

**New Paradigms for Reducing HIV-Related Tuberculosis in High-Burden Countries:
Community Trials of Novel, Epidemiologically Based Strategies to Control HIV-
Related Tuberculosis**

A Collaborative Program of
The Johns Hopkins University Center for Tuberculosis Research and
The University of Alabama at Birmingham
In Cooperation with
Centers for Disease Control and Prevention, Kenya
Aurum Health Research, Welkom, South Africa
World Health Organization
TB/HIV Working Group/Stop-TB Program
Rakai Project/Uganda Virus Research Institute, Uganda
Municipal Health Secretariat, Rio de Janeiro, Brazil
and Other International Partners

Executive Summary

Tuberculosis is the leading killer of people with HIV infection worldwide, and the HIV epidemic has seriously undermined tuberculosis control efforts in high prevalence areas. While new tools are clearly needed to reduce the incidence of morbidity and mortality from HIV-related tuberculosis, more effective public health strategies are also necessary to achieve maximal benefit from existing and future interventions. The primary global approach for the control of tuberculosis is the World Health Organization DOTS strategy (Directly Observed Therapy, Short Course), which is based on passive case detection and treatment of active disease. Epidemiologic analyses demonstrate that the DOTS strategy is insufficient to control tuberculosis in countries with high HIV prevalence. Case rates and mortality from tuberculosis are climbing, even in countries or settings where DOTS has been successfully implemented. In these settings, tuberculosis is driven by reactivation of latent infection in HIV-infected people, with subsequent transmission to contacts before the disease is recognized and treated. Because DOTS treats tuberculosis patients only after they have infected a substantial number of contacts, and does nothing to reduce the incidence of reactivation of latent tuberculosis in HIV-infected populations, tuberculosis will continue to escalate dramatically in settings of high co-prevalence of HIV and latent TB. Control of tuberculosis in this situation will require new public health paradigms that apply novel, epidemiologically based interventions to detect undiagnosed cases, treat latent infection and reduce susceptibility to disease. The recent ProTest initiative to link HIV voluntary counseling and testing (VCT) with specific TB interventions is a first step in this direction, and has generated important preliminary information on the possible feasibility of community level approaches. More intensive and far-reaching interventions are urgently required to combat tuberculosis in Africa, Asia and Latin America, where HIV is rapidly undermining all efforts to contain disease rates.

The purpose of this proposed initiative is to evaluate novel strategies to reduce morbidity and

mortality from tuberculosis in populations with high rates of HIV and tuberculosis co-infection. We will conduct community trials in high-impact areas to determine the most effective methods of improving TB control strategies for potential use in widespread disease control. On the basis of our preliminary observations in a number of settings, we propose to organize community-randomized trials of novel public health strategies for the control of HIV-related tuberculosis. Our interventions will combine traditional and newer technologies for TB management with new paradigms of disease control, including: active case finding in high risk populations using point of service diagnostics; community-wide HIV VCT with active tuberculosis case finding; VCT with preventive therapy using novel, short course treatments in those found to be co-infected; mass preventive therapy in high risk populations, such as miners; and district-wide provision of antiretroviral therapy to eligible HIV seropositive people as a tuberculosis control strategy. Through careful assessment of the impact of these interventions on community rates of tuberculosis and death, we will make a major contribution to the identification of effective strategies to reduce suffering and death from HIV-related tuberculosis worldwide.

This application is submitted by a consortium of investigators under the leadership of the Johns Hopkins Center for Tuberculosis Research. A steering committee of the principal researchers from each of the collaborating institutions will manage the program and will oversee the development of specific protocols in conjunction with national tuberculosis and HIV programs, local public health authorities, and experts in community randomized trials, tuberculosis, HIV and biostatistics. All protocols will also undergo independent peer review and will be monitored by data safety monitoring boards. A 7-year time line is proposed, reflecting the community dynamics of tuberculosis and the expected trends in tuberculosis prevention and control at the population level.

A. Objectives

The objective of this proposal is to evaluate the effectiveness of novel strategies to control HIV-related tuberculosis (TB) in high incidence, low-income countries. A consortium of investigators, clinicians and public health officials with demonstrated capabilities in conducting high-impact community based interventions and research on public health strategies will design, organize and implement a series of complementary intervention studies that will examine the influence of a variety of novel interventions on the incidence of TB and death in areas with high levels of HIV infection and TB. The proposed interventions should have a major impact on the incidence of TB and mortality in the communities where they are undertaken, and will serve as models for the many areas of the world where HIV-related TB is causing an enormous amount of suffering and death. This project will both directly benefit populations heavily affected by TB/HIV and catalyze a change in global public health strategies.

A.1. Specific Outcomes Anticipated

- Creation of a consortium of investigators and public health officials to design and run a series of complementary community-randomized studies of innovative tuberculosis control strategies in settings of dual epidemics of HIV and tuberculosis.
- Implementation of six community level studies in six high burden countries/areas, assessing the impact of novel TB control strategies on disease incidence, mortality, drug resistance and other outcomes.
- Documentation of substantial reductions in the number of tuberculosis deaths and tuberculosis cases within the communities where novel interventions are implemented.
- Comparisons of the relative impact of the alternative strategies for reducing tuberculosis case rates and death rates across a variety of community settings.

