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Tuberculosis as Part of the Natural History of HIV Infection in Developing Countries

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Abstract

An enhanced, refocused research agenda is critical to reducing the burden of tuberculosis (TB) in the human immunodeficiency virus (HIV) epidemic in developing countries. TB threatens HIV-infected patients before and after initiation of antiretroviral therapy, is difficult to diagnose, is rapidly fatal when it is drug resistant, and is being spread in clinics and hospitals. Research priorities include improved and point-of-care TB diagnostics; TB treatment and prevention during HIV infection, drug-resistant TB, and childhood TB; and optimization of TB and HIV program integration. With new TB diagnostics and drugs reaching approval, research must focus on effectively deploying these advancements. Research must include evaluations of individual, household, health care, and community approaches. Studies must apply implementation science to determine how to increase and adapt effective interventions to reduce TB burden in the context of HIV infection. Investment in this research will improve the lives of persons infected with HIV and contribute to efforts to reduce the global TB burden.

From the beginning of the AIDS epidemic, tuberculosis (TB) was recognized as a major cause of suffering and death; however, major research funding and efforts were not directed toward this problem [1–3]. Because antiretroviral therapy (ART) has become a reality worldwide, the failure to invest in research that addresses optimal ways to reduce TB burden in the population of patients infected with human immunodeficiency virus (HIV) has become even more obvious. Data show that TB poses a threat to the success of the global investment in HIV treatment and that cases of TB in HIV-infected persons are curtailing global progress in TB control [4]. For these reasons alone, a reexamination of priorities in HIV and TB research is needed.

Priorities in the research agenda must reflect the current landscape of TB in HIV-infected persons living in resource-limited settings. HIV-infected persons are at risk of TB throughout their course of disease, even after they respond to ART [5]. TB is challenging to diagnose, is rapidly fatal when it is drug resistant, and is being spread in households, clinics, hospitals, and communities [6,7]. Treatment and prevention studies for children and adults that incorporate new TB drugs and rapid diagnostic tests and that address all stages of HIV

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disease are clearly high priorities. Prevention research must move to the forefront of the agenda and encompass studies of reducing transmission in health care settings.

Optimization of HIV and TB care delivery is another essential focus area. Implementation science must be applied to discern ways to apply and improve care for HIV infection and TB, which have traditionally been diagnosed and treated at geographically separate sites. It must be applied to improve uptake of some of the simplest interventions, such as a 6-month course of isoniazid preventive therapy (IPT). Although not reviewed in this article, support for basic science in interactions between HIV infection and TB is essential for long-term gains in the field. In the immediate future, treatment and prevention studies and implementation science approaches to TB care for HIV-infected patients have the greatest potential to reduce TB burden [8].

TB DIAGNOSTICS IN HIV-INFECTED PATIENTS

Multiple studies have revealed the lack of sensitivity and specificity of symptom screening, acid-fast bacilli (AFB) microscopic examination, and chest radiograph for HIV-infected persons suspected of having TB [9–13]. For patients with advanced immune suppression, these traditional diagnostic tests are even less sensitive and specific. The consequences of poor diagnostic tests for TB prevention and control are enormous. The high early mortality rates among patients who receive ART in resource-limited settings have been, in part, attributed to missed TB cases [14], and autopsy studies confirm that undiagnosed TB is a major cause of death [15,16]. In addition, undiagnosed TB enables TB transmission in the home, community, and health care setting. The ultimate goal in TB diagnostics and of highest priority is an accurate, rapid point-of-care test for active TB that is accessible to the most remote clinics. Rapid screening for drug resistance at the time of initial TB treatment has also become essential. Although efforts are under way to develop such tests, there are new technologies that hold promise for resource-limited settings, and there is potential to improve delivery of even the most basic available tests.

