) to remove the possibility of confounding or effect-modification of these variables (See Appendix D for comparison of experimental intervention and CCP).

4.6 Study participant eligibility

Participants will be recruited from the Harlem Hospital TB Clinic and will include patients who are initiating treatment for LTBI. Providers in the TB Clinic use the latest CDC/ATS guidelines to determine candidacy for treatment of LTBI. Currently there are four drug regimens accepted by the CDC for the treatment of LTBI. Thus, the specific criteria used to determine participant eligibility is as follows:

1- Inclusion Criteria: Patients with the following characteristics will be eligible:
   • Recommended for initiation of a CDC recommended drug regimen for treatment of LTBI as per clinical guidelines
   • Able to tolerate prescribed drug regimen
   • Age of 18 years or older
   • Able and willing to sign consent form

2- Exclusion Criteria: Patients with the following characteristics will be excluded:
   • Ineligible for treatment for LTBI as per clinical guidelines
   • Receiving Directly Observed Preventive Therapy (DOPT)
   • Prescribed a drug regimen that is not recommended by CDC for treatment of LTBI
   • Evidence of active TB disease

4.7 Study Participant Recruitment, Availability and Retention

Tuberculin skin testing (TST) is performed at a variety of settings at Harlem Hospital Center and in the community. These include the Harlem TB Center, Infectious Diseases Clinic, medical clinics, inpatient wards and the Harlem community. Review of data for 1999 indicate that 348 patients were placed on LTBI treatment and that there were 1,911 visits for LTBI assessment and treatment. We anticipate that about 40% of those eligible for LTBI treatment will agree to participate in the study.

To enhance the generalizability of study findings, we plan to enroll a group of individuals with LTBI who are representative of the various stages of behavior change and thus with a broad range of adherence capabilities, rather than focusing on individuals who are likely to be more adherent. With this goal in mind, we will target for recruitment all individuals who are eligible for LTBI treatment and receive care at the TB Center. The collection of baseline data on the characteristics of these individuals will allow for an understanding of the patient factors associated with adherence. In addition, this diversity will give a clearer picture of the effectiveness of the proposed intervention and lead to more compelling findings.

The clinic provides comprehensive TB services, social services, substance use referrals, and patient education. The clinic’s population has following characteristics: 72% African American, 22% Latino, and 42% female, with an average age of 40. 38% history of homelessness and 48% foreign born. The majority of the clinic’s patients have Medicaid insurance or are uninsured, reflecting their low socioeconomic status. The patients are referred to the clinic from a variety of sources, including community providers, drug treatment programs, homeless shelters, the Harlem Hospital inpatient services and emergency room, and other Harlem Hospital clinics, as well as employee health services.

A marketing plan will be designed to recruit participants. It will target both the providers and the potential participants, and will include the development of flyers and brochures. The provider brochures will be distributed to clinicians and participant brochures will be distributed to eligible patients by the research staff. Further, information about these studies will be disseminated throughout the Harlem community via flyers and health education materials distributed throughout the Medical clinics and affiliated facilities, and handed out by outreach workers during presentations at local community centers, and neighborhood health fairs. Flyers advertising the study will be displayed prominently throughout the Hospital and at affiliated off-sites.

Recruitment will be via provider referral to the research staff and through active recruitment in the clinics. The research staff will review results of tuberculin skin tests at the various referral sites on a daily basis in order to identify potential study candidates. The staff will then directly contact the eligible candidates through their provider to inform them of the study and seek their participation.
4.8 The Intervention

The Tuberculosis Adherence Partnership Alliance Study will utilize the Precaution Adoption Process Model (PAPM) (See Section 2.6, Background and Significance) and compare it to Current Clinical Practice (CCP) in our clinical setting.

4.8.1 The Experimental Intervention:
The PAPM offers a stage model of health behavior change appropriate for the adoption of preventive treatment, particularly when the patient is asymptomatic as with LTBI treatment. The model posits seven stages of behavior change in response to a particular health concern. We have termed these stages: 1) “Unaware,” 2) “Unengaged,” 3) “Deciding,” 4) “Declined to Adopt,” 5) “Decided to Adopt,” 6) “Initiated,” and 7) “Completed.” We supplement the PAPM with constructs from the Health Belief Model and specific variables from the PAPM such as social support theory (see Section 2.6, Background and Significance).

The intervention will consist of two phases: 1) a cognitive phase which focuses on guiding participants toward making the decision to undergo LTBI treatment. This phase incorporates individuals in Stages 1, 2, 3, and 4; and 2) a behavioral phase which focuses on helping participants be adherent to LTBI treatment. This phase includes individuals in Stages 5, 6, and 7. The first phase will emphasize the use of such constructs from the Health Belief Model (HBM) as susceptibility, severity, perceived benefits, and perceived barriers. Additionally, the development of self-efficacy will be emphasized and informational and instrumental forms of social support will be offered. In the second phase, greater attention will be given to HBM constructs such as cues to action and self-efficacy, along with emotional and appraisal forms of social support.

The experimental intervention is comprised of three components: health education, social support, and assistance in overcoming tangible barriers to adherence. The participants’ readiness for behavioral change will be assessed with the PAPM staging questionnaire at baseline and at regular intervals thereafter (see Study Measurements, section 4.11 below). Based on this classification, participants will be treated with the appropriate protocol for that stage.

All processes are designed to encourage participants to move through the stages toward treatment completion. The PAPM stage model will not be applied rigidly but rather will offer suggestions for intervention elements to be emphasized as participants move through the stages. The model acknowledges that participants may progress through several stages rapidly, as they receive information and quickly make decisions (Weinstein et al. 1998). It does not assume that progress through the stages will necessarily be unidirectional, as changes in the patient’s perspective and/or circumstances may cause participants to return to earlier stages.

The intervention will be implemented through the use of peer workers, caseworkers, and health educators who will tailor their efforts to the specific issues associated with each stage (see Patient Precaution Adoption Process Model Stages in Appendix E). The experimental intervention will build on previous TB studies which have demonstrated the efficacy of using peer support in achieving health protective goals [138, 139, 194]. Experimental subjects will be paired with a peer worker who is a graduate of a self-administered LTBI treatment program. The specific tasks of the peer workers, caseworkers, and health educators are outlined below.

**Stage 1: “Unaware”:** The intervention goal in this phase is to address participants’ feelings of perceived threat; that is, the severity of the disease and their susceptibility to it. Persons in the first stage (“Unaware”) simply have no knowledge of the treatments for LTBI. Nor have they thought about the risk of TB to themselves or their friends, family or significant others. It is unlikely that we will identify many individuals in Stage 1 as enrollment occurs following tuberculin skin testing (TST).