- Mid-course adjustments in the design of interventions, to take advantage of knowledge gained from preliminary data and to evaluate additional variations on study strategies.
- Identification of operational, technical and behavioral obstacles to program success with development of strategies to address these problems.
- Documentation of impact of coordinated TB/HIV interventions on HIV outcomes.
- Dissemination of results through national, regional and global meetings and publications.
- Pilot expansion of successful strategies to additional communities within the high-impact areas to determine the generalizability of results.
- Change of global tuberculosis control policies to encompass more epidemiologically appropriate approaches to reducing death and illness from tuberculosis in the era of the HIV pandemic.

Performance indicators and milestones for this initiative are provided in Section C of the proposal.

B. Background and Rationale

B.1. Impact of the TB/HIV Co-Epidemics

TB is a major and increasing cause of morbidity and mortality worldwide. The estimated mortality from TB in 2000 was approximately 2 million people, making TB the second leading infectious agent of death in the world. The HIV epidemic has substantially worsened the TB epidemic in many populations, particularly those in sub-Saharan Africa, Latin America and southern Asia. More than 50 million people have been infected with HIV since the start of the pandemic, and current estimates show approximately 40 million prevalent infections, the majority in sub-Saharan Africa. HIV-related TB incidence is increasing as the HIV pandemic spreads and matures. The WHO estimates that one-quarter of all TB deaths occur in

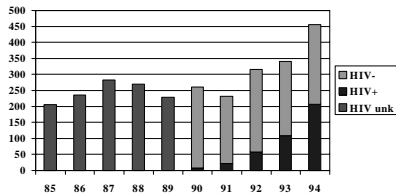
HIV-infected people, and this proportion is growing. In Africa, where AIDS is the leading cause of death from any disease, TB is the leading AIDS-related opportunistic infection. The WHO estimates that more than 10 million people with HIV infection died of TB in the 1990s, and millions more will die in the coming decade.

The principal public health intervention for the control of TB worldwide is the WHO DOTS strategy (Directly Observed Therapy, Short Course). The DOTS strategy emphasizes governmental commitment to TB control, registration and follow-up of cases, microbiologic diagnosis of passively presenting cases, and initially supervised short-course therapy with a reliable drug supply. Under DOTS, TB case detection is passive, meaning that TB health services are only provided to those who seek care. The epidemiologic model underlying the DOTS strategy assumes that with effective treatment of passively detected cases transmission of *M. tuberculosis* will decrease and will render the reproductive rate of the epidemic to less than one secondary case per incident case, resulting in decreased incidence. This model does not apply, however, where HIV is epidemic, as demonstrated by data from settings of high HIV prevalence. Control efforts in countries with a high burden of HIV and TB have been largely ineffective, even when the DOTS strategy has been vigorously implemented and when cure rates of HIV-related TB are quite high. While DOTS can clearly succeed as a medical intervention to reduce mortality in diagnosed cases of TB, it is clearly failing to reduce the incidence of TB in areas where HIV is epidemic. For example, while 90% of diagnosed TB patients are cured by DOTS in Botswana, 40% of AIDS-related deaths are due to undiagnosed TB.

HIV infection increases the risk of developing TB in people with co-infection, and at the community level this results in a remarkable increase in TB incidence. Figures 1-3 demonstrate the dramatic effect that HIV epidemics have had on TB incidence, in Thailand, South Africa and sub-Saharan Africa. As prevalence of HIV increased, the already high endemic incidence of TB has shot upward, creating a

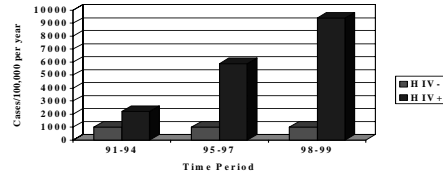
trajectory that has resulted in even greater disability and death.

Figure 1. HIV Prevalence and Number of TB Patients at Chiang Rai Hospital



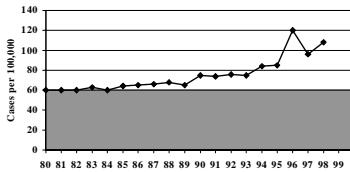
Yinai et al. AIDS 1995;10:527

Figure 2. Increasing Incidence of HIV-Related Tuberculosis in South African Gold Miners



Churchyard et al., 2000

Figure 3. TB Notification Rates in Sub-Saharan Africa, 1980-1998



WHO, 2000

While it is apparent that diagnostics and therapies are urgently needed to combat TB, it is also clear that implementing novel, epidemiologically based TB/HIV control strategies could have a substantial impact in reducing illness and death from TB. Epidemiologically based approaches to TB control can specifically target critical points in the community life-cycle of TB infection for interventions designed to reduce the numbers of new infections, cases and deaths.