New technologies for TB case identification include nucleic acid amplification tests (NAATs), mycobacterial antigen and antibody tests, phage-based methods, and detection of organic volatiles in breath or sputum samples from patients [17]. The advancements in rapid diagnostic testing using NAATs in particular are encouraging, but use of these tests remains limited by heterogeneity in the published test characteristics of commercially available tests [18], relatively poor sensitivity (60%–70%) for smear-negative active TB [19,20], high cost, and requirements for skilled technologists and complex equipment. To move forward, future studies of NAATs should standardize patient sampling methods to allow for comparisons among assays and undergo further validation in settings with a high burden of TB and HIV [18]. Of patients with advanced immunosuppression, ≥50% may have negative AFB smear results during active disease [11,21], and extrapulmonary disease is common. If NAATs are ultimately to replace sputum culture in settings with a high prevalence of HIV infection, the sensitivity of sputum NAAT for AFB smear–negative TB must be improved, and NAAT platforms must be developed that can be implemented quickly and inexpensively with use of existing laboratory infrastructure and with minimal requirements for skilled technicians. One promising technology is loop-mediated isothermal amplification, which does not require thermal cycling or refrigeration of NAAT reagents, can be performed by laboratory workers with minimal training, and provides an easy to interpret visual read-out. However, the sensitivity for smear-negative TB currently remains <50% [22,23]. Accelerated development of commercially available serum- and urine-based testing, such as methods using lipoarabinomannan [24,25], is also needed as an alternative to sputum in cases of paucibacillary, extrapulmonary, and pediatric TB.

In the near term, AFB microscopy will remain the most widely used diagnostic tool for TB case detection in resource-limited settings. Priority must be given to determining the optimal strategies for improving the sensitivity of microscopy, such as the use of fluorescence microscopy [26] and development of alternative specimen processing techniques in settings where culture is not available. However, even if maximally optimized, AFB microscopy does not allow for drug-susceptibility testing and is limited by poor sensitivity for HIV infection. Culture remains the gold standard in TB diagnosis, and greater sensitivity and speed of mycobacterial growth detection, compared with traditional culture methods, have been shown for automated liquid culture systems, such as the mycobacterial growth indicator tube. Another simple modification of traditional culture techniques that allows for detection of first-line TB drug resistance is exemplified by thin-layer agar techniques and the microscopic observation drug-susceptibility assay [27]. Research is needed to minimize liquid culture processing requirements and to reduce its complexity and cost, to extend its use beyond reference laboratories. Techniques, such as microscopic observation drug-susceptibility assay, need to undergo further operational research to define optimal quality and training components to make the procedure widely applicable (Table 1).

TREATMENT APPROACHES TO TB IN HIV-INFECTED PATIENTS

The highest-priority research questions with regard to treatment of TB in HIV-infected persons are the optimal timing of initiation of ART and which antiretroviral agents to use with standard, coformulated TB regimens. Current guidelines recommend starting ART before completion of TB treatment, and this was confirmed by the randomized controlled Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPiT) trial [28,29]. The primary unanswered question is when to start ART during TB therapy. There are 3 ongoing randomized studies (A5221, Cambodian Early vs Late Introduction of Antiretrovirals [CAMELIA], and SAPiT) that should inform this question during the next 1–2 years [30]. Observational studies on the optimal timing of ART during TB therapy are conflicting but favor earlier initiation of treatment [31,32].

Drug interactions between rifampin and HIV nonnucleoside reverse-transcriptase inhibitors and protease inhibitors (PIs) pose the greatest challenge in the choice of ART regimen for HIV-infected patients with TB. Rifampin lowers concentrations of nevirapine, efavirenz, and PIs, which can result in loss of viral suppression and HIV drug resistance. Over the long term, this poses a serious problem for HIV-infected patients who may not have access to second-line ART. The use of rifabutin in place of rifampin for TB treatment reduces the magnitude of these interactions; however, it has not been a feasible option in resource-limited settings, because rifabutin is not available in coformulated TB preparations and the drug itself is not widely available and is more costly than rifampin. Fortunately, the World Health Organization recently added rifabutin to the List of Essential Medicines for HIV-infected patients receiving PI-based ART, enabling use and evaluation of these drug combinations [33].