The study-specific health educator will provide information in such a way to help participants in Stage 1 acknowledge the risk of TB and its seriousness. Information will include basic information on TB disease and LTBI: how it is transmitted, what the symptoms are, and how one can protect oneself.

**Stage 2: “Unengaged”:** Persons in the second stage (“Unengaged”) are aware of TB and LTBI treatment, but have not personalized this information. Most likely, such individuals continue to have weak feelings of perceived threat; that is, they perceive themselves to be at low risk for developing TB disease. The goal of this stage is to lead the participant into seriously considering LTBI treatment. This involves several efforts: health education, social support to influence the participant’s decision-making process (informational support), and addressing tangible barriers to treatment adherence (instrumental support).

The study-specific health educator will provide health information about TB that will include specific information about tuberculin skin testing (TST) and LTBI treatment. These materials, which will be personally tailored to the participant’s needs and capacities, will include fact sheets and personal assessment exercises regarding susceptibility to TB infection and disease, severity of TB disease, perceived benefits of treatment, and perceived risks.

Peer workers will offer informational and instrumental forms of social support. Through written materials or in groups, they will discuss their own experiences in learning that they were at risk for TB and a candidate for LTBI treatment (appraisal support). These conversations will also impact on participants’ feelings of susceptibility and the severity of the disease, enabling participants to view their behaviors in a different light. Such discussions
will lead participants to consider the impact of their behaviors on their families, friends, and others in the community (self-evaluation).

Participants who experience tangible barriers to treatment, such as housing, entitlements and other needed services, will be referred to caseworkers in the TB Clinic, Harm Reduction Program, or other Harlem Hospital departments. Much of this work will undoubtedly focus on substance use issues, given the high prevalence of this problem in the Harlem patient population.

**Stage 3: “Deciding”:** Persons in this stage have acknowledged the import of their situation vis-à-vis LTBI, but have not yet made the decision to initiate LTBI treatment. However, they are actively involved in the process of weighing various alternatives. While material on perceived threat (susceptibility and severity) will continue to be presented, more attention is now given to the perceived benefits and perceived barriers encountered by the participant. The goal of this stage is to provide information to suggest that the perceived benefits of LTBI treatment outweigh the perceived barriers. This is accomplished through modifying the individual’s feelings of “unrealistic optimism”[195].

Intervention efforts in this stage will continue to focus on informational support from peer workers and the study-specific health educator. The peer workers will provide personal testimonials, sharing their own decision process in choosing to undertake LTBI treatment and their subsequent experiences which reflect on that decision. They will frankly discuss the benefits of and barriers to initiating LTBI treatment. Additionally, the peer workers will address issues which may impact LTBI treatment, such as substance use and homelessness. They will continue to provide instrumental support in helping participants obtain needed services to address these issues.

As in the previous two stages, the study-specific health educator will present individualized materials in an attempt to influence participants’ feelings of susceptibility. Caseworkers will continue to address life circumstances which present a potential barrier to treatment initiation and/or completion.

**Stage 4: “Declined to Adopt”:** Individuals in this stage have made a conscious decision not to commence LTBI treatment. However, this decision may be motivated by several factors. Some may simply want more time to think it over and thus have refused to start treatment. Others may have faulty information. For example, some individuals who are over the age of 35 or who were vaccinated with BCG may not be aware of current guidelines regarding these circumstances. Some may be motivated by a fear of side effects, particularly if they are currently receiving other treatments. And still others may be unwilling to adopt a new precautionary behavior; that is, they may not have internalized the value of taking preventive medications when they experience no symptoms.

Intervention efforts for Stage 4 individuals will be focused on the study-specific health educator, who will meet individually with participants to ascertain their reasons for not initiating LTBI treatment. Special emphasis will be given to the efficacy of current LTBI treatments, individuals who are appropriate candidates for LTBI treatment, and the management of side effects.

When appropriate, existing social support networks will be used. Family members, ministers, or other influential individuals may be enlisted in an effort to reinvigorate the benefits of completing LTBI treatment. Individuals who experience tangible barriers to treatment, such as homelessness or child care responsibilities, will receive assistance from caseworkers.

**Stage 5: “Decided to Adopt”:** Participants move to the “Decided to Adopt” stage when they express the intention to start LTBI treatment. The goal of the intervention in this stage is to help participants develop an actual plan or system for being adherent with the therapy. This involves the following objectives: 1) assisting the participant in fitting the regimen to his or her lifestyle and circumstances; 2) encouraging a commitment to adherent therapy; and 3) offering specific forms of social support for starting therapy.

Peer workers will provide emotional and appraisal support in this stage. Each individual will be assigned a peer worker - individuals who themselves have completed LTBI treatment, are from the Harlem community, have good communication skills, and are committed to controlling TB. Together they will work out a plan for the participant’s taking medication – a plan that fits the individual’s particular needs and barriers. The greater part of this plan will involve identifying appropriate cues to action. Such cues may consist of checking off days on a calendar, having a beeper-type alarm, or placing the pill bottle with LTBI medicines next to one’s toothbrush. The study-specific health educator will provide educational materials based on Health Belief Model constructs and specific PAPM variables, such as susceptibility, severity, perceived benefits, perceived barriers, and self-efficacy. Additionally, in their monthly meetings with patients, providers will also stress the importance of being adherent to LTBI treatment, thus serving as one of the most important cues to action.

The peer workers will discuss their personal experiences with LTBI treatment, emphasizing the positive outcomes they have experienced by confronting the situation and commencing treatment. These interactions will reinforce the idea that participants can change and commit to therapy, thus enhancing their feelings of self-efficacy. They will also offer emotional support by fostering an atmosphere of trust where relapses from medication adherence are viewed not as reasons for condemnation but rather opportunities to examine flaws in the original plan. Peers will serve for many participants as their new community or surrogate family.

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In this and succeeding stages, caseworkers will be available on an as-needed basis to assist participants in coping with personal problems that may interfere with treatment, such as loss of housing, income or benefit interruptions, conflicts with significant others, or relapse to substance use. It is anticipated that such problems will arise on a sporadic for most participants and may threaten ongoing progress.

**Stage 6: “Initiated”:** Participants move into the “Initiated” stage when they begin LTBI treatment. The goal of the intervention in this stage is to achieve continued adherence, which is accomplished through: 1) helping participants to identify and resolve difficulties in their medication plans; 2) providing emotional and appraisal support for adherence; 3) helping participants to incorporate adherence in their lifestyles; and 4) identifying and avoiding relapse situations.