The dynamics of TB in populations with high HIV impact are illustrated in Figure 4. Cases of TB stem primarily from the large pool of people with latent TB infection, who upon acquiring HIV are more likely to progress to active TB. HIV infection increases the risk of reactivation of latent TB infection by 80 to 100-

fold. When TB disease develops, with its disproportionate impact on HIV-infected people, many die without diagnosis or treatment. A person with active TB disease transmits infection to susceptible contacts, including HIV-negative adults and children. Those contacts with HIV infection have a greatly increased probability of developing active TB disease. The pool of those latently infected also expands, resulting in an upward spiral of TB disease incidence, particularly when HIV is subsequently acquired.

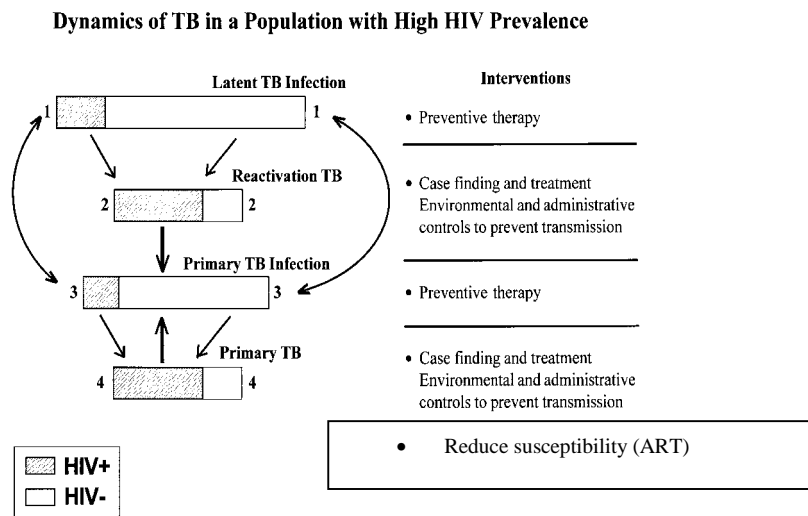


Figure 4. Community Life-Cycle of TB in HIV endemic areas. (From De Cock and Chaisson, 1999.)

The DOTS strategy intervenes passively at step 2 of this process, whereas steps 1 to 4 are also important components of the life cycle. In high incidence countries there is little if any attention paid to controlling the reservoir of TB in those with latent TB infection. Recently, UNAIDS and the WHO have endorsed TB preventive therapy for HIV-infected people as one component of a package of care to be provided in developing countries. The ProTest initiative promotes HIV counseling and testing linked to INH preventive therapy for those with HIV infection. Pilot projects have been conducted in several African

countries and have helped identify both the potential benefits and operational obstacles that this strategy entails. ProTest pilot projects demonstrate that district level interventions can be made to work in difficult settings, but also underscore the importance of more comprehensive interventions. This approach will require further scaling up and linkage to other TB and HIV control strategies, with careful evaluation, as proposed in this application.

In settings with epidemic HIV and TB co-infections, prevalent TB is common, and efforts to actively identify undiagnosed TB cases can have a high yield. In previous work completed by our groups, discussed below, we have found that when subjected to active case finding between 4 and 9% of HIV-infected adults in highly affected settings have active, *undiagnosed* TB. As shown in Table 1, in settings as diverse as Haiti, South Africa and Cambodia, we have found a high prevalence of active TB cases when we used active case finding in HIV-infected populations. Nonetheless, in most affected areas, public health efforts to identify TB cases are completely passive and wholly inadequate.

Currently, fewer than half of all TB patients worldwide are diagnosed and treated. Ineffective control programs have resulted in high rates of treatment failure. Thus, in high burden areas, TB control strategies need to interrupt the life-cycle of TB at all four possible points of intervention, including treatment of latent TB infection in those at high risk of progressing to disease; detecting those currently undiagnosed and actively transmitting infection (who also are at risk of death); and identifying and treating contacts of cases with newly acquired TB infection who risk progression to disease immediately or in the future.

Reducing susceptibility to TB is another effective approach to controlling the disease in HIV-infected populations. Treatment of HIV infection with antiretroviral therapy (ARV) has been shown to reduce TB risk by 80-90% in both developed and developing countries. While providing ARV in high-impact areas is fraught with challenges, it is necessary if HIV-related TB and other morbidity are to be controlled. Even with ARV, however, TB preventive therapy is still required. In South African patients

treated with ARV, TB incidence was reduced by 80%, but it was still 10-fold higher in people with HIV than in those without HIV. In Rio de Janeiro, provision of TB preventive therapy to HIV patients with access to ARV reduced mortality compared to ARV alone.

<u>Population Studied</u>	<u>Setting</u>	<u>Time Period</u>	<u>Prevalence of Newly Discovered Active TB in Population</u>
Women in HIV MTCT Program (N=438)	Soweto, South Africa	2001	5% of HIV+ women delivering infants
Patients in HIV Home Care Program (N=441)	Phnom Penh, Cambodia	2001	9% of home-based care enrollees
Adults in HIV VCT Program (N=5000)	Cape Town, South Africa	2000-2001	8% of all HIV+ adults (an additional 22% had known TB)
Adult residents of an urban shantytown (N=10,900)	Cite Soleil, Haiti	1991-2	6% of all HIV+ adults, 2% of all HIV- adults

Table 1. Prevalence of Active TB with Case Finding in HIV-Infected Populations.