For patients receiving first-line ART containing efavirenz or nevirapine, observational studies have shown that rifampin-based TB regimens can be coadministered with either drug with acceptable results but that efavirenz has better virologic efficacy [34,35]. A recent randomized controlled trial from Thailand that involved 142 patients receiving rifampin found a significantly higher proportion of patients receiving nevirapine-based ART with 12-h drug concentrations below the recommended minimum, compared with patients receiving efavirenz-based ART, although rates of virologic failure were no higher in the nevirapine treatment arm [36]. Effectiveness studies that compare regimens in a larger number of patients with use of optimal dosing of these agents would inform the field, and the results of a large randomized controlled trial comparing efavirenz-based ART with nevirapine-based

ART in patients receiving TB treatment in Mozambique is anticipated in 2011. For patients requiring PIs for second-line therapy, there is an urgent need to conduct studies to determine whether dose-adjusted HIV PI-based regimens can be safely given with TB regimens and to determine how these regimens compare with rifabutin-based regimens. End points of these studies must include outcomes for both HIV infection and TB. It is critical that TB response rates are not jeopardized. It is also critical that HIV drug resistance is prevented because of the limited availability of ART regimens in resource-limited settings.

Another important subject related to the treatment of TB in HIV-infected patients is the prospect of shortening the duration of treatment for TB. It is clear that treatment shortening will require new drugs, because data suggest that the current 6-month duration of current first-line drugs is at the margin of acceptable efficacy and may not be a sufficient duration for HIV-infected subjects [37]. Randomized trials of the efficacy of new drugs, compared with standard drugs, are needed [38]. Potential drug interactions between these new agents and antiretroviral agents must be identified early, and studies must be performed to determine necessary dose adjustments. To accelerate identification of successful drugs for treatment shortening studies, development of surrogate markers for TB treatment failure, such as time to culture conversion with use of liquid media, is a priority.

In the past, concern regarding immune reconstitution inflammatory syndrome (IRIS) had been used to support delayed initiation of ART [39]. Because delaying ART initiation until after completion of TB therapy results in reduced survival [29], a key area of investigation is the prevention and management of paradoxical TB-related IRIS, defined as the subset of ART-associated TB in which patients present with an exaggerated, inflammatory presentation of TB [40]. In a South African randomized, placebo-controlled trial, use of prednisone during the first 4 weeks of ART reduced the need for medical interventions and patient symptoms without a significant increase in adverse drug reactions or in the number of steroid-associated infections [41]. Similar studies are needed that assess the optimal duration of corticosteroid therapy for IRIS, the treatment of severe IRIS, and strategies to rule out other opportunistic infections before steroid therapy and that investigate novel ways to prevent IRIS.

DRUG-RESISTANT TB

The strong association of MDR- and XDR-TB outbreaks with HIV infection, the extremely high associated mortality, and the lack of adequate second-line anti-TB therapy or TB drug-susceptibility testing in resource-limited settings have been described as the “perfect storm” [42]. To limit the spread and the impact of drug-resistant TB, several areas of research must be addressed simultaneously: rapid drug-susceptibility testing, MDR- and XDR-TB treatment, acquisition and transmission epidemiology of MDR- and XDR-TB, and prevention of MDR-and XDR-TB in contacts of infectious persons.

The MDR- and XDR-TB crisis necessitates a paradigm shift in the approach to identification of drug-resistant TB. Waiting months for culture-based susceptibility results, if available at all, contributes to inadequate treatment of drug-resistant TB and to the high mortality and ongoing spread of drug resistance. Development of diagnostics that allow rapid identification of rifampin resistance at the time of TB diagnosis and treatment initiation must be prioritized to limit the spread of and the mortality associated with drug-resistant TB. Nucleic acid–based testing can identify resistance rapidly, without the lengthy delays associated with culture-based methods. NAATs using line-probe assays can rapidly identify drug resistance but currently still require skilled technicians and expensive laboratory equipment [43]. Integrated NAAT platforms are also in development that allow for sputum processing, nucleic acid testing, and identification of TB and rifampin resistance in a single

automated unit, but the requirements for electricity, equipment maintenance, and cost may limit their use in peripheral laboratories and point-of-care implementation. Research to simplify NAAT-based resistance testing to allow rapid, affordable implementation with limited technical requirements at peripheral laboratories will be crucial in the effort to contain and treat MDR-and XDR-TB.

In the meantime, culture-based drug-resistance assays, such as the microscopic observation drug-susceptibility assay may be able to increase the speed of drug-resistance testing and should be developed further to allow safe, low-technologic implementation in peripheral laboratories. Studies are also needed to investigate the performance of the microscopic observation drug-susceptibility assay in regions with a high prevalence of HIV infection and its performance with second-line agents. How host and treatment factors, such as degree of immunosuppression, duration of TB treatment, and choice of HIV and TB regimen, influence the development of acquired MDR-TB in HIV-infected patients must also be clarified.