The individualized intervention will capitalize on the personal experiences of the peer worker to provide social support and practical advice for adherence. Participants will meet at least weekly with their peer workers either in person or over the telephone to discuss their experiences and problems with treatment. These discussions will focus on helping participants create appropriate cues to action, teaching participants tips for remembering to take medications and for avoiding “triggers” for non-adherence (e.g., negative feelings about themselves, situations where they are tempted to engage in substance abuse). The peer workers will use appraisal support in acknowledging their clients’ successes. Such experiences will likely reinforce participants’ growing feelings of self-efficacy.

Peer workers will provide instrumental support through system navigation to provide participants with help in obtaining needed services and in supporting them during monthly clinic visits. In situations where it is appropriate, the peer workers will enlist help from members of the participant’s existing support network. When the participant relapses to non-adherence, the peer worker will help him or her reestablish adherence with a nonjudgmental attitude. While much of their work together is focused on adherence to LTBI treatment, peers will continue to assist participants in dealing with other life problems (e.g., housing, income, substance use). When specific referrals are needed, peers will refer participants to caseworkers (e.g., referrals to substance abuse treatment programs or other services, advocating for the participant with housing or entitlement programs).

Support groups will be available for participants in the “Initiated” stage, facilitated by the study-specific health educator and peer workers. These groups will provide participants with the opportunity to discuss specific issues around medications and adherence while also receiving emotional support from persons in similar circumstances. Group discussions will address participants’ perceived benefits and perceived barriers to treatment, including stigma, the difficulties of the regimen, taking medications when asymptomatic, medication side effects and dealing with specific triggers for non-adherence such as substance use. Certificates, prizes, and informal celebrations will be used to acknowledge and reward those who have been adherent.

**Stage 7: “Completed”:** The “Completed” stage begins when participants feel comfortable with the new behavior which they have adopted. While the turning point will vary greatly across individuals, many on LTBI treatment will feel that their new habit has become engrained approximately four months into a six or nine-month regimen. For such individuals, the cues to action and perceived benefits have led to a successful outcome. Peer workers will continue to provide emotional and appraisal support for staying adherent, but will also help participants to address triggers for relapse. Common causes for adherence relapse include deaths of family members or friends, diagnosis of serious illness (HIV infection) and relapse into substance use. When it does occur, peer workers will provide emotional support to reinforce the participant’s capacity to be adherent.

The high point of the intervention occurs when participants have taken the CDC-recommended number of doses within the recommended time frame. While they have “Completed” the regimen, several important steps remain. The participants’ success at completing treatment is publicly acknowledged in a “graduation” ceremony. While reinforcing the participant’s feelings of satisfaction, such events also bolster feelings of self-efficacy, which may then carry over to other health-protective behaviors such as HIV prevention measures. The graduates will be encouraged to develop, and share with others, their personal stories about how they began treatment and how they overcame problems with the regimen. They will then be invited to share these experiences, either as volunteers or as peer workers. Also, the study-specific health educator will provide information about signs and symptoms of active TB disease, including the fact that routine follow-up x-rays are not necessary.

**4.8.2 Current Clinical Practice (Control) Group:**

The control group will receive the current clinical practice of LTBI treatment at Harlem Hospital (see Appendix D). This is consistent with current clinical practice at other sites throughout the country. Activities utilized to ensure adherence in the CCP include patient education, frequent follow-up visits, incentives to cover transportation costs, and prescription refills. At monthly follow-up visits, providers and other Clinic staff will review patient medications, dosages, specific instructions and potential adverse effects, along with discussing adherence. Patients are routinely sent reminder calls prior to scheduled monthly follow-up visits. A variety of existing support groups are available for participants in this group, mainly through the Harlem Harm Reduction Program, including stress management, women’s groups and groups addressing substance use. Social services are also available through the assigned caseworker in the TB Clinic.
Clinical providers play a key role in providing cues to action when they communicate with patients. It is essential that they, together with the entire health team, use consistent messages about who should be screened for LTBI, who should be treated, options for regimens, procedures for monitoring and the importance of adherence. Training for providers will be conducted on-site at the Charles P. Felton National TB Center. Content will be as outlined in the new ATS/ALA.CDC Statement on Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection (in press). Former commonly held beliefs, such as “BCG always causes a positive TST” and “people over 35 years of age should not take LTBI treatment” will be dispelled. Decision making and communication skills will be emphasized about skin testing and treatment of LTBI to all health staff. In addition, a provider reminder card has been developed (See Appendix K) in order to have these guidelines within provider reach at all times.

4.9 Staff/Peer Recruitment and Training

4.9.1 Peer Workers:
The role of the peer workers will be to provide various forms of support and to serve as role models in order to help patients with LTBI better adhere to treatment. Peer workers will stress benefits of treatment, assist in overcoming barriers, identify cues to action and increase self efficacy.[131]. Special care will be taken in identifying and recruiting those individuals who are, or have the potential to be, natural helpers.

Qualifications: Peer workers will have had LTBI and completed treatment at Harlem Hospital; have a reputation amongst professional staff for having good judgment, giving sound advice, being discrete, and demonstrating a capability to be empathetic. Additionally, peer workers will embody the combination of social, cultural, ethnic, environmental, and communication values, norms, and beliefs of other patients with LTBI and are eligible for its treatment. Peer workers will report directly to the program coordinator.

Training for peer workers will reflect both their existing roles as patients who have completed treatment for LTBI who are/were adherent to therapy and those proposed in the intervention. This effort will build on the successful training of peer workers for the Pathways toCompletion and HATS. The overall purpose of training will not aim to change peer workers or to have them mimic professionals. Rather, the training program will be designed to enhance the peer workers’ role of helping and advising in a way that is consistent with moving patients in the experimental group from one stage to the next.

The initial training program will last at four weeks and will be divided into afternoon and morning sessions. Content for the afternoon sessions will be grouped into two broad categories that are intended to enhance the peer workers’ ability to provide different forms of social support [130]. First, “TB/LTBI Knowledge” sessions will focus on strengthening peer workers’ emotional and appraisal support skills by fostering discussion of fears that patients may have about TB disease, LTBI, and LTBI treatment regimens, and by role playing possible responses to patients in different stages of change. These sessions will also cover practical topics designed to increase the peer workers’ comfort in providing information and instrumental support, including information about TB and HIV-related services offered throughout Harlem Hospital and the local community. Second, “The Role of the Peer Worker” sessions will use interactive exercises to more explicitly endow the peer workers with the skills needed to become effective providers of all types of social support. These sessions will focus on: working with patients one-on-one in a supportive way (“How to give advice and assistance”); facilitating individual participation (“Leading a good discussion”); and developing actual medication taking plans (“How to plan for the future”). Peer workers will also be given opportunities to practice using the program’s custom-developed education brochures, learning how to match patient’s questions and concerns to specific segments of the brochures. The final afternoon sessions will acquaint the peer workers with the concept of evaluation, explaining both the rationale for monitoring peer workers’ activities (“Finding out what works”) and the steps that peer workers can take to keep track of what they do.