Thus, an abundance of epidemiological data and a number of epidemic modeling studies confirm that additional interventions will be required to significantly lessen the burden of TB on resource poor nations with severe HIV epidemics. Previous assessments of TB control strategies have focused on process measurements, such as cases identified or treatments completed, rather than on health indices, such as community incidence of TB disease and death. Novel strategies to improve TB control must be evaluated for their ability to reduce the burden of disease in heavily affected communities. Rather than the proportion of patients successfully treated, the definition of TB control should be a community-wide

reduction in the incidence of disease and death.

B.2. Beyond DOTS for Controlling HIV-Related TB

In countries with high levels of HIV infection and explosive TB rates, TB control strategies must also encompass other epidemiologically based TB interventions in addition to treatment of active cases.

The principal strategies that require community-wide evaluation include:

- Community-wide detection and treatment of latent TB infection in HIV-infected people
- Active case finding for prevalent TB amongst HIV-infected people
- Contact tracing and treatment in contacts of active cases
- Mass preventive therapy in very high risk populations
- Reducing susceptibility through treatment of HIV infection with ARVs

Treatment of latent TB infection in HIV-infected, tuberculin positive individuals in developing countries reduces TB incidence between 40 and 80%. A recent analysis from Brazil demonstrates, as did an earlier study from Haiti, that the use of TB preventive therapy in a cohort of HIV-infected adults significantly reduced mortality. Long-term follow-up data from a preventive therapy trial in Uganda shows that rifampin-based regimens lowered TB incidence and mortality significantly over a 4-year period. Meta-analyses of clinical trials of TB preventive therapy confirm that INH reduces TB incidence in tuberculin positive, HIV positive people, but, to date, an impact on mortality has not been documented.

There is a clear need to expand TB preventive therapy within HIV-infected populations and to evaluate the impact of community-level programs on TB incidence and mortality. Operationalizing preventive therapy in developing countries is obviously an enormous challenge. Feasibility studies in several settings have uncovered important problems in compliance with screening procedures, follow up and treatment. Applied public health research in this area is an urgent priority.

Active case finding is an important strategy for reducing TB morbidity and mortality. This approach identifies prevalent TB cases before they would otherwise present for care, reduces the risk of death from TB, and stops the transmission of infection to contacts. In HIV endemic areas, active case finding can have an unusually high yield, as we have demonstrated in previous studies (Table 1).

Evaluation of contacts of active cases is an efficient method of active case finding. It offers the additional benefit of identifying candidates for treatment of latent TB infection. In a study in Haiti, where the prevalence of HIV in TB patients was 42%, we found that 10-15% of contacts evaluated had active TB. In a project currently underway in Rio de Janeiro, 4% of household contacts of TB cases are being found to have active TB and 45% have latent TB infection. In many countries with high TB/HIV incidence, contact evaluations will detect a substantial number of active cases. More extensive use of contact evaluation coupled with preventive therapy to at-risk contacts has the potential to reduce the community incidence of TB in resource poor settings.

Mass preventive therapy is a radical strategy that was employed to reduce TB incidence in South African gold miners before the HIV epidemic. In the early 1960s, five major mines participated in a two-year program that administered isoniazid as part of the daily beer ration. The incidence of TB at these mines fell by more than 70% compared to earlier years, and were 60-80% lower than rates at comparable mines that did not have an isoniazid program. While the intervention appeared to be highly effective, proper evaluation was not undertaken and the duration of the program was limited. Current rates of TB are almost 4-fold higher than when the intervention was piloted, suggesting that mass preventive therapy is likely to have an even larger impact. Careful studies of mass preventive therapy in populations with extremely high rates of HIV-related TB are necessary to ascertain the feasibility and impact of this strategy in the current era.

Finally, reducing susceptibility to TB by treating HIV infection with ARVs is known to be effective in

the U.S. and Europe. Preliminary results from Brazil and South Africa suggest this benefit will also accrue in resource poor settings. Broader availability of ARVs in high impact areas could reduce TB morbidity and mortality substantially. As access to ARVs increases in developing countries, the impact of treating HIV to reduce susceptibility to TB can be effectively evaluated.