TMC 207, a new second-line TB agent, was shown to be more effective than placebo in reducing the time to sputum TB culture conversion and in increasing the proportion of patients with culture conversion among patients with MDR-TB who are receiving a second-line treatment regimen in a recent randomized control trial. However, only 6 patients with HIV infection were included in the trial, and none were receiving ART [44]. Expedited studies of the compatibility of TMC 207 and ART are needed, followed by further efficacy studies with a larger number of HIV-infected patients with MDR-TB. Similar studies with new TB agents in development for treatment of MDR-TB in HIV-infected patients should be prioritized. The impact on mortality of the combination of new agents for treatment of MDR- and XDR-TB and for HIV-infected patients must be determined. In addition, the potential of new second-line agents for prevention of MDR- and XDR-TB in contacts of infectious persons needs to be evaluated.

TB PREVENTION AMONG HIV-INFECTED PATIENTS

The dramatic scale-up of ART in resource-limited settings has brought not only TB treatment but also prevention of TB in HIV-infected persons to the forefront. TB prevention strategies with known efficacy include rapid identification and treatment of active TB cases (in source patients), infection-control measures to reduce nosocomial transmission of TB, IPT during latent TB infection, and ART to reduce the incidence of TB among HIV-infected patients [45–47]. Research priorities in TB prevention center on adapting and improving these known strategies for HIV infection in resource-limited settings.

Infection-control measures are often limited in overburdened hospitals and clinics. Delays in TB diagnosis result in TB-infected and uninfected patients and health care workers sharing time together in crowded wards and waiting rooms. Much of the evidence for the use of negative pressure ventilation and ultraviolet germicidal irradiation to reduce airborne transmission of TB predates the emergence of the HIV epidemic by several decades [48,49], with a few recent exceptions [45,50,51]. Research of new, low-cost ventilation methods is needed, and existing options need to be compared in HIV and TB clinics and wards. Creative and culturally acceptable strategies of extending infection control to populations at high risk outside the hospital also need to be evaluated. At present, there is insufficient research clarifying where, when, and how often community TB transmission is occurring in areas with a high burden of TB and HIV infection. Studies using TB molecular genotyping and the development of new methods to identify TB transmission hot spots are needed to create targeted interventions to reduce community transmission [52,53].

Treatment of latent TB, primarily studied using IPT in HIV-infected patients who have positive tuberculin skin test results, clearly reduces the incidence of active TB [46,54]. Additional studies are needed to clarify the best choice of drugs, the ideal approach to maximizing the duration of efficacy while limiting adverse effects, and the best way to screen for active TB in HIV-infected patients. Results of a randomized controlled trial comparing 9 months of daily isoniazid therapy with 3 months of weekly isoniazid and rifapentine therapy for latent TB are expected in December 2010. Continuous TB preventive therapy and tolerability in patients receiving ART need further investigation [55].

ART is one of the most potent tools in TB prevention, and increasing ART access in countries with a high TB burden is a necessary step in reducing TB incidence. Observational cohort studies have shown reductions in the risk of TB among persons receiving ART, even with $CD4^+$ T cell counts as high as 500 cells/μL [56]. A recent survey of community prevalence of TB showed that a reduction in the prevalence of TB in a population with HIV infection paralleled broad-scale uptake of ART [57]. Determining the benefits and risks of early ART initiation, with a principal goal of reducing community TB rates and understanding the long-term protective effects of ART for TB prevention, are key research areas.

A TB vaccine with efficacy in HIV-infected patients could potentially reduce TB incidence to a much greater extent than existing prevention methods but has yet to be fully realized. A whole cell inactivated *Mycobacterium vaccae* vaccine significantly reduced the incidence of sputum and blood culture-confirmed TB by 37% in a study involving HIV-infected persons with a history of bacille Calmette-Guérin (BCG) vaccination and a high $CD4^+$ T cell count in Tanzania and merits further evaluation in patients with advanced HIV disease [58]. Recombinant BCG vaccines, recombinant fusion proteins, such as M72/AS01E, and nonreplicating viral vector vaccines, such as MVA85A, appear to be safe for HIV-infected persons with high $CD4^+$ T cell counts who are receiving or not receiving ART, and an efficacy study of MVA85A is ongoing, with a phase III noninferiority trial of recombinant BCG, compared with BCG, planned for 2011 [59,60]. A study of the safety and immunogenicity of M72/AS02A in HIV-uninfected adults with a positive tuberculin skin test result is ongoing; evaluation in HIV-infected patients is anticipated in late 2010. Additional research and phase III trials of TB vaccine development are needed, including trials with safety and efficacy end points in HIV-infected persons, particularly during advanced HIV disease [61,62].