Morning sessions will be devoted to observational/experiential learning where peer workers will be assigned to “shadow” different health professionals in order to understand the role and function of each team member. At the conclusion of each morning session, peer workers will be required to complete a brief checklist specifying who they shadowed and what they saw related to the type of social support provided. These experiences will provide the context for the afternoon discussions.

Study investigators and other experts at the institution will serve as trainers for all sessions in the “TB/LTBI Knowledge” category. Dr. Colson and the coordinators of the Pathways to Completion and HATS Studies will serve as trainers for the “Role of the Peer Worker” sessions. The TAPAS program coordinator will serve as trainer for sessions related to reporting and evaluation, and he/she will be responsible for developing morning shadowing assignments. In addition, ongoing education sessions will be provided monthly to review and reinforce key concepts and skills from the initial training and to update workers on new developments in LTBI management.

4.9.2 Health Educator

Qualifications will include a bachelor’s degree (or preferably a masters) in health education or a related discipline, and at least three years of experience in health education. Excellent skills in communicating and writing are essential. Familiarity with NYC health care institutions, knowledge of tuberculosis, and ability to speak Spanish or French are desirable. The health educator will report directly to the program coordinator.
Training for the health educator will include completion of the CDC self-study modules on Tuberculosis 1-9, as well as attending the basic TB Control course offered by the New York City Department of Health Tuberculosis Control Program. Other on-the-job training and outside short courses will be arranged, as needed. In addition, the health educator will receive intensive training on counseling techniques, adherence and behavioral models.

4.10 Study measurements

Several instruments will be utilized to collect data from study participants. Appendix F includes copies of all the questionnaires to be used in the study and Appendix G shows schedule of administration of the questionnaires.

1. Measures of Adherence

While no gold standard exists for measuring medication adherence [196], several different methods have been utilized with varying success. Methods include indirect measures such as self-report, physician assessment, electronic monitoring devices, pill count, medication refill rate, monitoring for an expected therapeutic outcome, and direct measures such as direct observation, measuring levels of the drug or tracer compounds in body fluids, biologic markers and monitoring clinic attendance. In general, direct methods are more objective and yield more reliable assessments of adherence, though each method has limitations [197]. Problems with serum or urine therapeutic drug monitoring include a lack of information about non adherence between measures, inconvenience, expense, and the fact that levels are subject to the variability of individual pharmacokinetics [25, 53, 198, 199].

We elected not to utilize additional adherence measures such as pill counts which cannot determine whether pills were ingested or discarded, when they were ingested, or whether the appropriate number of pills were taken at the correct intervals [31, 53, 200-202]. Pill counts have been shown to overestimate adherence [201, 202] and are not widely used in clinical practice because of the difficulty of ensuring that all pills are brought back to clinic. Self-report, however, has the advantage of potentially revealing the reason for non adherence. In this study, we plan to use a combination of tools to assess adherence, including the indirect measures of self-report, peer and provider assessments, medication refill rate and electronic monitoring devices, and the direct measures of clinic attendance. We have chosen these measures because they are informative, easy to use and replicate, and are not too costly or cumbersome for this patient population.

a. Self-report adherence questionnaire: We developed an adherence assessment instrument to obtain self-reported adherence with LTBI medications from those participants receiving LTBI treatment. The questionnaire will be administered every 2 months by research assistants blinded to the participant’s group assignment. This questionnaire evaluates adherence through an in-depth assessment of pill-taking behavior during the prior 3 days, while also asking about general adherence during the previous weekend and the more remote past. Such careful questioning has been shown in prior studies to yield correct information, particularly when obtained in a nonjudgmental manner [201, 203, 204]. Limiting the recall to a recent period of time has also been shown to enhance the accuracy of self-report [205]. While some studies have found this method of interviewer-based self-report to overestimate adherence [206, 207], self-report has the advantages of being quick and inexpensive as well as being the only method that can provide the reason for non adherence [25, 201]. This instrument will be administered at month 1, month 2, and every 2 months (during treatment) and at completion of therapy.

b. Computer touch-screen adherence questionnaire - Since written self-reports have been shown, in some settings, to provide more accurate information than that obtained through interview [205], a computer touch-screen adherence questionnaire will be evaluated as well. The computer touch-screen technology has been previously utilized for many functions, and even populations with limited education and interaction with computers have felt comfortable with the touch-screen technology [208]. This technology was perceived as more confidential [208], and the results have been shown to be more accurate than with traditional modalities [209]. An audio component will facilitate use of this technology for persons with low literacy for whom written, nonverbal questionnaires are not possible. This questionnaire will be administered at month 1, 2, every 2 months (while on treatment) and end of treatment.

c. Confidential adherence scale: Participants receiving LTBI treatment will also be asked to complete in private a one-page confidential self-reported scale. The participant will be asked to indicate their degree of adherence/non adherence during the prior week and then leave it in a sealed envelope for the research assistant. The adherence scale results will be compared to the adherence questionnaire results to assess for social desirability bias with the questionnaire, and will not be used as the primary endpoint. This will be administered at month 1, month 2, every 3 months (while on treatment) and end of treatment.

d. MEMS: Prescription bottles equipped with the Medication Event Monitoring System (MEMS®) cap will be distributed and collected at each monthly visit. The MEMS utilizes an electronic device that is placed into the cap of the prescription bottle and records the date and time that the cap is removed. Alternative measures of adherence, such as pill counts and urine tests, have been shown to overestimate drug intake when compared to the MEMS [202]. And while it does not prove actual ingestion of the medication, it has been demonstrated to be a reliable method for assessing compliance[74, 210, 211]. The use of the MEMS caps will allow for the reliable assessment of adherence to treatment of LTBI in this study. The MEMS data will be collected at monthly intervals during treatment period.
e. Clinic visit adherence: Adherence with clinic visits will be tracked for all participants throughout the study by the research assistants, who will abstract information from clinic charts and clinic schedules. Adherence with clinic visits is a secondary outcome. Previous studies have demonstrated that poor clinic attendance can be a good indication of non-adherence [212, 213].