C. Project Plan

We propose to conduct a series of population-based studies of novel public health strategies for controlling HIV-related TB in resource-poor settings focused on the approaches enumerated above. Our initiative will rely on community-randomized trials designed to compare novel strategies for TB control at the population level, and to measure the endpoints of TB incidence and mortality over time. Community randomized trials are powerful tools for assessing the impact of public health strategies in large populations, such as for STD control strategies, vaccination policies and other public health interventions intended to alter community disease rates. Documentation of the relative contribution of each of the proposed novel strategies to reducing disease burden is an essential step in formulating responsible TB control policies for heavily affected areas. Using DOTS as the standard of care, we will design a series of complementary studies that address the important research questions for controlling HIV-related TB at the population level. Among the strategies we will assess are DOTS alone versus DOTS plus contact tracing and treatment of latent TB in household contacts of HIV/TB cases; DOTS versus active case finding in high prevalence populations (Voluntary Counseling and Testing [VCT] participants) using conventional (sputum smear, x-rays) or novel diagnostic methods (e.g., rapid, inexpensive culture methods, molecular detection assays); DOTS versus DOTS with active community-wide case finding in high prevalence populations; aggressive use of preventive therapy with INH or short course treatments for latent TB infection in HIV-infected people; mass preventive therapy in HIV-infected gold miners versus routine VCT services with

selected INH prophylaxis; and district-wide promotion of VCT with ARVs for eligible individuals versus DOTS alone. We hypothesize that by implementing novel comprehensive and epidemiologically targeted control strategies we will reduce the incidence of TB at the community level more than a policy of DOTS alone.

Our proposed research strategy will utilize and augment local clinical, public health and investigative resources by establishing and strengthening collaboration between productive investigators and public health officials responsible for TB and HIV control. Our multidisciplinary approach will create unique opportunities for both creating new knowledge and applying recent advances in epidemic modeling, molecular diagnostics, treatment of latent infection, and antiretroviral therapy to the control of TB in developing countries. Critical information, available only from community randomized trials, will determine the impact of new TB control strategies of TB on the incidence of disease at the population level, and will discern which approaches result in substantial declines in TB morbidity and mortality. This information will also be essential for performing cost-effectiveness analyses that will be essential for sustained responses.

Strategy	S. Africa	Kenya	Uganda	Cambodia	Brazil	TBD
Active Case Finding		X	X	X	X	X
Targeted PT		X		X	X	X
Mass PT	X		X			X
Contact Evaluation		X			X	X
ART		X			X	X

Table 2. Matrix of interventions to be evaluated. PT= preventive therapy, ART= antiretroviral therapy.

We will design, implement and analyze six complementary studies in high burden areas, encompassing the range of alternative strategies outlined above. In each location, one or more of the strategies will be compared to standard of care that will usually include DOTS and HIV VCT in community

locations. Table 2 is a matrix illustrating the proposed strategies to be evaluated and the proposed sites at which they will be studied. Each trial will take advantage of local epidemiological circumstances, prior experience and health services infrastructure. In all sites, interventions will utilize approaches that bring together TB control and AIDS control programs and resources.

A brief description of the proposed studies is presented below. Please note that a critical early step in this initiative is to bring together the collaborating investigators to thoroughly consider design considerations and finalize protocols.

Study 1. South Africa – Mass Preventive Therapy for Gold Miners

HIV infection has resulted in an extraordinary upsurge in TB incidence in South African miners, and is now the leading cause of death in miners, more than 50% greater than trauma. Constant re-exposure to infectious TB cases in closed environments and hostels results in high relapse and re-infection rates, especially in those with HIV infection. Active case finding is already practiced in mining populations, but has not controlled the escalation in TB incidence that has resulted from the HIV epidemic. In the 1960s a pilot project provided INH to all miners at five major shafts and appeared to reduce TB incidence by 80%. Similar efforts in Alaskan natives in the 1950s contributed to a 90% reduction in TB infections and disease in that population. The purpose of this study is to evaluate the impact of providing INH preventive therapy to all miners without active TB through an employee health program. We will randomize 10 major mine shafts to receive either mass preventive therapy or individual HIV VCT with INH given to those testing HIV positive. The outcome will be the incidence of TB over a five-year period in the populations of randomized miners. If mass preventive therapy is found effective in this unique epidemiologic setting it will justify expansion to other settings where high rates of transmission exist. This project will be undertaken by collaborators from Aurum Health Services, Welkom, South Africa, and the London School of Hygiene and Tropical Medicine.

Study 2. Kenya – Comprehensive Community-Wide TB Control Interventions

Kenya suffers escalating rates of TB and HIV, particularly in poor populations in urban settings. Despite a relatively strong national TB control program, TB incidence is soaring. This study will evaluate the impact of a two-phase comprehensive TB/HIV control intervention in urban slum populations in Nairobi. In the first phase, we will compare alternative strategies of expanded TB/HIV control activities in high incidence settings. One set of communities will be randomized to active case finding as part of community-based HIV VCT centers, along with short-course preventive therapy using potent rifamycins for HIV-infected people with latent TB; alternative communities will be randomized to a strengthened DOTS program that provides evaluation of all contacts of new TB cases, using outreach workers to identify and screen household contacts for active disease and latent infection. This will allow us to compare approaches taken primarily through HIV services (VCT) with those taken through TB services (contact evaluation and treatment). In the second phase, antiretroviral therapy will be offered to residents of selected communities, permitting a factorial analysis of the relative contributions of TB control measures versus reducing susceptibility with ARVs. This project will be carried out with collaborators from the Centers for Disease Control and Prevention and the Kenyan Ministry of Health.