TB AND HIV COINFECTION IN CHILDREN

Pediatric TB and HIV coinfection presents unique challenges in diagnosis, prevention, and treatment. The main pediatric research priorities include developing improved diagnostic tools; determining appropriate timing, dosages, and duration of ART and TB therapy; and adapting TB prevention strategies to the perinatal and household setting.

AFB smear–negative TB is more common in children than in adults, and obtaining expectorated sputum samples from young children is often not possible. Alternatives, such as obtainment of gastric aspirate samples and the string test, may improve the yield of AFB microscopic examination for children but remain inadequate or poorly studied [63,64]. Development of new TB diagnostics, particularly those that use serum or urine specimens, is a high priority, because TB- and HIV infection–related symptoms are often indistinguishable in young children and radiographic manifestations of TB are highly non-specific [65]. In addition, tests that can differentiate latent from active TB are urgently needed because of the abysmal performance of tuberculin skin testing and the mortality benefit of IPT among HIV-infected children [66,67]. To this end, the use of existing

interferon-γ release assays needs further investigation in a pediatric population. The optimal duration of IPT in children (both receiving and not receiving ART) and the long-term adverse effects of IPT also need to be determined.

In part as a consequence of the difficulty of diagnosis of TB in children, few clinical trials have been performed to determine optimal treatment approaches for coinfected children, and treatment guidelines are largely extrapolated from studies of coinfected adults. An urgent priority is the development of infrastructure for pediatric clinical trials of TB and HIV coinfection. Such a network can address critical questions of optimal treatment dosages and duration and pharmacokinetics of ART and anti-TB therapy. Clinical trial data are lacking for basic questions. What is the optimal ART and TB treatment dosage, particularly for children aged <2 years? What is the optimal duration of TB therapy for coinfected children? When should ART be initiated in children with active TB? What are the optimal dosages and the toxicity and efficacy of PI-based HIV therapy in coinfected children receiving rifampicin, particularly in children with perinatal exposure to nevirapine? Research is also needed on pediatric coformulated treatment, because adherence and pill burden are even greater barriers to care, particularly for teens, compared with adults [65].

Prevention of TB in HIV-infected children requires a slightly different approach from prevention in adults. Because of the increased risk of TB among HIV-infected adults, HIV-infected children are at increased risk of TB transmission during the perinatal period and in the home. Because mother-to-child transmission of both HIV and TB are preventable with adequate treatment of infected mothers, studies optimizing implementation of HIV and TB screening in pregnant women are needed. The development of novel methods to interrupt household transmission of TB in HIV-infected children must be prioritized. Although BCG vaccination reduces the incidence of disseminated TB among HIV-uninfected children, BCG vaccination is not recommended for HIV-infected children on the basis of their elevated risk of disseminated BCG disease and their poor immune response to BCG [68,69]. Additional studies of childhood immune responses to TB need to be performed as part of a strategy for development of vaccines that reduce acquisition, reactivation, and dissemination of TB in HIV-infected children.

IMPLEMENTING HIV AND TB CARE DELIVERY

Implementation science refers to the study of the dynamic, multilevel, and multidisciplinary processes required to adapt existing knowledge into real world practice and developing, testing, and optimizing strategies of health care delivery. Implementation science recognizes the multiple levels at which successful implementation operates, starting with the local clinic and/or interpersonal level and proceeding through the national and/or programmatic level to global and/or regional coordination and leadership. In addition, the integration of skills across multiple disciplines, including biomedical science, social and behavioral sciences, environmental health and engineering, economics, ethics, and law, will be needed to optimize HIV and TB care delivery. Rigorous studies comparing implementation strategies across communities through cluster randomization and the development of novel study designs are needed that move beyond descriptive studies of project implementation, monitoring, and identification of barriers through operational research [8,70]. Because global investment in HIV and TB care has increased in recent years, implementation research into the best ways to deliver care for patients with TB and HIV coinfection must be a major priority (Table 2).