f. Provider assessment: An estimate of adherence will also be collected from the provider at baseline and month 1, 2, and every 2 months (while on treatment) and end of treatment. Though providers have been shown to be poor predictors of adherence [29, 31, 214], these studies were conducted among medical interns and residents and not experienced clinicians with long-term patient-provider relationships. Provider adherence assessments will be compared to self-report and provider adherence assessments and will not be used as the primary endpoint.

g. Pharmacy records: All patients receiving LTBI treatment obtain their medications from the pharmacist assigned to the clinic. Data on dispensing of the medications to each participant will be collected on a monthly basis.

h. Peer assessment: For participants receiving LTBI treatment who are assigned the experimental intervention and assigned peer worker, estimates of participant adherence will also be collected from the peer at month 1, 2, every 2 months (while on treatment) and at end of treatment. Peer assessments will be compared to self-report and provider assessments and will not be used as the primary endpoint.

2) The PAPM Staging Questionnaire: This questionnaire will be administered to all study participants prior to randomization to determine their stage according to PAPM at study entry. The questionnaire was developed for this study, by the study team and was piloted on a random sample of 15 patients eligible for LTBI (see Preliminary experience, section III.A.1.a. These data will also be utilized to guide the intervention for participants randomized to the experimental group (see Intervention, section 4.8). The staging will be done at baseline, month 1, 2, every 2 months during treatment and end of treatment.

3) Perceived benefits/perceived barriers: An assessment questionnaire was developed for this study to measure the participants’ assessments of the benefits of and barriers to adherence with LTBI medications. The questionnaire was based on decisional balance scales developed for contraceptive use[215], with the content of the benefits/barriers incorporating input from providers and patients currently on treatment for LTBI. Research assistants will administer the questionnaire at baseline, month 1, 2 and at completion of treatment.

4) Self-Efficacy: A self-efficacy assessment questionnaire was developed for this study to measure a participant’s perceived ability to be adherent with LTBI medications. This questionnaire was based on scales developed for contraceptive use by[215], with the content incorporating input from patients and providers. Research assistants will administer the questionnaire at baseline and at month 1, 2 and at completion of treatment.

5) Participant demographic characteristics that may affect adherence will be assessed through questionnaire administered by research assistants at baseline and at completion of therapy. A detailed questionnaire originally developed for a TB adherence study will be used to assess baseline demographics including age, gender, race/ethnicity, education level, socioeconomic status, type of residence/dwelling and marital status [216]. A brief follow-up questionnaire will be utilized at end of treatment to address demographic factors that could change during the study such as employment, housing status and current marital/relationship status (see Appendix J).

6) Substance use information will be collected using the alcohol/drug use section of the Addiction Severity Index (ASI). The ASI has established reliability and validity across various populations and has been utilized in over 2,000 drug/alcohol treatment facilities, including the Harlem methadone maintenance treatment programs[217]. The section on alcohol/drug use will be used to collect information on the use of various types of substances, such as alcohol, opioids, stimulants, sedatives/hypnotics, hallucinogens, and others (e.g. marijuana and solvents). Route of administration and current and past patterns of use are also elicited, in addition to participation in substance use treatment. Data will be used to categorize participants as substance and non-substance users, as well as to quantify the degree of substance use. This survey will be administered at baseline, month 1, 2 and completion of treatment.

7) Knowledge and attitudes concerning TB treatment will be assessed at baseline using an instrument developed by the investigators[218] [219]. Knowledge items will assess participants’ information on such issues as TB transmission, symptoms, testing and treatment. Attitudinal items will be based on constructs suggested by various theoretical models, including the Health Belief Model [37], Social Learning Theory [107], the Theory of Reasoned Action [220] and Social Action Theory [126]. Constructs include intentions, perceived risk, perceptions of group norms, self-efficacy, cues to action and costs and benefits. This survey will be administered at baseline and at completion of treatment.

8) Social supports and social networks will be assessed with the Norbeck Social Support Questionnaire [221] at baseline and at completion of therapy. This instrument measures 3 overall variables: Total Functional, Total Network and Total Loss (individual items include tangible, emotional and informational support, reciprocity, size of network and frequency of contact). Internal consistency was tested through
intercorrelations for these variables; these intercorrelations ranged from .54 - .98. Test-retest reliability coefficients ranged from .85 - .92.

9) **Quality of life** will be assessed at baseline and at completion of treatment using the SF-12 [222]. The SF-12 assesses eight health concepts: limitations in physical activities, limitations in social activities, limitations in usual role activities due to physical or emotional problems, bodily pain, general mental health, vitality and general health perceptions. The SF-12 has been shown to retain the reliability and validity of longer forms of the Medical Outcomes Study instruments [223]. Internal consistency coefficients were greater than .78 for all but the role function scale (0.50).

10) **Life events** (both negative and positive) that can affect adherence, such as death of a spouse, loss of housing or new employment, will be assessed using an instrument developed by Dr. Sally Findley, a co-investigator on a number of previously described TB programs, and others for the REACH Asthma Study at Harlem Hospital [224]. This survey will be administered at baseline and completion of treatment.

11) **Mental health** will be assessed at baseline utilizing the Brief Symptom Inventory [225], a 53-item scale with nine symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. Internal reliability coefficients for all nine dimensions ranged from .71-.55; test-retest reliability coefficients ranged from .68-.91 for all dimensions and .90 for the global score).

12) A brief standardized version of the Marlowe-Crowne Social Desirability Scale questionnaire will be conducted at baseline and at completion of therapy to control for the possible effect of social desirability responses on participants’ self-reported adherence. A 13-item form of the Scale was highly correlated with the original Scale (r = .93). The internal consistency reliability coefficient was .76 [226].

13) **Health utilization** will be assessed using a questionnaire developed by the investigators for the Pathways to Completion Study and will be administered on a monthly basis during treatment. It assesses utilization of health resources including outpatient, emergency and inpatient services, as well as use of drug treatment services. This information will be used for cost benefit analysis.

14) **Participant assessment of the intervention components** will be elicited using a questionnaire at an exit interview conducted at intervention completion. All participants will be asked about their perceptions of their provider, the nature of their patient-provider relationship, the other clinical staff members and the clinic setting. Participants in the experimental group will be asked what the most helpful component was for them. They will also be asked to evaluate the usefulness of each of the specific components and for those assigned peers to evaluate their assigned peer worker.