Study 3. Uganda – District-Wide Case Finding and Mass Preventive Therapy

The Rakai district of Uganda is a rural area where HIV prevalence is nearly 20% amongst adults and TB case rates exceed 250/100,000. TB control services are limited, but have been targeted for strengthening by the Ugandan Ministry of Health. Rakai is the setting of previous important studies of mass preventive therapy for sexually transmitted diseases as an HIV control measure, and the infrastructure for community-based mass therapy is in place. This study will compare a strategy of population-wide active case finding for TB combined with mass preventive therapy for all those without active disease to a strategy of active case finding only. Novel diagnostic techniques for finding active cases will be utilized, and both

routine INH and short course preventive therapy regimens will be compared in a factorial design. This project will be performed in collaboration with colleagues from Columbia University and the Rakai Project/Uganda Virus Research Institute.

Study 4. Cambodia – TB Case Finding and Preventive Therapy Among HIV Patients

Cambodia has a rapidly growing HIV epidemic that is concentrated in impoverished residents of urban areas. TB is the leading cause of death and is often undiagnosed and untreated. Previous work in Phnom Penh found that 9% of HIV homecare participants had active TB, and 40% of these patients died before the culture results were available. In this study, we will evaluate the impact of case finding among all HIV patients identified through VCT programs and HIV home care programs, using rapid diagnostic methods to provide timely diagnoses. In addition, we will randomize VCT participants and home care clients to receive short course or life-long preventive therapy. This study will be done in collaboration with the University of Alabama-Birmingham, the Cambodian Ministry of Health and HIV/TB NGOs in Phnom Penh.

Project 5. Brazil – Comprehensive TB Control Interventions in a Setting of Routine Availability of HAART

Brazil has the largest number of AIDS cases and TB cases in Latin America. Brazil is unusual in that it is the only developing country that has made ARVs available routinely to all patients in its public sector clinics. Despite this, TB remains one of the most common infections in people with HIV and an important cause of death. Brazil has had extremely poor TB control practices over the past decade, though DOTS is now accepted and is being implemented slowly throughout the country. This project will take advantage of the unique situation in which HAART is freely and widely available to assess the impact of TB control strategies implemented on the backdrop of widespread use of ARVs. We will perform community randomized evaluations of active TB case finding among HIV-infected people in public sector clinics and

VCT sites in Rio de Janeiro, with targeted preventive therapy among HIV seropositive people. Pilot experience with this approach has demonstrated a high yield, particularly in poorer districts and *favelas*. This study will be conducted in collaboration with the Municipal Health Department of Rio de Janeiro and the Federal University of Rio de Janeiro.

Study 6. Sub-Saharan African Country To Be Determined – Comprehensive National TB Control Strategies in Combination with Antiretroviral Therapy

The WHO has identified five additional sub-Saharan African countries with high HIV/TB burdens that are committed to changing their TB control paradigms. Each of these countries has piloted the ProTest initiative, and each is now committed to expanding TB control to include case finding, preventive therapy, and contact evaluation. At least several will be prepared to offer pilot ARV therapy in selected districts within the next two years. In collaboration with the WHO, we will select a partner country for studying the impact of this comprehensive approach in a factorial manner. Districts will be randomized to receive 3 of 4 interventions (active case finding, preventive therapy, contact evaluation, and ARVs). The design will also permit cross-over to some extent, though communities receiving access to ARVs will not have these withdrawn. This design will permit a careful evaluation of the relative contributions of these various strategies for reducing TB morbidity and mortality as isolated or combined interventions.

C.1. Implementation Plan

The proposed initiative is a collaboration of a number of organizations with extensive experience in providing community based clinical services and conducting rigorous clinical research on interventions to control TB and HIV. The lead institution will be Johns Hopkins University, in collaboration with the University of Alabama at Birmingham. These institutions and investigators have collaborated extensively over the past four years in conducting operational research on TB control in high burden countries.

Cooperating institutions include the Centers for Disease Control and Prevention-Kenya; the World Health Organization; the TB/HIV Working Group of the STOP-TB program; Aurum Health Research, Welkom, South Africa; Ministry of Health, Kenya; the Rakai Project/Uganda Virus Research Institute; Columbia University; Ministry of Health, Cambodia; the Secretariat of Health, Rio de Janeiro; the Federal University of Rio de Janeiro; and a number of other partner NGOs and governments from countries with high HIV/TB incidence.

The consortium will be lead by a steering committee of investigators and public health experts who will review and set the research agenda, and oversee the development of specific intervention trials. A core staff of investigators (including epidemiologists, clinicians, biostatisticians, data managers and nurses) will design the specific protocols and evaluation methods and will supervise and monitor ongoing field trials. Field investigators will oversee the implementation of specific protocols with the support and oversight of the core staff and the steering committee.