Implementing prevention

With regard to prevention, research in implementing infection-control strategies, IPT, TB-intensified case finding, and HIV voluntary counseling and testing must be prioritized.

Studies comparing symptom screening with routine microscopy at patient triage points on the outcome of nosocomial TB transmission are needed. Despite the proven benefits of IPT, implementation of IPT by TB and HIV programs has been slow, in part, because of concerns regarding the duration of efficacy, poor adherence, and the challenges of ruling out active TB before IPT in settings where AFB smear microscopy is the only available diagnostic tool [71]. Additional research identifying the most significant barriers to implementation of IPT and addressing these concerns needs to be performed. Identifying optimal strategies and novel methods to expand HIV voluntary counseling and testing into the community to allow for ART initiation earlier during the course of HIV infection must also be prioritized.

Implementing diagnostics

No other area is likely to have as great an impact on outcomes of HIV infection and TB in resource-limited settings as improvements in diagnostic testing implementation. Because of the benefits of liquid culture and NAATs over traditional TB diagnostic methods, trials comparing improvement of specimen transportation to centralized reference laboratories with expanding culture and NAAT methods to remote settings should be performed. Research is needed to evaluate the effectiveness of limiting TB and HIV diagnostic evaluations to 1 day and to optimizing patient follow-up, because multiple visits for a diagnostic evaluation and loss to follow-up are both major obstacles to patients obtaining necessary care. Finally, in areas where new diagnostics are not within reach, research is needed to identify the major obstacles to implementation of routine, high-quality sputum microscopic screening for symptomatic patients. Novel use of technology that is (relatively) widely available in resource-limited settings, such as mobile phones for both AFB microscopy interpretation [72] and patient follow-up, should be studied. Because there are guidelines supporting intensified case finding [73], the cost-effectiveness of different methods of enhanced TB and HIV infection case finding is also a significant research priority.

Implementing treatment

Not surprisingly, integration of TB and HIV services has been shown to result in high adherence to ART and TB treatment and in improved outcomes of HIV infection and TB [74]. Because a large proportion of patients undergoing evaluation at TB clinics are HIV infected [75] and unrecognized TB is a predictor of early mortality among HIV-infected patients initiating ART [14], TB and HIV care can no longer occur separately. However, such a strategy may not be the best choice for all situations. A major research priority is determining the relative costs and benefits of colocation, compared with coordination of HIV and TB programs across a variety of settings. Optimal strategies to ensure a continuous supply chain of HIV and TB treatment need to be developed at every level of care. In addition, studies are needed to evaluate whether a single adherence support model for TB and HIV therapy or separate models for short-term TB treatment and lifetime HIV treatment are superior. Because of the clear importance of identifying drug-resistant TB but with limited resources for drug-susceptibility testing, research of the most cost-effective strategies for drug-susceptibility testing is needed.

CONCLUSIONS

International political and financial commitment to meeting the unmet research and programmatic needs of developing countries, despite the current global economic crisis, is critical to averting the disastrous effects of undiagnosed and untreated HIV infection and TB in the future. Collaboration among institutions in developed and developing countries and between TB and HIV programs at the local and international level must also continue to improve. Lastly, the time between discovery and implementation of validated research

findings must be shortened through implementation science to lessen the impact of these inextricably linked epidemics.

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Table 1

Priority Research Areas for HIV Infection and Tuberculosis (TB)