15) **Peer contact with participants will be tracked using the Peer Contact Form:** This form will be used by the peer workers to document the frequency and types of contacts with participants, including telephone contact, home visits, referrals and follow-up of referrals. The health educator will assess these forms weekly to ensure consistency of the intervention.

16) **Literacy questionnaire (REALM):** The Rapid Estimate of Adult Literacy in Medicine (REALM) will be used at baseline to assess participants' ability to read common medical words and lay terms for body parts and illnesses. It is designed to assist medical professionals in estimating a patient's literacy level so that the appropriate level of patient education materials or oral instructions may be used. Literacy has been correlated with adherence levels.

### 4.11 Study Workplan

#### 4.11.1 Study Team

The study team will consist of the investigators discussed above and an appropriate staff recruited and trained to implement the study. The investigators have diverse experience and expertise including: TB, study design, clinical trials, behavioral interventions, peer programs, training/education, biostatistics and epidemiology. The principal investigator will be responsible for the overall conduct of the study. The investigators will meet on a biweekly schedule during startup period and monthly basis thereafter.

The study staff will consist of a program director, a health educator, two research assistants, five peer workers and an administrative assistant. The team will meet on a weekly basis to discuss study progress. In addition, case management meetings will take place on a weekly basis to ensure that all the patients enrolled in the study are appropriately managed.

#### 4.11.2. Study Team Responsibilities:

- **The study coordinator** will oversee the progress of the study, supervise its staff, maintain regular communication with the research team, and participate in the case management meetings. She/he will randomize participants into the intervention and control groups, will supervise the peers and monitor the relationships between peers and participants.
- **The research assistants** will recruit study participants, administer baseline questionnaires and staging questionnaires, and collect adherence measures. Dr. Diamond and Ms. Hirsch will supervise the data entry and maintenance of the database.
The **health educator** will develop health education materials and activities tailored to facilitate the participants’ movement through the stages of the PAPM. He/she will also develop marketing plan for the study and educational materials for the providers and will develop support groups for participants in the enhanced experimental intervention group as well as regular support for the peer workers. The health educator will also participate in case management meetings.

The **peer workers** will use individualized education and motivation strategies appropriate to the PAPM stage in weekly meetings with the participant at the clinic, home, or other agreed upon site. Health education will include risks of TB disease, the benefits of LTBI treatment, and potential side effects from medications. They will provide individualized informational, appraisal and emotional support to participants in the intervention group and will attempt to increase perceived benefits, identify cues to action and promote self efficacy. They will facilitate communication between participants and providers, escort participants to appointments, and participate in case management meetings (see section 4.8 for details).

**Administrative Assistant:** He/she will be responsible for administrative duties related to all research activities, including processing correspondence and reports. The Administrative Assistant will also be responsible for maintaining research charts, duplicating questionnaires, sending reminder notices to study participants, assisting in tracking efforts, and preparing meeting arrangements

### 4.11.2 Participant Management

Study participants will continue to receive their LTBI treatment by their care providers. The study will not interfere with treatment decisions by their providers.

- **Informed consent:** A written consent will be obtained from participants after informing them of study details.
- **Baseline evaluation:** At the baseline evaluation, all participants will be asked to complete a variety of questionnaires to gather information about adherence (for persons already receiving LTBI medications), stage according to PAPM model, perceived benefits/perceived barriers, self-efficacy, demographic characteristics, knowledge and attitudes about TB and TB treatment, literacy, substance use, mental illness, social supports and quality of life (see Study Measurements, section 4.10. above). Questionnaires will be administered by research assistants who are not involved in the care of the participant and are blinded to their study arm assignment. Incentives will be provided for transportation costs. The medical record of participants will be reviewed to obtain the currently prescribed regimen.

Upon completion of the baseline evaluation, participants will be randomized to either the experimental or current clinical practice (CCP) arm of the study.

- **Follow-up evaluation:** Participants in both groups will continue to be followed by their providers (typically at 1-month intervals). All study participants will be asked to complete follow-up adherence (for those receiving medications), perceived benefits and barriers, and self-efficacy questionnaires administered by research assistants at intervals described above (See Appendix G for schedule). Additional participant questionnaires will address knowledge and attitudes about TB, social supports, substance use, quality of life, life events and social desirability, as well as specific demographic characteristics such as current insurance, employment and housing status. Research assistants will track clinic visit attendance, medication refill rates and MEMS caps throughout the study. Additionally, hey will obtain the adherence assessment data from the providers for all study participants.

Participants assigned to the experimental group will receive an intervention designed for their specific baseline stage (see Intervention, section 4.8.). This will include varying degrees of case management, health education, support groups and social support provided by peers. For those participants assigned a peer, their individual peer worker will complete questionnaires during the intervention to estimate the participant’s adherence with LTBI medications. Peers will keep track of all contacts with participants using an instrument initially designed for the Pathways to Completion Study (see Appendix N, Peer Contact Form). Weekly participant case-management meetings will be conducted by the study coordinator and will include all peer workers. These meetings will focus on the peer activities and monitor the progress of participants in the experimental group.

- **Exit interview:** A detailed questionnaire will be administered to each participant at treatment/intervention completion to elicit participants’ evaluation of the intervention and its components. Participants in the experimental group will be asked which facet of the intervention, if any, benefited them the most and then the specific aspects that were most helpful. Participants will also be asked to evaluate the various components of their clinical care including their provider, the setting, nursing staff, clerical staff and peer worker (if applicable).

Study timeline: *(See Appendix H for timeline)*

**Phase I – Startup period** *(September 29, 2000 – March 31, 2001): During the first six months of the project we will 1) recruit and train project staff, 2) recruit and train the peer workers for the experimental arm of the study, 3) finalize participant recruitment procedures, 4) develop marketing plan, 5) develop study-specific educational materials and 6) develop a database and tracking system.*
Phase II – Participant recruitment, tracking, and assessment period (April 1, 2001- March 31, 2005): During the next four years, participants will be actively recruited and enrolled into the study (see Recruitment, Section4.7). During this period we will 1) recruit participants for the study, 2) conduct baseline assessments, 3) randomize participants to the experimental and control groups, 4) conduct the intervention, 5) administer the follow-up questionnaires, 6) collect other measurements, and 7) continuously attempt to retrieve any missing data and track participants. Study participants will be tracked and assessed with formal questionnaires at regular monthly intervals when they are resupplied with medications to treat LTBI. (Participants on 2-3 month regimens will be assessed every two weeks.) Participants in the peer group will have additional (at least weekly) contacts with their peer workers. The intervention will last for the duration of treatment, depending on the regimen prescribed for treating LTBI. Additional activities during this period will include: 1) data entry for all initial and follow-up assessments, 2) weekly case management conferences to discuss the status and progress of participants in the experimental arm of the study, 3) ongoing training and retraining of peer workers as needed, 4) monitoring of program staff activities, and 5) monthly record reviews of key follow-up measures.