Key personnel will include:

Richard E. Chaisson, M.D., Johns Hopkins University, Principal Investigator

Michael E. Kimerling, M.D., University of Alabama-Birmingham

Kevin De Cock, M.D., CDC – Kenya

Mario Raviglione, M.D., WHO Stop-TB

Paul Nunn, M.D., WHO Stop-TB

Gavin Churchyard, M.D., Ph.D., Aurum Health Services

Maria Wawer, M.D., Columbia University

Solange Cavalcante, M.D., M.P.H., Secretariat of Health, Rio de Janeiro

Afranio Kritski, M.D., Ph.D., Federal University of Rio de Janeiro

Jacqueline Coberly, Ph.D., Johns Hopkins University

Lawrence Moulton, Ph.D., Johns Hopkins University

To assure that the highest scientific standards are maintained and that human subjects are protected from unnecessary risks and harm, the steering committee will seek independent peer review of all protocols before they are finalized, independent data safety and monitoring will be required of all studies, and local, national and international institutional review board approvals will be obtained for each study.

C.2. Alliance Rationale and Roles

The consortium of investigators and public health officials joining in this initiative bring a variety of skills, resources and perspectives to the program. An undertaking as ambitious as this requires a partnership of productive and capable investigators, visionary public health officials, and individuals with access to and a commitment to populations in great need. The research described in this proposal is the product of ideas developed and formulated over the past several years by several of the key personnel. All of the key participants have a track record of prior collaboration in conducting innovative research or tackling difficult public health policy issues together. Each institution will contribute in-kind resources, such as educational materials, technical expertise, clinical personnel, clinical infrastructure and materials, and forums for communication and information dissemination. The Principal Investigator will establish the Steering Committee from the participating institutions, and this committee will provide oversight to the conduct of all research activities using a consensus approach.

C.3. Anticipated Obstacles and Sustainability

The obstacles to be overcome in undertaking this initiative are numerous and important. A critical component of success is the will to succeed, which is shared strongly by all participants. Attitudes towards TB control are mired in dogma and tradition, and many in the TB community worldwide oppose any strategies beyond DOTS. It is our strong belief, however, that anyone with any familiarity with the catastrophic situation in Africa and other high burden areas will be open to the novel approaches proposed

in this application. Logistical and technical considerations will be of paramount concern in implementing our proposed strategies. Each of the participating institutions has extensive experience in overcoming such challenges in the field, and we anticipate that our experience will be enormously valuable in this regard. In addition, rapidly changing epidemiologic conditions may affect the performance of our studies. For example, if ARVs are suddenly introduced broadly in a study location, this could influence the impact of other interventions being evaluated. Frankly, we would welcome this development, though we are not optimistic that it will occur. However, based on the experience to date, it is unlikely that any single intervention, including ARVs, will control HIV-related TB by itself.

Sustainability of the interventions is another crucial issue that we have considered. The primary purpose of this initiative is *proof of principle*, to document that radical approaches to controlling TB that go well beyond the DOTS strategy can succeed in areas with devastating HIV epidemics. We believe that demonstration of this principle would contribute enormously to the generation of political will to sustain intervention programs. We believe that both national resources within countries, and international resources such as the Global Fund for AIDS, TB and Malaria will be required to sustain the interventions that we hope to document are effective in controlling HIV-related TB.

C.4. Plans for Dissemination of Results

Results of the projects will be shared widely with interested and affected parties. We will use international forums, such as the IUATLD annual meeting, global AIDS conferences, and other scientific congresses to report on trial outcomes. In addition, in each of the countries where studies are performed we will organize symposia to educate and seek feedback from stakeholders about the purposes of the trials as they are being planned and implemented, and to disseminate and discuss results as they become available. We will also organize regional workshops and seminars to share information with public health officials and clinicians from neighboring countries. We anticipate having several consultations at the WHO

in Geneva during the initiative, and will use the TB/HIV Working Group as a forum for dissemination of outcomes.

C.5. Milestones and Performance Indicators

Objective 1: Create a consortium to design and manage studies

Milestones:

- Partners meeting to organize consortium and agree to goals
- Sign letters of commitment from institutions/investigators
- Execute subcontracts for specific projects and functions
- Assure ethical review processes
- Finalize individual protocols for each site
- Develop standardized forms and data management system
- Develop website for sharing of protocols, forms and project information
- Create data safety monitoring and review system
- Design audit and quality assurance system
- Conduct annual scientific and fiscal reviews of projects
- Prepare interim reports on project outcomes
- Prepare final reports on project outcomes

Objective 2: Implement six community level trials in high burden areas

Milestones:

- Implementation of South African Trial
- Implementation of Kenyan Trial
- Implementation of Ugandan Trial
- Implementation of Cambodian Trial
- Implementation of Brazilian Trial
- Implementation of Fourth African Trial

Objective 3: Document reductions in TB incidence and deaths

Milestones:

- Annual report on TB incidence based on trial and surveillance data from population under investigation

Objective 4: Comparisons or relative impact of alternative strategies

Milestones:

- Development of statistical models for attributing changes in case and death rates to interventions
- Preliminary analyses of impact of same interventions in different settings
- Preliminary analyses of impact of different interventions in same setting
- Preliminary analyses of impact of different interventions in different settings
- Final analyses comparing interventions within and across settings

Objective 5: Mid-course adjustments in intervention design

Milestones:

- Annual scientific review of projects (see objective 2)
- Annual protocol team meeting to consider amendments/redesign
- Annual presentation to steering committee