Research area	Priorities
Diagnostics: TB case detection in HIV-infected persons	Development of an accurate, rapid, point-of-care test accessible to remote clinics; development of sputum NAAT with improved sensitivity to diagnose AFB smear–negative TB; advancement of serum- and urine-based testing with efficacy for smear-negative and extrapulmonary TB; strategies to reduce the cost, complexity, and processing requirements of mycobacterial liquid culture
Treatment for TB and HIV infection	
Treatment for HIV infection	Defining the optimal timing of ART during coinfection; comparative efficacy studies of first-line ART regimens using optimal ART dosages during TB therapy; determination of the safety and efficacy of dose-adjusted HIV protease inhibitors coadministered with rifampin
Treatment for TB	Comparative studies of rifabutin- and rifampin-based regimens; development of TB treatment–shortening strategies for HIV-infected patients; early identification of appropriate dosages and drug interactions between new TB drugs and ART; development of surrogate markers for TB treatment failure; determination of the optimal duration of corticosteroids for IRIS and development of novel methods to prevent IRIS
Drug-Resistant TB	Role of new TB agents in HIV-infected patients with MDR- or XDR-TB; determination of the efficacy of new TB agents to prevent disease in contacts of persons with MDR- or XDR-TB; impact of ART use, level of HIV immunosuppression, and choice of TB treatment regimens on the acquisition and transmission of MDR- and XDR-TB; determination of the performance of existing drug-susceptibility testing with second-line agents
TB prevention	
Infection control	Development of novel, low-cost, and culturally acceptable TB infection-control strategies; epidemiologic studies clarifying where, when, and how often community TB transmission is occurring in areas with a high burden of TB and HIV infection
IPT	Determination of the best choice of drugs for TB prevention to achieve prolonged efficacy with minimal adverse effects in HIV-infected persons; improvement in strategies for ruling out active TB before IPT
Vaccines	TB vaccine development in HIV-infected adults and children
Pediatric TB and HIV infection	Development and validation of non–sputum-based TB testing in young children; optimal use of interferon-g release assays in children; optimal duration and development of guidelines for IPT use in HIV-infected children; improvement in pediatric clinical trials infrastructure to address the optimal treatment duration, dosages, and pharmacokinetics of ART and anti-TB therapy; TB prevention strategies in HIV-infected children that incorporate household-level infection control and vaccine development

NOTE. AFB, acid-fast bacilli; ART, antiretroviral therapy; IPT, isoniazid preventive therapy; IRIS, immune reconstitution inflammatory syndrome; MDR, multidrug resistant; NAAT, nucleic acid amplification testing; XDR, extensively drug resistant.

Table 2

Examples of Implementation Science Research Questions for Tuberculosis (TB) and HIV Infection

Research area, evidence-based intervention	Priority implementation research agendas	Disciplines required
Prevention		
IPT	Long-term efficacy, adherence, and drug resistance surveillance during IPT implementation	Biomedical science, epidemiology, modeling
Intensified TB case finding	Determination of optimal TB screening method for all patients presenting to HIV clinics	Medical informatics, decision analysis, epidemiology, anthropology
Infection control	Comparison of administrative interventions (triage) to reduce nosocomial transmission in outpatient waiting rooms and inpatient wards; modification or construction of HIV and TB clinics to maximize ventilation or incorporate UVGI	Architecture, engineering, environmental health, biomedical science, epidemiology, business management
Diagnosis		
Expedited, point-of-care TB diagnostics	Comparison of strategy of country- and/or region-wide dissemination of existing TB nucleic acid amplification testing vs capacity-building for specimen transportation to centralized reference laboratories (with an emphasis on rural and hard-to-reach communities)	Business and/or economics, education and/or training, biomedical science, modeling, engineering
MDR-TB screening	Development of TB DST surveillance networks and determination of the optimal algorithm for obtaining DST in TB and HIV–coinfected patients	Epidemiology, biomedical science, education and/or training, modeling
Treatment		
Treatment for HIV infection and TB	Community- and/or region-wide comparison of colocation vs coordination of TB and HIV care (including assessment of nosocomial transmission, stigma, adherence, drug supply, cost, convenience, adverse events, and drug interactions); adherence support in primary TB treatment and its impact on prevention of MDR and XDR	Biomedical science, behavioral science, public policy, business and/or economics, epidemiology, anthropology
Treatment for MDR- and XDR-TB	Assessment of efficacy and feasibility of home-based vs hospital- and/or clinic-based DOT; assessment of household transmission vs nosocomial transmission of MDR- and XDR-TB with different treatment strategies	Ethics, behavioral science, economics, modeling, environmental health

NOTE. DOT, directly observed therapy; DST, drug-susceptibility testing; IPT, isoniazid preventative therapy; MDR, multidrug resistant; UVGI, ultraviolet germicidal irradiation; XDR, extensively drug resistant.