Phase III – Analysis and reporting (April 1, 2005 – September 29, 2005): In the last phase of the project, staff will complete data entry, clean data, and prepare analyses of the study groups. This analysis will begin as soon as the first study group has completed all follow-up. Activities in this phase include 1) estimation of treatment completion in the two groups, 2) analysis of treatment effects on adherence as well as on laboratory markers of adherence, 3) comparison of the different methods used to measure adherence, 4) determination of correlates of adherence, 5) assessing the impact of the interventions on adherence rates, 6) analysis of participant feedback about components of intervention, and 7) comparing changes in PAPM stage during the study in the two groups, and 8) synthesis, report writing and dissemination of results.

4.11.3 Data storage and management

Two separate data systems will be developed. The first system will be a tracking system developed in Microsoft Access. The tracking system will contain contact information allowing the research team to maintain close contact with the study participants. This system will include a tickler system that will produce reminders of upcoming events and a security system. The security system will give access only to those persons in need of this information to complete the tasks of their position maintaining confidentiality for all research participants. This system will be updated on a daily basis.

A separate system also in Microsoft Access, will be developed for the entry and storage of research data. Double data entry will be performed. Data fields in this system will be restricted to valid responses to eliminate out of range entries. For example, an item requiring a yes/no response will accept only those two possibilities. Pull-down menus will be available for each item with the range of possible responses. Data will be entered into this system on a weekly basis. Weekly error reports will be produced and relayed to the appropriate research staff. Data from both systems will be stored on the Sun Ultra2 located in the Irving Center for Clinical Research (ICCR). This system is backed up on a nightly, weekly and monthly basis and tapes are stored in fire-proof cabinets in the office of the Director of the Informatics Core. This office is located in a different building from the computer. A second set of monthly tapes will be stored in the office of the Principal Investigator at Harlem Hospital. Data analysis will be performed using SPSS 10.0 and EPI-INFO 5.1. EPI-INFO will be used for relative risk ratios. SPSS will be used for descriptives and all multivariate statistical analysis. DBMS/Copy will be used to transfer data from Microsoft Access to the statistical packages.

4.11.4 Statistical Methods and Data Analysis

a) Randomization Plan: Study participants will be randomized to the experimental group or control group based on a randomization plan produced using SAS/Proc Plan. The randomization scheme will be stratified by LTBI treatment duration, less than or equal to 2 months or greater than 2 months. A permuted block randomization will be used. A block size of 8 will be used in the computation of these schemes. The interviewers will be blinded to the randomization results.

b) Sample Size: Sample size estimates for several different comparisons between the experimental and control group at differing levels of power are presented in Table below. It is assumed that 60% of the control group will achieve completion of treatment on time and that for the experimental group, the proportion adherent to the selected criteria for the primary endpoint was varied from 70% to 85%. All calculations assume an alpha of 0.95 for a two-tailed test. Sample calculations were based on the assumptions that 80% of the experimental group and 60% of the control group would achieve on time treatment completion. Based on the information provided in the table above, in order to obtain a power of 0.80, 80 participants per group is required to test the primary hypothesis [227]. This number was increased by 10% to account for attrition. This results in a per group sample size of 90 and a total sample of 360 with 180 participants in each arm of the study.
c) Data Analysis

All data analysis will be performed in accordance with the intent-to-treat principle. Missing data will only be imputed for analyses where complete records are needed using Rubin’s multiple imputation procedure. It is expected that less than 15% will be lost to follow-up. The same principles will apply to patients missing one or more visits. A 0.05 level of significance will be used as the criterion for accepting or rejecting a null hypothesis.

i. Primary endpoint (Classification of success versus failure) and primary analysis:

The primary analysis in this study will focus on adherence versus non adherence to ingestion of CDC-recommended number of doses within prescribed timeline (See Appendix C). Participants in both the experimental and control groups will be classified as either success or failure based on these criteria.

Crude odds ratios, relative risk and attributable risk for adherence will be computed for both the treatment and control groups using Taylor series [228] at the end of treatment. A chi-square test will be used to examine whether the observed difference is statistically significant. The classification of success and failure at the end of treatment will be used as the dependent measure.

ii. Secondary Analysis: The description below follows the order of secondary objectives (Section 4.3)

a. Baseline adherence patterns will first be described using descriptive statistics. Chi-squares will be computed for categorical measures and Pearson correlations and t-tests will be computed for continuous measures. Next, logistic regression will be used to identify the demographic, clinical, social and behavioral characteristics of participants defined as succeeding or failing. Separate models will be calculated for both the experimental and control groups. The characteristics under investigation include knowledge and attitudes, social support, mental illness, substance use, quality of life, life events, gender, race/ethnicity, education level, socio-economic status, type of residence/dwelling, and marital status. This analysis will include baseline measures. Due to the large number of prognostic factors data reduction techniques will used. Techniques to be used include the elimination of measures with little or no variation and the elimination of factors that are highly correlated with each other. The remaining factors will be grouped into theoretically meaningful groups. Logistic regression models will be computed for each theoretical group. Factors significant at 0.25 or less from each of these models will be candidates for the final logistic models [229]. Interaction terms will be included in the models.

b. T-tests will be used to assess the impact of baseline knowledge and attitudes on adherence to LBTI treatment comparing the experimental and control groups. For this analysis a measure of adherence will be computed which includes the entire treatment period and takes into account participant lapses in treatment.

c. T-tests will be used to assess the impact of baseline social support on adherence to LBTI treatment comparing the experimental and control groups. For this analysis a measure of adherence will be computed which includes the entire treatment period and takes into account participant lapses in treatment.

d. Crude odds ratios, relative risk and attributable risk for self-reported adherence will be computed for both the treatment and control groups. Measures of adherence to be used in this analysis include the self-adherence questionnaire, the computer touch screen and the confidential adherence scale. The same criteria as used in the primary analysis will be used for this objective.

e. This analysis will focus on the length of time participants required to complete their LBTI drug regimen. Measures will be developed that account for factors that lengthen treatment times including treatment lapses and missed doses. First, chi-squares, t-tests and ANOVA models will be used to compare the timely completion of LBTI between the experimental and control groups. Chi-squares will be used to compare the proportion in each group requiring more time to complete LTBI regimens. T-tests and ANOVA models will be used to compare the amount of additional time required.