Objective 6: Identification of obstacles to program success

Milestones:

- Development of process review procedures for each protocol
- Stakeholder meetings and focus groups
- Annual scientific review of projects (see objective 2)

Objective 7: Pilot expansion of successful strategies to additional communities

Milestones:

- Approval for expansion from Ministry of Health
- Preparation of expansion protocol and data monitoring plan
- Implementation of expansion project

- Evaluation of pilot results
- Identification of funding for sustainability

Objective 8: Dissemination of results

Milestones:

- National meetings
- Regional meetings
- International conferences

Objective 9: Changes in global disease control strategies

Milestones:

- New WHO/UNAIDS policies for control of HIV-related TB incorporating results of studies
- New IUATLD policies for control of HIV-related TB incorporating results of studies

Performance indicators

We will use a variety of performance indicators to assure the timeliness and effectiveness of the activities being undertaken in this initiative. Each protocol will be evaluated regularly by study monitors who will utilize well-established methods for judging performance, including recruitment progress, retention levels, number of protocol violations, adherence to study timelines, completeness and timeliness of forms, and accuracy of data. In addition, managerial performance indicators will be assessed for regulatory, fiscal and administrative activities. This will include adherence to procedures for IRB and DSMB reporting, budget reporting, expenditure audits, and personnel management, including training and evaluation of staff. Finally, we will conduct qualitative assessments of process indicators, such as cooperation between TB and HIV programs.

D. Organizations

The organizations participating in this collaborative effort include universities, global health agencies, national public health research institutions, NGOs, and local health officials.

The Johns Hopkins University is a private, research university whose mission includes discovery, education and care. The Hopkins School of Medicine is a global leader in medical innovation and research, and the School of Public Health is the largest in the world. The Center for Tuberculosis Research is committed to improving global tuberculosis control through innovative research, training and clinical practice.

The University of Alabama-Birmingham is a public research medical institution with a strong commitment to global health. The University is a leading US medical research institution, and its School of Public Health is involved in a variety of programs to improve global health.

The Centers for Disease Control and Prevention is the United States' public health and prevention agency that has responsibility for TB and HIV control. CDC has maintained international programs dedicated to understanding improving the control of both HIV and TB for more than 15 years.

The World Health Organization is a UN-chartered global health agency responsible for surveillance, research, program support and policy development. The Stop-TB program is the global organization coordinating efforts to reduce TB incidence and mortality in more than 200 countries. Inclusion of the WHO in this project will greatly increase participation by National TB and AIDS Programs in the target countries, and will also facilitate the translation of results from the projects into global policies.

Aurum Health Research is an NGO in Welkom, South Africa, dedicated to clinical care and research for the health problems of miners. Aurum has conducted cutting edge epidemiologic and clinical studies on the TB epidemic in gold miners, and has evaluated a number of novel strategies to improve TB control in this setting.

The Rakai Project is a joint program of the Uganda Virus Research Institute, Columbia University and Johns Hopkins University. The project supports a series of primary care clinics where community-based trials can be undertaken and has a staff of clinicians, outreach workers and educators capable of implementing interventions.

The Municipal Health Secretariat of Rio de Janeiro is the public entity responsible for assuring health care and disease control to citizens of that city. In addition to programs in primary care, TB control and HIV prevention and treatment, the Secretariat conducts clinical and operational research on public health strategies.

E. Budget

A budget of \$42.7 million in direct costs is requested to support this ambitious initiative. A 7-year budget period is proposed, to allow the interventions proposed sufficient time to substantially alter the community dynamics of TB in the affected sites. Mathematical models of TB interventions suggest that even massive interventions that fundamentally disrupt transmission of infection and to disease take a number of years to reverse upward trends in incidence. A 7-year time frame will allow us to ensure that the impacts are real, sufficiently documented and sustained, as opposed to brief fluctuations in disease trends over a shorter period of time.

Funds are requested for the Scientific and Administrative Core facility at Johns Hopkins University, which will provide scientific leadership and administrative oversight for the initiative. Included in the core costs are salary support for the Principal Investigator and support for medical officers who will write protocols and provide clinical and technical support to field projects, a project coordinator, a research nurse supervisor for training and field audits, an epidemiologist, a biostatistician, a data manager, an administrator, a secretary, and two post-doctoral fellows who will be based in the field. Travel funds for

field visits and to bring collaborators to planning and annual meetings are also included.

Subcontracts for individual trials are listed separately and are currently estimated for the proposed work plan. Each subcontract includes personnel costs, travel related to the project, office and communications costs, computers and software, field activities expenses, and clinical supplies, including diagnostics, some drugs and disposables.

A subcontract to the World Health Organization is included to provide for coordination of country efforts with national AIDS and TB control programs, and for technical support and project consultation. Personnel costs will cover medical officers and an epidemiologist. Funds for consultants from the TB/HIV Working Group to review protocols, conduct training for field staff, and serve on the DSMB are also included, as are travel costs and general office expenses.

Indirect costs of 10%, excluding equipment, are budgeted in accordance with Gates Foundation guidelines.