Next, multiple regression analysis will be used to identify factors that contribute to extended treatment times. The same explanatory variables used in the analysis for secondary objective 1, described above will be used in this analysis.

f. Logistic regression will be used to determine which component(s) of the intervention was most effective in enhancing compliance based on the results of the exit interview.

g. Measures will be developed assessing whether or not participants have been compliant with clinic visits. The first measure will be an overall binary compliant/noncompliant measure. The second measure will be a continuous measure of the proportion of clinic visits completed. A chi-square analysis will be used to assess the binary measure and a t-test and ANOVA will be used to assess the continuous measure.
h. Pearson's correlations will be used to compare self-reported adherence rates will provider and peer assessments of participant adherence. All of the self-reported adherence measures discussed above will be included in this analysis.

i. Pearson's correlations will be used to assess the relationship between self-reported adherence and adherence as measured by MEMS caps.

j. T tests and chi-squares will be used to compare self-reported adherence rates to pharmacy records, separate analysis will be calculated for the experimental and control groups and for the length of recommended treatment regimens.

k. Pearson's correlations will be used to compare the participant's self-reported adherence collected via the interview to the computer assisted touch screen measure of adherence.

l. This analysis will be the same as that described for the primary analysis. In this analysis, separate ratios and risk scores will be calculated for the LBTI treatment regimens. Differences will be assessed between treatment regimens less than or equal to 2 months and regimens greater than 2 months. In addition, differences between each of the treatment regimens will be assessed.

m. In the analysis the number and type of adverse events will be tabulated. Adverse events will be grouped according to severity. T-tests will be used to compare the impact of treatment completion with the number of adverse events. Chi-square analysis will be used to assess the groupings of severity with treatment completion.

n. Pearson correlations will be used to compare participant satisfaction with TB care, clinic administrative and nursing staff, clinic setting and providers. Separate correlations will be computed for the experimental and control groups. The correlations will be compared using a 0.05 level of significance.

o. This analysis will assess the proportion of subjects that did not complete treatment according to LBTI guidelines within the recommended time frame among the experimental and control groups. A chi-square analysis will be used to statistically assess the difference between these proportions.

p. Cost analysis: The purpose of the economic analysis will be to compare the cost effectiveness of the experimental intervention compared to traditional, self-administered LTBI treatment. Data on outcomes and costs in subsequent years will be discounted using standard discount rates (3%). Three types of costs will be measured: 1) Participant costs include travel time, program time, and out-of-pocket monetary costs associated with the program, such as costs of child care. In periodic surveys, we will ask participants questions about time and out-of-pocket costs in the preceding week (to minimize recall bias). The value of the time for the study population will be based on data from the 1993-1995 Harlem Household Survey conducted by the Harlem Center for Health Promotion and Disease Prevention. This random household survey of 1,000 Central Harlem adult residents covered all living quarters in Harlem, including shelters and abandoned buildings, and is therefore very appropriate for estimation of income levels for the study population. Detailed questions were asked on both level of income and hours worked, making it possible to impute income at the level of work effort expected by peer workers who would otherwise be working in the community. We will update these data using information on hourly wages in New York City from the Current Population Survey. We will also use the 2000 Census to update these figures in 2002 or 2003. 2) We will collect accounting data on program costs in terms of labor, equipment, pharmaceutical, and other expenditures from financial records maintained by the model programs. We will value equipment at lease rates, pharmaceuticals at hospital pharmacy costs, and professional staff and other paid staff (including paid peer workers) at salary plus fringe costs, weighted by the proportion of time devoted to the program. We will assess the costs of training peer counselors by computing the costs of training-related materials and trainer and trainee time (valued according to its opportunity costs as ascertained in a baseline survey). We will amortize the training costs over the expected time that trainees will spend in the program. 3) Most medical service use by program participants is expected to occur at Harlem Hospital and will be measured from health utilization questionnaire and confirmed by chart review and costed at Harlem charge rates. We will survey participants about their use of medical services outside Harlem Hospital in the previous month and will impute costs to these services using Harlem charge rates. We will also compute patient costs associated with these medical visits (e.g., time and out-of-pocket costs).

Sensitivity Analyses: In a series of sensitivity analyses we will: a) vary the length of the training program amortization period, b) vary the cost of trainee time, c) convert Harlem medical care costs to charges using cost-to-charge ratios, d) vary the discount rate used, e) use imputed rather than reported child-care and transportation costs, and f) use regression techniques to adjust costs and outcomes for confounding differences in participant characteristics in the model programs.

5 Human Subjects

5.1 Protection of rights of participants

A consent form will be developed by the investigators and will be approved by the Columbia University Institutional Review Board at Harlem Hospital. The consent will include description of the nature of the study, the nature of the information to be obtained from participant interviews, the tracking procedures to be used, the potential risks and
benefits associated with participation, the procedures developed to ensure confidentiality, the names of persons or organizations with access to the data, the assurance that nonparticipation or withdrawal from the study will not jeopardize the care of the participant at Harlem Hospital, and the names and telephone numbers of contacts to obtain more information regarding the study. The consent will be signed by the participant or the guardian and dated and witnessed as per normal procedures. Informed consent will be obtained by research staff in a private setting to assure confidentiality. The staff will emphasize the voluntary nature of the participation and the ability of the subject to withdraw from the study at any time. The staff will be trained in the importance of maintenance of confidentiality and in the components of full-informed consent. The signed consent form will be kept in each participant's research record. Each participant will be assigned a personal identifier that will be used on all research instruments. Participants’ names will not appear on research materials. The list of participant names and identifiers and all other research records will be kept in a locked cabinet.

5.2 Inclusion of women and minorities in research
Harlem Hospital serves a predominantly minority, inner city population, and this is reflected in the demographics of patients seen in the Charles P. Felton National TB Center and the Infectious Diseases Clinic. The patients are overwhelmingly African American and Latino (over 90%), and approximately 32% are women. Over 1,000 participants enrolled in CPCRA trials at Harlem Hospital, nearly 40% were women, 94% minorities and over 50% were current or former injection drug users.

Further, the Division of Infectious Diseases and the Charles P. Felton National TB Center are committed to the inclusion of women and minorities in all of its research. Inclusion of women and minorities is a top priority in recruitment for all of its programs and studies. Further, every effort is made to recruit staff who matches the demographics of the patient population, and multicultural sensitivity is a key component of staff training.

6 Invertebrate animals (not applicable)
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Appendices